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NCT Number:	NCT01838395
Sponsor Study Number:	BL-8040.01
Official Study Title:	A Phase IIa, Multicenter, Open-Label Study Designed to Evaluate the Safety and Efficacy of Escalating Doses of BL-8040 in Adult Subjects with Relapsed/Refractory Acute Myeloid Leukemia
Document Version and Date:	Clinical Study Protocol, version 7, 15 March 2015

Investigational Product BL-8040	Abbreviated Title: Phase IIa Study Evaluating Safety and Efficacy of BL-8040 in Relapsed/Refractory AML Patients	Protocol No. BL-8040.01
Phase: IIa		Version and Date Final Version 7, 15 Mar 2015

CLINICAL STUDY PROTOCOL

A PHASE IIA, MULTICENTER, OPEN-LABEL STUDY DESIGNED TO EVALUATE THE SAFETY AND EFFICACY OF ESCALATING DOSES OF BL-8040 IN ADULT SUBJECTS WITH RELAPSED/REFRACTORY ACUTE MYELOID LEUKEMIA

Sponsors: BioLineRx, Ltd.
[redacted]

IND No. [redacted]

Investigational Medicinal Product BL-8040 (previously BKT-140)

Principal Investigator(s): [redacted]

Protocol Number: BL-8040.01

Study Phase: IIa

Contract Research Organization: [redacted]

Statistics and Data Management and Pharmacokinetic Analysis: [redacted]

Sponsor Contact: [redacted]

Study Safety Officer: [redacted]

Protocol Version and Date: Version 7, March 15, 2015

Protocol Signature Page

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Protocol Identification	BL-8040.01
Study Phase	IIa
Sponsor	BioLineRx Ltd., ISRAEL

Sponsor Representatives

We, the undersigned, have read this protocol and agree that it contains all necessary information required to conduct the trial and that the protocol is in compliance with International Conference on Harmonization (ICH) and Good Clinical Practice (GCP) guidelines and applicable local regulations.

[redacted]
Drug Development Manager — Date: 15 MAR 2015

[redacted]
Medical Director — Date: 15 MAR 2015

[redacted]
VP Medical Affairs — Date: 15 MAR 2015

Principal Investigator

By signing below, I, the Investigator, approve the protocol and agree to conduct the clinical trial according to all stipulations of the protocol as specified in both the clinical and administrative sections, CRF and any protocol-related documents (subject to any amendments agreed to in writing between the Sponsor and Principal Investigator). I agree to comply with the ICH-GCP, World Medical Association Declaration of Helsinki (and relevant updates) and applicable local regulations. I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of BioLineRx Ltd. I understand that the study may be terminated or enrollment suspended at any time by sponsor, or by me, at my center, if it becomes necessary in my opinion, to protect the best interests of the study subjects.

Name | Investigator Signature | Date

Center's Name | City, Country

Protocol Version History Page

Version	Main Changes
01	Original
02	• Clarification of 3+3 design in synopsis and protocol body • Clarification of MTD definition • Clarification of role of Data Monitoring Committee during dose escalation and expansion. • Dose limiting toxicity definition amended in synopsis and protocol body. Stopping rules and dose limiting toxicity section moved to Study Design section in synopsis for clarity. • Study procedures separated from study design in synopsis and introduced into self-contained section.
03	• Removed reference to specific CD markers to be used in characterization of leukemic blast cells by FACS analysis in "Study Procedures" section of synopsis, Sections 5.2 and 5.7.4 • Reinstated footnote on page 12 which was accidentally removed during previous amendment. • Removed all references to Day 7 pre-dose sampling for FACS and FISH analyses throughout. • Secondary objectives amended because BL-8040 effect on leukemic cell mobilization and apoptosis when combined with high-dose Ara-C will not be possible following removal of Day 7 FACS and FISH analyses. • References to white cell and blast counts amended throughout the document to correct the unit from "/mL" to "/µL." • Reference to approximately 3 US sites [redacted] • Deleted check marks from Appendix A, Schedule of Assessments, for coagulation sampling on Day 2 and Day 7 pre-dose sampling for FACS and FISH analyses. • Edited faulty hyperlinks within document.
04	• [redacted] replaces [redacted] as VP Medical Affairs. • Replace TUNEL assay with caspase-3 staining – deletion of reference 30. • Addition of FACS analysis to Day 30 bone marrow aspirate.

05	• Synopsis Study Design and Investigational Product – Eligible subjects may receive one or more injections during the daily administration in case the dose is split and injected into more than one site at the discretion of the investigator. • Section 6 – In addition to the division of injections, reconstitution and administration instructions will be provided in a separate study manual.
06	• Addition of sixth dose level (2.0 mg/kg) with corresponding increase in potential patient recruitment to "**escalation phase**" to 36 patients. • Increase in total patient recruitment to 70 patients. • Removal of restriction on concomitant treatment with high dose steroids.
07	• Update number of participating sites. • Inclusion criteria amended to only include patients in first relapse. • Clarifications provided to inclusion criteria for relapse/refractory patients. • Addition of exclusion criteria – extramedullary AML. • Protocol amended to allow Investigator's to administer a second treatment cycle to subjects in the expansion phase. • Study procedures and Schedule of assessments adjusted accordingly. • Increase in screening window for performing baseline BM biopsy from 72 hours to 7 days. • Addition of anti-drug antibody assessments. • Addition of telephonic long-term follow up to monitor AML status and survival. • Addition of time windows for post-dose safety, efficacy and PK assessments. • Addition of flexibility to discontinue PK collections during the expansion phase at the Sponsor's discretion. • Addition of efficacy endpoints – CRc and OS during the long-term follow-up. • Minor change to concomitant medication section specifically relating to BL-8040 injection site and systemic reactions.

TABLE OF CONTENTS

Page

List of Tables

PROTOCOL SYNOPSIS

Study Title	A Phase IIa, Multicenter, Open-label Study Designed to Evaluate the Safety and Efficacy of Escalating Doses of BL-8040 in Adult Subjects with Relapsed/Refractory Acute Myeloid Leukemia
Protocol No.	BL-8040.01
Clinical Sites	Approximately 5 sites in the USA and 5 sites in Israel are planned. Additional sites may be added in the event of slow recruitment.
Study Phase	IIa
Therapeutic Indication	Treatment of Acute Myeloid Leukemia (AML) in relapsed/refractory adult subjects
Study Objectives	**Primary** • To assess the safety and tolerability of escalating repeated doses of BL-8040 administered as monotherapy for two days, followed by five days of combined administration with high-dose Ara-C in AML adult subjects with relapsed or refractory disease **Secondary** • To assess the clinical efficacy (response rates) of escalating repeated doses of BL-8040 administered as monotherapy for two days, followed by five days of combined administration with high-dose Ara-C in AML adult subjects • To assess the apoptotic effect of BL-8040 on leukemic blasts when administered as monotherapy • To assess the effect of BL-8040 on mobilization of AML blasts to peripheral blood (PB) when administered as monotherapy • To assess the single and multiple dose pharmacokinetic profile of BL-8040 **Exploratory** • To assess additional pharmacodynamic parameters relevant to CXCR4 inhibition
Study Design	This will be an open-label, multicenter, phase IIa, dose escalating study in subjects with relapsed/refractory AML, defined according to WHO criteria [(1)], including subjects who failed chemotherapy only and those who failed previous Autologous Stem Cell Transplantation (ASCT) / Allogeneic Stem Cell Transplantation (AlloSCT), provided at least 6 months have passed from transplant. Eligible subjects will receive subcutaneous (SC) injections of BL-8040 ("monotherapy period") over two days (one dose per day that may be administered into one or more injection sites) followed by concurrent administration of BL-8040 with standard salvage chemotherapy ("combined period") over 5 days. BL-8040 administration during the "combined period" will also be one dose per day into one or more injection sites, at the discretion of the Investigator. During the "combined period," BL-8040 will be administered 4 hours prior to chemotherapy.

The chemotherapy will consist of cytarabine (Ara-C) 1.5 or 3 g/m^2/d per dose (based on age), administered intravenously (IV) over 3 hours, for 5 days[a] and will not be escalated.

The first part of the study (Part 1) will include escalating dose groups and be considered the **'escalation phase'**. Six potential dose levels (see Table 1) will be investigated starting at dose level 1. Patients will be accrued in a conventional 3+3 design. Applying this study design, the first cohort of 3 patients will be treated at dose level 1 and evaluated for dose escalation.

Table 1 Planned BL-8040 dose escalation schedule

Dose Level	BL-8040 dose (free base) per SC injection	Sample size (N)
1	0.5 mg/kg	3
2	0.75 mg/kg	3
3	1.0 mg/kg	3
4	1.25 mg/kg	3
5	1.5 mg/kg	3
6	2.0 mg/kg	3

If at dose level 1 and beyond, 0 out of 3 patients experience dose-limiting toxicity (DLT), then the next cohort of 3 patients will be treated at the next dose level. If 1 out of 3 patients develop DLT, an additional 3 patients will be treated at the same dose level. If no more DLT develops at that dose, i.e. 1 out of a total of 6 patients develops DLT, the dose escalation continues to the next dose level. At any given dose, if greater than 1 out of 3 patients or 1 out of 6 patients experience DLT, the dose level exceeds the maximum tolerated dose (MTD). In this situation, 3 more patients will be treated at the next lower dose if there are less than 6 patients already treated at that dose. MTD is defined as the highest dose level in which 6 patients have been treated with less than 2 instances of DLT.

The decision to proceed to the next higher dose level will be made by an independent Data Monitoring Committee (DMC)[b] after review of relevant safety data collected up to and including Day 30 (± 2 days; Day 28 ± 2 of chemotherapy) of the last subject of the previous dose group. The DMC may recommend evaluation of intermediate doses (or doses lower than the starting dose of 0.5 mg/kg) of BL-8040 in combination with Ara-C.

Dose escalation will be permitted until the MTD is established and protocol specific stopping rules for toxicity are met. If no MTD is reached, dose escalation will continue up to dose level 6 (2.0 mg/kg). It is anticipated that up to 36 eligible patients will be required for the dose escalation.

At the discretion of the Sponsor, additional subjects may be enrolled into a selected dose group to confirm safety, efficacy and pharmacokinetic (PK) profile for the selected dose, bringing the study up to approximately 70 subjects in total. This portion of the study will be considered the **'expansion phase'** (Part 2). The DMC, in consultation with the Sponsor and Investigators, will decide on the selected dose level for expansion based on safety data, MTD, other relevant toxicity considerations, and all available pharmacokinetic (PK) and correlative

[a] Subjects ≤ 60 years will receive Ara-C **3** g/m^2/d, and those > 60 years will receive Ara-C **1.5** g/m^2/d

[b] Data Monitoring Committee will be comprised of 3 members appointed by the Sponsor including at least one clinician, and persons knowledgeable of the investigational drug.

pharmacodynamic (PD) data.

During Part 2 of the study, at the Investigator's discretion and after discussion with the Sponsor, subjects may be treated with a second cycle of BL-8040 in combination with Ara-C if they are considered to have had clinical benefit during the first treatment cycle, but failed to achieve complete remission (CR or CRi). In the event that subjects receive a second treatment cycle, the dosing regimen will be identical to that in the first treatment cycle. The second treatment cycle will start after clinical response assessment has been completed for the first treatment cycle, i.e., no sooner than Day 30 (± 2 days; Day 28 ± 2 of chemotherapy).

During Part 2 of the study, any DLT occurring at a frequency of > 30% will stop accrual. In this situation, the DMC, in consultation with the Sponsor and Investigators, may recommend a lower dose level for the expanded cohort.

Stopping Rules and Dose Limiting Toxicities

Dose-limiting toxicity (DLT)[a] is defined as a clinically significant adverse event or abnormal laboratory value assessed as unrelated to disease progression, intercurrent illness or concomitant medications and occurring during the safety period (30 days)[b] that meets any of the following criteria (refer to Table 2 for CTCAE severity grading):

- CTCAE grade 3 AST (SGOT) or ALT (SGPT) or bilirubin for ≥ 7 days
- CTCAE grade 4 AST (SGOT) or ALT (SGPT) of any duration
- All other clinically significant, non-hematological NCI common terminology criteria that are CTCAE grade 3 or 4

To be considered a DLT such toxicity must be possibly, probably or definitely related to BL-8040.

An adverse event must be clinically significant to define DLT e.g. nausea and vomiting, alopecia, study drug-related fever, electrolyte abnormalities (including K, Na, Cl, HCO_3, Mg, Ca, bilirubin) that are ≤ grade 3 will not constitute DLT. Myelosuppression and cytopenias are expected outcomes of leukemia treatment and per se will not constitute DLT. Only prolonged myelosuppression, as defined by the NCI criteria specific for leukemia, i.e. marrow cellularity < 5% on Day 42 or later (6 weeks) from start of therapy without evidence of leukemia, will be considered in defining MTD and DLT.

Subjects experiencing ≥ grade 3 BL-8040-related toxicity, either in the monotherapy or combined treatment period (excluding hematological toxicity), will be withdrawn from the study, but followed for toxicity. Subjects who experience toxicity, which is not related to BL-8040, either during monotherapy or within the combination therapy period, will be allowed to continue BL-8040 treatment at the Investigator's discretion.

BL-8040 injections will be stopped in case of a significant increase in WBC and/or blasts (WBC ≥ 60,000/μL and/or blasts ≥ 50,000/μL, respectively) measured prior to administration of the next BL-8040 injection and/or evidence of leukostasis, TLS or grade 3-4 allergic reaction. These subjects will be withdrawn

[a] Only drug related or possibly related grade 3-4 define DLT. For example, bone pain at grade 3/4 will not necessarily be defined as DLT, based on physician's decision and accounting for other administered drugs.

[b] In case of prolonged BM recovery it will be evaluated again at 6 weeks and considered part of the DLT assessment. The safety period for subjects who receive a second treatment cycle in the expansion phase will be 30 days after the start of the second treatment cycle or up to 6 weeks in the event of delay in BM recovery.

	from the study and will be followed-up for safety for up to 6 weeks. In addition, during the **escalation phase**, subjects with blast values of ≥ 30,000 and < 50,000/µL and/or WBC counts of ≥ 50,000 and < 60,000/µL 24 hrs following BL-8040 injection on Days 1-6, will be withdrawn from the study and replaced. During the expansion phase of the study, subjects with blast values of ≥ 30,000 and < 50,000/µL and/or WBC counts of ≥ 50,000 and < 60,000/µL, 24 hrs following the first BL-8040 injection, will not receive the second injection. Provided there are no signs of leukostasis on detailed physical examination, they will proceed directly to the combination therapy stage (protocol Day 3). In this situation, subjects will not receive BL-8040 prior to the first dose of Ara-C[a], but will receive BL-8040 prior to Ara-C on subsequent days provided blast count is < 30,000/µL and WBC count is < 50,000/µL. Similarly, subjects with blast values of ≥ 30,000 and < 50,000/µL and/or WBC counts of ≥ 50,000 and < 60,000/µL 24 hrs following the second BL-8040 injection will be given the first dose of Ara-C without receiving BL-8040[b], provided there are no signs of leukostasis on detailed physical examination, but will receive BL-8040 prior to Ara-C on subsequent days provided blast count is < 30,000/µL and WBC count is < 50,000/µL. Subjects who do not receive BL-8040 on Days 2 and/or 3, will not provide the full data set required for assessment of secondary endpoints relating to leukemic blast apoptosis and mobilization. However, they will be considered eligible for assessment of the secondary efficacy endpoint relating to response rate. During the combination therapy, if blast values are ≥ 30,000/µL, BL-8040 administration will be discontinued.
Study Procedures	The study will comprise a screening period, a treatment period (monotherapy and combined treatment) and a follow-up period. For each dose group, visit scheduling and assessments will be similar. During the expansion phase, at the Investigator's discretion and after discussion with the Sponsor, subjects may be treated with a second cycle of BL-8040 in combination with Ara-C if they are considered to have had clinical benefit during the first treatment cycle, but failed to achieve CR or CRi. **Screening Period (Day -3 to Day 0)** After signing informed consent, adult men and women subjects aged 18-75 years will be screened for study eligibility by assessment of inclusion and exclusion criteria. Screening procedures will include • Collection of demographic data, medical history, physical examination (including height, weight and assessment of cerebellar function), vital signs (blood pressure, pulse rate, oral temperature, O_2 saturation levels

[a] Subjects who skip Day 2 due to blast counts ≥ 30,000 and < 50,000 and or WBC counts ≥ 50,000 and < 60,000/mL 24 hrs following the 1st dose of BL-8040, will proceed directly to protocol Day 3. All Day 3 assessments and procedures will be performed with the exception of BL-8040 administration and the following **post-dose** assessments: PK profiling, ECG measurements, WBC count (differential and leukemic cells), partial biochemistry and assessment of CXCR4 receptor occupancy, leukemic blast apoptosis and mobilization (FACS and FISH). BM biopsy and/or aspiration must be performed prior to Ara-C administration.

[b] Subjects with blast counts ≥ 30,000 and < 50,000 and/or WBC counts ≥ 50,000 and < 60,000/mL 24 hrs following the 2nd dose of BL-8040, will undergo all Day 3 assessments and procedures with the exception of BL-8040 administration and the following **post-dose** assessments: PK profiling, ECG measurements, WBC count (differential and leukemic cells), partial biochemistry and assessment of CXCR4 receptor occupancy, leukemic blast apoptosis and mobilization (FACS and FISH). BM biopsy and/or aspiration must be performed prior to Ara-C administration.

and respiration rate), Eastern Cooperative Oncology Group (ECOG) performance status, 12-lead electrocardiogram (ECG), Echocardiogram (ECHO)/Multiple Gated Acquisition (MUGA), chest x-ray and safety laboratory evaluations (hematology, biochemistry, coagulation [PT and aPTT] and a serum pregnancy test for women of childbearing potential).

- Screening for HIV, HCV, HBV serology.
- Clinical evaluation of leukostasis [2] related symptoms (visual symptoms, shortness of breath and decreased oxygen saturation in blood measured by pulse oximetry) and tumor lysis syndrome (TLS, according to Cairo–Bishop criteria [3]; Appendix D).
- Bone marrow (BM) biopsy and aspirate will be conducted within 7 days prior to commencement of the treatment for baseline assessment of leukemic cell numbers and apoptosis in BM.
- CXCR4 levels and other relevant parameters will be assessed by immunohistochemistry (IHC) and/or other techniques in pre- BL-8040 BM biopsy samples and will be analyzed for correlation to efficacy.

Treatment Period (Day 1 to Day 7)

Monotherapy period – On Day 1 (Baseline, enrollment day) and Day 2, eligible subjects will receive BL-8040 monotherapy administered by SC injection(s), once daily in the morning.

Subjects considered suitable for a second treatment cycle during the expansion phase will receive BL-8040 monotherapy on Days 1 and 2 of the additional cycle as described above.

Combined therapy period – On Days 3-7, subjects will be treated once daily in the morning with BL-8040 SC injection(s) followed by chemotherapy 4 (± 0.5) hours later. The chemotherapy will consist of Ara-C 1.5 or 3 g/m^2/d administered IV over 3 hours[a].

Subjects considered suitable for a second treatment cycle during the expansion phase will receive BL-8040 in combination with Ara-C on Days 3-7 of the additional cycle as described above.

The following assessments will be conducted during the treatment period:

- Laboratory safety evaluations[b]:
  - Hematology (CBC) and biochemistry samples will be collected daily on Days 1-7 prior to administration of BL-8040.
  - Coagulation (PT and aPTT) will be evaluated on Day 1 pre-dose and 24 hrs post-dose, and on Day 7 at 24 hrs post-dose.
  - WBC counts, including differential and leukemic cell count, will be measured on Days 1, 2, 3 and 7 at 4 and 8 hrs post BL-8040 injection.
  - Partial biochemistry samples (electrolytes and kidney function) will be collected on Days 1, 2, 3 and 7 at 4 and 8 hrs post BL-8040 injection.
  - Additional hematology, biochemistry and coagulation samples may be collected at the discretion of the Investigator or upon

[a] Subjects ≤ 60 years will receive Ara-C **3** g/m^2/d, and those > 60 years will receive Ara-C **1.5** g/m^2/d

[b] Subjects considered suitable for a second treatment cycle during the expansion phase will undergo the same laboratory safety evaluations during the second cycle with the exception of coagulation and partial biochemistry evaluation.

	Sponsor's request. • Anti-drug antibody (ADA) and complement activation: o Blood samples for assessment of ADA and complement activation will be collected pre-dose and at 4 hrs post BL-8040 administration on Days 1 and 7. On Day 3 an ADA sample will be collected pre-dose only. • Pharmacokinetic (PK) sampling[a]: o Blood samples for BL-8040 PK analysis will be collected on Days 1, 3 and 7 at pre-dose, 0.25, 0.5, 1, 2, 4, 8 and 24 hrs post BL-8040 administration. o Samples will also be collected on Day 5 at pre-dose and 0.5 hr post BL-8040 administration. o PK sampling may be discontinued during the expansion phase at the discretion of the Sponsor. The Sponsor will notify sites when PK sample collection can be halted. • 12-lead ECGs: o 12-lead ECGs will be recorded on Days 1, 3 and 7 at pre-dose, 0.5, 1, 2, 4, 8 and 24 hrs post BL-8040 administration. For subjects receiving a second treatment cycle during the expansion phase, ECGs will only be recorded on Days 1 and 7 of the second cycle at pre-dose and 4 hrs post BL-8040 administration. o Additional ECGs may be recorded at the discretion of the Investigator or upon Sponsor's request. • BM biopsy and/or aspirate[b]: o Bone marrow biopsy and/or aspiration will be performed on Day 3 (prior to BL-8040 injection) for quantitative assessment of leukemic blast number and apoptosis of leukemic cells in the BM[c] using caspase-3 staining. • Fluorescence-activated cell sorting (FACS) analysis[d]: o Leukemic blasts in peripheral blood (PB) will be assessed by analysis of surface markers on Days 1 and 3 at pre-dose, 4[e] and 24 hrs post BL-8040 injection. Additional signaling pathway proteins may be assessed at the discretion of the Sponsor. o Leukemic cell apoptosis in PB will be assessed by Annexin V and Propidium iodide (PI) analysis on Days 1 and 3 at pre-dose, 4[e] and 24 hrs post BL-8040 injection. o CXCR4 occupancy will be measured in the PB of dose escalation phase subjects, using the CXCR4 antibodies 12G5 and 1D9, on Days 1 and 3 at pre-dose, 4[e] and 24 hrs post BL-8040 injection. • Fluorescent In Situ Hybridization (FISH) analysis[f]:

[a] PK sampling will only be performed during the first treatment cycle for subjects in the expansion phase.

[b] Day 3 BM sampling will only be performed during the first treatment cycle for subjects in the expansion phase.

[c] Subjects who do not undergo BM evaluation on Day 3 will still be included in the safety and efficacy evaluation.

[d] FACS analysis will only be performed during the first treatment cycle for subjects in the expansion phase.

[e] 4 hr post-dose samples on Day 3 to be taken prior to administration of Ara-C.

[f] FISH analysis will only be performed during the first treatment cycle for subjects in the expansion phase.

- In the expansion phase of the study, subjects with identifiable chromosomal abnormalities will be assessed by FISH in PB and/or BM aspirate collected on Days 1 and 3 at pre-dose, 4[a] and 24 hrs post BL-8040 injection.

- Clinical evaluations:
  - Vital signs, physical examination, including assessment of cerebellar function and recording of adverse events (AEs) and concomitant medications will be performed daily on Days 1-7 prior to administration of BL-8040. For expansion phase subjects receiving a second treatment cycle, the same assessments will be performed daily on Days 1-7 prior to administration of BL-8040.
  - Clinical evaluation of leukostasis [(2)] related symptoms (visual symptoms, shortness of breath and decreased oxygen saturation in blood measured by pulse oximetry) and tumor lysis syndrome (TLS, according to Cairo–Bishop criteria [(3)]) will be assessed on Day 1 and upon commencement of such symptoms or when WBC $\geq$ 30,000/μL.

Follow-up period

The follow-up period will start after completion of Ara-C chemotherapy and continue for up to 6 weeks after initiation of salvage chemotherapy with Ara-C, i.e., up to Day 44. Expansion phase subjects who receive a second treatment cycle will also be followed for up to 6 weeks after initiation of Ara-C during the second cycle, i.e., up to Day 44 of the second cycle.

Bone marrow biopsy and aspiration will be performed on Day 30 (± 2 days; 28 ± 2 days from initiation of salvage chemotherapy) unless, in the opinion of the Investigator, earlier biopsy/aspiration is indicated based on early appearance of blast cells in PB. The follow-up period will end when a BM biopsy and/or aspirate, performed between Day 20 – 44, provides definite assessment of response to therapy. Bone marrow aspirate collected during this time frame will be examined by FACS analysis for final assessment of leukemic cell numbers.

In subjects who do not show sufficient BM recovery by Day 30 (in the absence of leukemic cells), BM biopsy and aspiration will be repeated 2 weeks later (Day 44) to exclude aplasia. Additional bone marrow aspirations may be performed at the Investigator's discretion to assess response.

Haematology and biochemistry tests will be performed twice a week for the duration of the follow up period. Follow-up assessments will also include time to recovery of WBC and platelets, recording of AEs and concomitant medications and collection of an ADA sample at the end of the follow-up period.

For expansion phase subjects receiving a second treatment cycle, bone marrow biopsy/aspiration and follow-up assessments following the second treatment cycle will be performed as described above. However, ADA sample collection will only take place at the end of the follow-up period following the first treatment cycle.

Long-term Follow-up

Subjects participating in the expansion phase will be followed for up to 5 years after completion of the Follow-up period. Sites will contact subjects by telephone at approximately 3 month intervals (± 1 month) after the end of the follow-up period to determine AML status and survival.

[a] 4 hr post-dose samples on Day 3 to be taken prior to administration of Ara-C.

Study Duration	The study duration for each subject will be up to 7 weeks as follows[a]: **Study Period** — **Duration** Screening period — 7 days Treatment Period: Monotherapy period — 2 days Combined therapy period — 5 days Follow up period — up to 5 weeks (measured from end of salvage chemotherapy with Ara-C)
Planned Sample Size	The exact number of subjects enrolled will depend on the toxicity observed in each dose group and the number of dose groups required to reach MTD. If all six dose groups are required and if each dose group is expanded to 6 subjects (see stopping rules below), then a total of 36 subjects will be enrolled into the dose escalation part of the study. Once a dose has been selected for the **expansion phase,** additional subjects may be enrolled in that dose group up to a total of approximately 70 subjects in the study.
Inclusion Criteria	1. Adult men and women subjects aged 18 to 75, inclusive. 2. Confirmed diagnosis of relapsed/refractory AML (WHO criteria [(1)]; Appendix B). ▪ Refractory subjects after up to 2 cycles of induction therapy[b] or first complete response (CR1) duration ≤ 90 days. ▪ Relapse occurring > 90 days and ≤ 24 months since CR1[c]. 3. AML relapse > 6 months since autologous or allogeneic stem cell transplantation, provided they are in first relapse and: ▪ No active graft-versus-host disease (GVHD > grade 1). ▪ No treatment with high dose steroids for GVHD (up to 20 mg Prednisolone or equivalent, Appendix G). ▪ No treatment with immunosuppressive drugs with the exception of low dose cyclosporine and tacrolimus (blood levels of 0.5-0.6 µg/mL). 4. Clinical laboratory values should be as follows: ▪ WBC < 30,000/µL ▪ Blasts in PB ≤ 20,000. Treatment with Hydroxyurea is permitted up to 24 hrs prior to BL-8040 administration to achieve blast counts < 20,000 prior to enrollment. ▪ Creatinine < 1.3 mg/dL; if Creatinine is > 1 mg/dL the Creatinine clearance should be > 40 mL/min as calculated using the Cockcroft-

[a] The study duration for subjects participating in the expansion phase who receive a second treatment cycle will be up to approximately 13 weeks.

[b] Subjects who have failed to respond to up to 2 prior induction treatment regimens will be considered eligible. Prior induction therapy must include at least 1 cycle of an anthracycline (e.g., at least 45 mg/m^2/dose daunorubicin or at least 9 mg/m^2/dose idarubicin) or anthracenedione (e.g., at least 10 mg/m^2/dose mitoxantrone) and cytarabine-based regimen.

[c] Relapsed subjects must have achieved a CR or CRi lasting > 90 days, resulting from no more than 2 cycles of induction cytotoxic chemotherapy including at least 1 cycle of an anthracycline (e.g., at least 45 mg/m^2/dose daunorubicin or at least 9 mg/m^2/dose idarubicin) or anthracenedione (e.g., at least 10 mg/m^2/dose mitoxantrone) and cytarabine-based regimen. An unlimited number of consolidation cycles following CR1 are allowed.

	Gault formula. 5. Women of childbearing potential and all men must agree to use an approved form of contraception (e.g. oral, transdermal patch, implanted contraceptives, intrauterine device, diaphragm, condom, abstinence or surgical sterility) prior to study entry and for the duration of study participation through 30 days after the last dose of BL-8040. Confirmation that female subjects are not pregnant must be established by a negative serum β-human chorionic gonadotropin (β-hCG) pregnancy test result obtained during screening. Pregnancy testing is not required for post-menopausal or surgically sterilized women. 6. Subject is able and willing to comply with the requirements of the protocol. 7. Subject is able to voluntarily provide written informed consent.
Exclusion criteria	1. Administration of conventional chemotherapy within 2 weeks of enrollment date. In the event that subjects have received chemotherapy > 2 weeks from the date of enrollment, they may be included provided they have recovered from the associated non-hematological toxicities to ≤ grade 1. 2. Life expectancy of ≤ 2 months. 3. Known allergy or hypersensitivity to any of the test compounds, materials or contraindication to test product. 4. Use of investigational device or agents within 2 weeks of enrollment date. 5. Low Performance Status (ECOG > 2; Appendix E). 6. O_2 saturation < 92% (on room air), evidence of TLS > grade 2 (according to the Cairo-Bishop criteria [3]) or leukostasis [2]. 7. Abnormal liver function tests: o Serum aspartate transaminase (AST/SGOT) or alanine transaminase (ALT/SGPT) 2 x upper limit of normal (ULN). o Serum bilirubin. Total bilirubin > 2.0 mg/dL (34 µmol/L), conjugated bilirubin > 0.8 mg/dL. 8. Left ventricular ejection fraction < 40 %. 9. History of myocardial infarction or cerebrovascular accident within 6 months of enrollment date. 10. Presence of active, uncontrolled infection. 11. Known central nervous system disease (e.g., Alzheimer's disease). 12. Acute promyelocytic leukemia. 13. Exposure to high dose Ara-C within 6 months of enrollment. 14. Subject has concurrent, uncontrolled medical condition, laboratory abnormality, or psychiatric illness which could place him/her at unacceptable risk, including, but not limited to: o Subject has been diagnosed or treated for another malignancy within 3 years of enrolment, except in situ malignancy, or low-risk prostate, skin or cervix cancer after curative therapy o A co-morbid condition which, in the view of the Investigators, renders the subject at high risk from treatment complications. 15. Female subjects who are pregnant or breastfeeding. 16. Prior clinically significant grade 3-4 non-hematological toxicity to high dose Ara-C or grade ≥ 2 of neurological toxicity. 17. Seropositive for HIV antibodies (HIV1 and HIV2), Hepatitis C antibody (Hep C Ab) or a Hepatitis B carrier (positive for Hepatitis B surface antigen [HBsAg]). 18. Unable to comply with study requirements in the opinion of the Investigator.

	19. Extramedullary AML involvement (including CNS involvement).
Investigational Product Route and Dosage Form	BL-8040 (formally named BKT140) is a highly selective CXC chemokine receptor 4 (CXCR4) antagonist co-developed by [redacted] and BioLineRx, Ltd. as a novel therapy for treatment of cancer. BL-8040, a white to off-white powder synthetic polypeptide, is freely soluble in water. It is manufactured in accordance with cGMP by [redacted] On Days 1 and 2, subjects will receive once daily SC injections of BL-8040 in the morning according to the dose group to which they are assigned. Between Days 3 and 7, BL-8040 will be administered once daily 4 (+/- 0.5) hrs prior to administration of standard chemotherapy (chemotherapy will be initiated on Day 3). The same instructions are applicable for expansion phase subjects who receive a second treatment cycle. The BL-8040 injection site will be rotated on Days 1-7, to minimize the severity of any local injection site reactions. At the discretion of the Investigator, a single dose administration may be split and injected into more than one site. The same instructions are applicable for expansion phase subjects who receive a second treatment cycle. During the expansion phase of the study, subjects with blast values of ≥ 30,000 and < 50,000/µL and/or WBC counts of ≥ 50,000 and < 60,000/µL, 24 hrs following the first BL-8040 injection, will not receive the second injection. Provided there are no signs of leukostasis on detailed physical examination, they will proceed directly to the combination therapy stage (protocol Day 3). In this situation, subjects will not receive BL-8040 prior to the first dose of Ara-C, but will receive BL-8040 prior to Ara-C on subsequent days provided blast count is < 30,000/µL and WBC counts is < 50,000/µL. Similarly, subjects with blast values of ≥ 30,000 and < 50,000/µL and/or WBC counts of ≥ 50,000 and < 60,000/µL 24 hrs following the second BL-8040 injection will be given the first dose of Ara-C without receiving BL-8040, provided there are no signs of leukostasis on detailed physical examination, but will receive BL-8040 prior to Ara-C on subsequent days provided blast count is < 30,000/µL and WBC counts is < 50,000/µL. The planned dose escalation scheme will be as shown in Table 1. Dose modifications may include dose reductions, including doses lower than the starting dose of 0.5 mg/kg, and intermediate doses, but the maximum dose to be tested will not exceed 1.5 mg/kg. **Chemotherapy** Chemotherapy will consist of Ara-C 3g/m^2/day for subjects ≤ 60 years (performance status permitting) and 1.5 g/m^2/day for subjects > 60 years administered IV over 3 hours. **Rescue medication** Leukostasis: Initiation of chemotherapy will be expedited in subjects experiencing leukostasis. Additionally, leukopharesis should be considered. Subjects

	developing shortness of breath with reduced saturation should be carefully monitored and receive oxygen. TLS: Subjects should be hydrated vigorously (urine output and fluid input should be monitored). Allopurinol and Rasburicase should be considered.
Concomitant Medications	The following concomitant medications/therapies will be allowed during the treatment period: ▪ Allopurinol up to 300 mg/day (with adjustment to kidney function) and/or Rasburicase (up to 0.2 mg/kg/day, for up to 5 days). ▪ Clinically appropriate measures in case of BL-8040-related local injection site reactions (e.g., corticosteroids, anti-histamines, local treatments etc.) and preventive treatment before subsequent doses; also relevant for subjects with systemic reactions. ▪ Systemic and allergic treatment for chemotherapy-related allergic reactions. ▪ Antiemetic drugs (e.g., Ondansetron) as required clinically based on local guidelines for patients experiencing nausea while treated with BL-8040 only, and as a preventive approach during the combined treatment period. ▪ Gastrointestinal and kidney protective medications, routinely used in patients receiving chemotherapy, aiming to avoid peptic pain and TLS respectively (Losec, allopurinol, respectively). ▪ Prophylactic antibiotics (e.g., quinolone or cephalosporin), antifungals (e.g., voriconazole) and antivirals (e.g., valacyclovir). ▪ Blood products, commonly required in patients receiving chemotherapy for AML. ▪ Low-dose steroids (100 mg hydrocortisone or equivalent) are allowed as pre-medication for blood transfusion or with IV anti-fungals. ▪ B6 – provided to avoid neurotoxicity. ▪ Steroid eye drops - to prevent Ara-C induced inflammation. Additional medications/therapies to manage treatment or disease emergent conditions will be allowed at the discretion of the Investigator in consultation with the Sponsor, in advance where possible. In case there is a change in therapy related to an AE, the Sponsor or Investigator may decide to withdraw the subject (refer to Section 4.6).
Study Endpoints	Safety Endpoints • Safety and tolerability will be the primary endpoints of this study and will be evaluated on the basis of the following parameters: • General safety: Vital signs (oral temperature, blood pressure, pulse rate, respiratory rate and O_2 saturation), 12-lead ECG and physical examination. • Toxicity according to the latest version of NCI-CTCAE (currently V4.03, refer to Table 2) for AEs and clinical laboratory profile as follows: o Screening: record and report screening results, however not considered treatment emergent AEs. o Throughout the study: record and report all AEs and SAEs according to GCP. Efficacy Endpoints • Efficacy endpoints will be secondary endpoints for this study. The following secondary endpoints will be assessed:

	• Response rates as assessed at final BM evaluation based on Cheson 2003 criteria [4] (Appendix C):
	  ○ Complete response (CR)
	  ○ Complete response with incomplete hematological recovery of platelets or neutrophils (CRi)
	  ○ Partial response (PR)
	  ○ Overall response defined as the sum of CR, CRi and PR.
	  ○ Complete Response composite (CRc) defined as the sum of CR and CRi.
	• Change in leukemic cell apoptosis in PB and BM.
	• Kinetics of mobilization of leukemic blasts from BM to PB.
	• Overall survival (OS) during the long-term follow-up defined as time from enrollment to death from any cause.
	
	Pharmacokinetic Endpoints
	• PK analysis of multiple injections of BL-8040.
	• For PK analyses, blood samples will be collected on Days 1, 3 and 7 at pre-dose, 0.25, 0.5, 1, 2, 4, 8 and 24 hrs post BL-8040 administration. Additional samples will be collected on Day 5 at pre-dose and 0.5 hr post BL-8040 administration.
	• Non-compartmental PK parameters for BL-8040 (see below) will be derived from the individual concentration obtained at each of the PK time-points. Additional PK parameters may be derived if considered necessary:
	  ○ C_{max} - maximum BL-8040 plasma concentration
	  ○ T_{max} - time to reach the maximum BL-8040 plasma concentration
	  ○ AUC_{0-t} - Area under the BL-8040 plasma concentration-time curve from time of administration up to the last time point with a measurable concentration post dosing, calculated by linear up-logarithmic down trapezoidal summation
	  ○ $AUC_{0-\infty}$ - Area under the BL-8040 plasma concentration-time curve extrapolated to infinity, calculated as: $AUC_{0-\infty} = AUC_{0-t} + C_{last}/\lambda_z$, where C_{last} is the last measurable concentration
	  ○ λ_z - elimination rate constant, determined by linear regression of the terminal points of the ln-linear plasma concentration-time curve
	  ○ $t_{1/2}$ - terminal elimination half-life, defined as $0.693/\lambda_z$
	
	Exploratory Endpoints
	• CXCR4 receptor occupancy
	• Additional pharmacodynamic endpoints relevant to CXCR4 inhibition.
	• Anti-BL-8040 antibody titers

Statistical Analysis	**Analysis Sets:** Intention-To-Treat (ITT) analysis set: All enrolled subjects who receive at least one dose of study medication. Per-Protocol (PP) analysis set: All enrolled subjects who complete the study according to the protocol without major protocol violations.

General Statistical Methods

All measured variables and derived parameters will be listed individually and, if appropriate, tabulated by descriptive statistics. Summary statistics will be provided for all safety, exploratory and baseline/demographic variables. For categorical variables, frequency tables including percentages will be presented. For continuous variables, descriptive statistics such as number of available observations, mean, median, standard deviation (SD), minimum and maximum will be tabulated. All available data and the tabulation of results will be displayed by initial dose level and with all levels pooled as a whole if applicable.

DLT will be determined by definition and will be summarized by dose level. MTD will be determined by study structure and DLTs.

The data will be analyzed as described in the Statistical Analysis Plan.

Safety Analysis:

Changes in vital signs and routine laboratory data will be presented with descriptive statistics to demonstrate the trend of change.

Number of subjects with physical abnormality at each scheduled visit will be tabulated by body system and by dose level. ECG examination results will be displayed in descriptive statistics and by dose level with number of subjects with abnormal findings tabulated for each schedule visit.

Adverse event incidence will be summarized descriptively by system organ class and preferred term using the latest version of Medical Dictionary for Regulatory Activities (MedDRA; currently version 14.0) and by dose level. The worst severity grade of AEs, as determined by the latest version of the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE; currently version 4.03), and their relationship to study medication will be analyzed by System Organ Class, preferred term and by original dose level. The action taken and outcome will also be analyzed accordingly.

By subject list of toxicity severity grade will be presented in time-sequence manner using the latest version of NCI-CTCAE (currently 4.03) with System Organ Class and preferred term. The number and incidence of subjects experiencing toxicity will be tabulated by worst severity grade in each MedDRA term. Subjects experiencing toxicity $\geq$ grade 3 for each type of toxicity will be calculated and presented by original dose level.

Efficacy Analysis

95% Confidence Interval (CI) will be calculated for proportion of subjects defined in the secondary efficacy endpoints [4] (Appendix C) who achieve:

Complete Response (CR)

Complete Response with incomplete hematological recovery (CRi)

Partial Response (PR)

Overall Response (OR) defined as sum of CR, CRi and PR.

Complete Response composite (CRc) defined as the sum of CR and CRi.

Overall survival (OS) during the long-term follow-up.

GLOSSARY

Subject and patient will be used interchangeably throughout this document.

Abbreviation/Term	Definition
β-hCG	β-human chorionic gonadotropin
µg	Microgram
µL	Microliter
ADA	Anti-drug antibody
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT/SGPT	Alanine Transaminase/Serum glutamic pyruvic transaminase
AlloSCT	Allogeneic Stem Cell Transplantation
AML	Acute Myeloid Leukemia
aPTT	Activated Partial Thromboplastin Time
Ara-C	Arabinofuranosyl Cytidine / Cytarabine / Cytosine Arabinoside
ASCT	Autologous Stem Cell Transplantation
AST/SGOT	Aspartate Aminotransferase/Serum glutamic oxaloacetic transaminase
AUC	Area under the curve
BM	Bone Marrow
BMI	Body Mass Index
C_{max}	Maximum plasma concentration
CBC	Complete Blood Count
CFR	Code of Federal Regulations
CI	Confidence Interval
CR	Complete response
CR1	First Complete response
CRc	Complete Response composite
CRF	Case Report Form
CRi	Complete response with incomplete hematological recovery
eCRF	Electronic Case Report Form
CRO	Contract Research Organization
CTCAE	Common Terminology Criteria for Adverse Events
CXCR4	CXC Chemokine Receptor Type 4
dL	Deciliter
DLT	Dose limiting toxicity
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
FACS	Fluorescence-activated cell sorting
FDA	Food and Drug Administration
FISH	Fluorescent In Situ Hybridization
g	Gram
GCP	Good Clinical Practice
G-CSF	Granulocyte Colony-Stimulating Factor

Abbreviation/Term	Definition
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
GVHD	graft-versus-host disease
HBsAg	Hepatitis B Surface Antigen
HBV	Hepatitis B Virus
HCT	Hematocrit
HCV	Hepatitis C Virus
Hep C Ab	Hepatitis C Antibody
HGB	Hemoglobin
HIV	Human immunodeficiency virus
HSC	Hematopoietic Stem Cells
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
INR	International Normalized Ratio (for blood coagulation tests)
IRB	Institutional Review Board
ITT	Intention-to-treat
IV	Intravenous
kg	Kilogram
λ_z	Elimination rate constant
m	Meter
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
min	Minute
mL	Milliliter
MM	Multiple Myeloma
MTD	Maximum tolerated dose
MUGA	Multiple Gated Acquisition
N	Number of subjects
NCI	National Cancer Institute
NOAEL	No Observed Adverse Effect Level
NOEL	No Observed Effect Level
OR	Overall response
OS	Overall survival
PB	Peripheral blood
PD	Pharmacodynamic
PI	Principal Investigator
PI	Propidium Iodide
PK	Pharmacokinetic
PP	Per Protocol
PR	Partial response
PT	Prothrombin Time
QA	Quality Assurance

Abbreviation/Term	Definition
QC	Quality Control
RBC	Red Blood Cell
SAE	Serious Adverse Event
SC	Subcutaneous
SD	Standard Deviation
SOC	System Organ Class
SOP	Standard Operation Procedures
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	Treatment Emergent Adverse Event
TLS	Tumor lysis syndrome
T_{max}	Time to reach the maximum plasma concentration
$T_{1/2}$	Terminal elimination half-life, defined as $0.693/\lambda_z$
ULN	Upper limit of normal
US	United States
USP	United State Pharmacopeia
WBC	White Blood Cell
WFI	Water For Injection
WHO	World Health Organization
WMA	World Medical Association

1 INTRODUCTION

1.1 THERAPEUTIC INDICATION

Acute myeloid leukemia (AML) represents a group of clonal hematopoietic stem cell disorders in which both failure to differentiate and overproliferation in the stem cell compartment result in accumulation of non-functional cells termed myeloblasts [5]. The annual age-adjusted incidence of AML in the US is 3.6 cases per 100,000 people (2005 - 2009), with a median age at diagnosis of 66 years [6]. The five-year relative survival in US patients diagnosed over the period 2002-2008 was 23.4% [6]. Both prognosis and treatment are based on the presence or absence of specific genetic abnormalities which play an important role as diagnostic criteria for sub-classification of AML [1; 7; 8].

The standard treatment paradigm for AML is remission induction chemotherapy with an anthracycline/cytarabine based combination, followed by either consolidation chemotherapy or allogeneic stem cell transplantation, depending on the AML risk group. The AML risk group predicts the likelihood of cure with chemotherapy alone (based on cytogenetic and molecular parameters) and the patient's expected ability to tolerate an allogeneic stem cell transplantation (highly dependent on age, performance status and co-morbidities) [9; 10; 11; 12]. Approximately 70-80% of subjects enter complete disease remission with several anthracycline-based chemotherapy combinations. Consolidation with high-dose cytarabine or allogeneic stem-cell transplantation in high-risk patients limit overall relapse rate to approximately 50% [13].

Another potential consolidative approach is the employment of autologous stem cell transplantation [14].

1.2 INVESTIGATIONAL THERAPY

BL-8040, formerly BKT-140, is a highly selective CXC chemokine receptor 4 (CXCR4) antagonist co-developed by [redacted] and BioLineRx Ltd. as a novel therapy for treatment of cancer. The investigational drug binds to CXCR4 with high affinity (IC_{50} 0.5-10 nM) and inhibits its function [15]. The chemokine CXCL12 (SDF-1-stromal-derived-factor-1) and its receptor, CXCR4, play a pivotal role in the trafficking of hematopoietic stem cells to the bone marrow (BM) [16]. In addition, BL-8040 exhibits CXCR4-dependent selective cytotoxicity toward malignant cells of hematopoietic origin in both in vitro and in vivo models. BL-8040 significantly and preferentially stimulated leukemic apoptotic cell death. BL-8040 treatment induced morphological changes, phosphatidylserine externalization, decreased mitochondrial membrane potential, caspase-3 activation, sub-G1 arrest and DNA double-stranded breaks [17].

1.2.1 Nonclinical Studies[a]

The nonclinical development of BL-8040 has encompassed a large number of pharmacodynamic (PD), pharmacokinetic (PK), safety pharmacology, and single and repeated dose toxicity studies.

Nonclinical studies in mice demonstrated the ability of BL-8040 to mobilize progenitor and stem cells from the BM, as well as various WBC types, such as neutrophils and monocytes [18;

[a] The active peptide doses referred to in the "Nonclinical Studies" section are 80.63±1.18% of the indicated dose in the text. The indicated doses were calculated based on total content (including active peptide, peptide impurities, acetic acid and water content).

[19]. In vitro and in vivo nonclinical studies have shown that, in addition to its activity as a mobilizer of WBCs, BL8040 exhibits a CXCR4-dependent preferential anti-tumor effect against malignant cells of hematopoietic origin [(17)].

Repeat dose toxicity studies in rats included two pivotal studies of 14 days (2, 6 and 15 mg/kg) and 28 days repeated doses (1, 3 and 6 mg/kg). Studies in dogs (5 and 7 days) were conducted at doses of up to 9 mg/kg, and an additional 28-day study was performed at doses of up to 3 mg/kg. The No Observed Adverse effect Level (NOAEL) in the 5 and 7 day repeat dose toxicity studies in dogs was set in the range of 2.7-3 mg/kg. The 28-day repeat dose toxicity study set the NOAEL at 1 mg/kg. The clinical symptoms observed in rats and dogs from the first day of dosing consisted of transient erythema and peripheral edema. In dogs, reactions similar in nature were noticed from a few minutes up to approximately 2 hours following SC injection. BL-8040 seemed to be better tolerated with repeated doses over time as the magnitude of the systemic reactions was less pronounced with time and not aggravated with increasing dose. There were no histopathological changes (except at the injection site) or significant changes in ECG, ophthalmological findings, clinical chemistry or hematology variables and no target organ for toxicity could be identified.

Safety pharmacology studies were conducted in rats (respiratory and neurobehavioral studies at 3, 9 and 27 mg/kg dose) and dogs (cardiovascular study at 0.3, 3 and 9 mg/kg dose). The NOAEL in both rat studies was determined to be 3 mg/kg for BL-8040 administered by the SC route. At higher doses, dose-dependent effects were described, including a respiratory stimulant effect, piloerection, decreased urination and decrease in body temperature. In dogs, the No Observed Effect Level (NOEL) was determined to be 0.3 mg/kg with higher doses inducing a dose-dependent hypotensive effect followed by a dose-dependent hypertensive effect. These effects were combined with a dose-dependent tachycardia, which correlated with the hypertensive effect. A shortening in PR and PQ intervals as well as QRS duration was found especially at the peak of tachycardia, suggesting that these electrocardiographic changes are likely a consequence of the tachycardic properties of BL-8040. The QT interval was also found to be shortened in a dose-dependent manner. Analysis of QTc interval changes using the probabilistic method or the QT deviation method suggests that the QT interval shortening was related to a decrease in ventricular repolarization duration rather than a consequence of tachycardic properties of BL-8040.

As indicated above, in contrast to the findings of the safety pharmacology study, the pivotal repeated dose toxicology studies performed on dogs reported no clear effect of BL-8040 on ECG parameters, including QT interval, blood pressure or pulse values examined 30 minutes and 24 hours after injection of BL-8040.

Metabolic stability was evaluated in liver microsomes from male rat, male dog and pooled human microsomes. BL-8040 did not show degradation over the incubation period in rat liver microsomes. Degradation was observed in dog micrososmes ($t_{1/2}$ = 5-7 hrs) and more rapidly in human microsomes ($t_{1/2}$ = 1.3 hrs). No difference was found between incubations of microsomes with and without NADPH, suggesting that this degradation is not NADPH dependent and not related to CYP or FMO enzyme families and therefore it is considered highly unlikely that BL-8040 will have drug interactions based on CYP-450 metabolism.

For additional information please refer to the Investigator's Brochure.

1.2.2 Clinical Studies[a]

A single phase IIa, non-randomized, open label, single dose, dose-escalation, safety study of BL-8040 (formerly BKT-140) in multiple myeloma (MM) subjects has been completed (study BKTSC001). Eighteen subjects received a 10-day mobilization regimen consisting of one-day (Day 0) treatment with cyclophosphamide (3-4 g/m^2) followed by daily evening administration of G-CSF (5 µg/kg) from Day 5 until the end of stem cell collection. On Day 10, a single SC injection of BL-8040 was administered at the following dose levels: 0.03, 0.1, 0.3 or 0.9 mg/kg (four subjects per dose group[b]).

Injection of BL-8040 was associated with a favorable safety profile, with no apparent trend toward risk with a specific dose. No clinically significant, consistent or cumulative abnormalities were observed for the safety parameters evaluated, including AE incidence, laboratory values, vital signs, ECG or physical examinations, as well as Karnofsky performance status. PK assessments were conducted pre-dose and 10 min[c], 30 min, 1, 2, 4, 8 and 24 hrs following study drug administration. BL-8040 was absorbed quickly and peak concentrations in the plasma were reached after 30 minutes, followed by a rapid decline.

Preliminary efficacy analysis indicated a dose-dependent effect of BL-8040 on WBC and CD34+ stem cell mobilization, potentially synergizing with chemo-mobilization with G-CSF, allowing for collection of optimal CD34+ cells in a single apheresis.

Based on the clinical experience to date, the following adverse events may be anticipated following administration of BL-8040: hot flushes, itching, injection site redness and swelling, chest pain, fever, shivering, allergic-like reaction, dyspnea and hypokalemia.

1.3 STUDY RATIONALE

AML is the most common type of leukemia in adults, yet continues to have the lowest survival rate of all leukemias. Despite progress in the understanding of leukemia pathophysiology, 20-40% of patients do not achieve remission with the standard induction chemotherapy and 50-70% of first complete remission patients are expected to relapse within 3 years. The prognosis following AML relapse remains uniformly poor [20; 21].

High dose cytarabine (Ara-C) based therapy has been the cornerstone of salvage chemotherapy for relapsed or refractory AML for many years. The complete response rate in this clinical setting is approximately 30% [21]. Addition of other cytotoxic agents such as mitoxantrone, mitoxantrone and etoposide (MEC) has produced increased toxicity without being confirmed to significantly improve complete response rates.

Emerging data have highlighted the importance of the BM niche for AML growth [22; 23; 24; 25]. The interaction of malignant blasts with the BM micro-environment, mediated through the chemokine receptor CXCR4 and various adhesion molecules including VLA-4 and CD44, is postulated to function as a "tumour survival factor," promoting tumour growth and protecting malignant cells from chemotherapy-induced apoptosis [24; 25; 26; 27; 28]. A recent clinical trial investigating AMD3100 (plerixafor) in combination with chemotherapy in patients with

[a] In the first clinical study, the indicated doses were calculated based on total content (including active peptide, peptide impurities, acetic acid and water content). For example, 0.9 mg/kg was equivalent to 0.73 mg/kg active peptide. In the current study, the doses represent the active peptide dose only.

[b] Two additional subjects received a fifth of the planned dose in the first cohort (0.006 mg/kg)

[c] PK and PD assessment 10 minutes post-dose was performed only for the last three subjects in the last dose group

relapsed AML, observed leukemic cell mobilization, resulting in an overall response rate higher than expected in patients with advanced AML [29].

In vitro studies demonstrated that BL-8040 binds and inhibits the CXCR4 chemokine receptor with high affinity. It was shown in vitro and in vivo to be a specific antagonist of CXCR4, and to have a slow dissociation rate from the receptor. In in-vivo animal studies, as well as in clinical study BKTSC001, BL-8040 demonstrated accelerated mobilization of adult WBCs (neutrophils, monocytes, lymphocytes) and normal stem-cells. In addition to its activity as a mobilizer of WBCs, BL-8040 exhibits a CXCR4-dependent selective cytotoxicity toward malignant cells of hematopoietic origin. BL-8040 significantly and preferentially stimulated apoptotic cell death of cells from AML patients [17].

The current study aims to demonstrate the safety and efficacy of escalating repeated doses of BL-8040 administered as monotherapy and concurrently with high-dose Ara-C in the treatment of relapsed/refractory AML adult subjects.

During the combined treatment period, BL-8040 will be administered 4 hrs before infusion of high-dose Ara-C. This is due to the fact that the peak mobilization effect observed in both nonclinical and clinical studies occurred at 4 hrs post-dose. It is therefore envisaged that peak concentrations of Ara-C will coincide with the peak mobilization of leukemic blasts into the peripheral blood. As BL-8040 has a short half-life (less than one hour), the potential for drug-drug interaction with Ara-C is low. Furthermore, in vitro metabolic studies have indicated that it is highly unlikely that BL-8040 will have drug interactions based on CYP-450 metabolism.

The starting dose of BL-8040 in this study was determined based on free base concentrations calculated from nonclinical studies and the completed Phase IIa clinical study (BKTSC001). Single dose administration of BL-8040 up to 0.9 mg/kg[a], added to a G-CSF chemo-mobilization regimen in MM subjects, appeared to be safe and well tolerated in the first clinical study with BL-8040 (BKTSC001). Animal studies did not show any organ toxicity at exposures exceeding those observed in the single dose human clinical trial BKTSC001 at the top dose of 0.9 mg/kg (13 fold in rats and 8 fold in dog based on AUC). The AUC in study BKTSC001 increased approximately proportionally with dose between 0.3 and 0.9 mg/kg (4.2 times), making it likely that the exposure (AUC) of patients in the starting dose cohort of 0.5 mg/kg[b] will be proportional to the exposures observed in the previous clinical study. $AUC_{0\text{-}24}$ measured in clinical study BKTSC001 for patients in the two highest dose cohorts (0.3 and 0.9 mg/kg) was 186 and 782 ng.hr/mL, respectively. Thus, it is expected that exposure (AUC) in the first dose cohort in study BL-8040.01 will be approximately 480 ng.hr/mL. The AUC value is not expected to increase with successive daily administrations of BL-8040 in the current study, as the BL-8040 half-life ($t_{1/2}$) was found to be short (less than one hour). Thus, the exposures reached in the toxicological studies are expected to exceed (21 fold in rats and 13 fold in dogs based on AUC) the predicted exposure of patients to the study drug at the starting dose of 0.5 mg/kg in study BL-8040.01.

[a] In the first clinical study, the indicated doses were calculated based on total content (including active peptide, peptide impurities, acetic acid and water content). For example, 0.9 mg/kg was equivalent to 0.73 mg/kg active peptide. In the current study, the doses represent the active peptide dose only.

[b] Dose calculation terminology has changed between study BKTSC001 and study BL-8040.01, such that 0.5 mg/kg in BL-8040.01 is equivalent to 0.6 mg/kg in study BKTSC001 and 0.75 mg/kg in BL-8040.01 is equivalent to 0.9 mg/kg in BKTSC001.

2 STUDY OBJECTIVES AND ENDPOINTS

2.1 STUDY OBJECTIVES

Primary

- To assess the safety and tolerability of escalating repeated doses of BL-8040 administered as monotherapy for two days, followed by five days of combined administration with high-dose Ara-C in AML adult subjects with relapsed or refractory disease.

Secondary

- To assess the clinical efficacy (response rates) of escalating repeated doses of BL-8040 administered as monotherapy for two days, followed by five days of combined administration with high-dose Ara-C in AML adult subjects
- To assess the apoptotic effect of BL-8040 on leukemic blasts when administered as monotherapy
- To assess the effect of BL-8040 on mobilization of AML blasts to peripheral blood (PB) when administered as monotherapy
- To assess the single and multiple dose pharmacokinetic profile of BL-8040.

Exploratory

- To assess additional pharmacodynamic parameters relevant to CXCR4 inhibition.

2.2 STUDY ENDPOINTS/OUTCOMES

2.2.1 Safety Outcomes

Safety and tolerability will be the primary endpoints of this study and will be evaluated on the basis of the following parameters:

- General safety: vital signs (oral temperature, blood pressure, pulse rate, respiratory rate and O_2 saturation), 12-lead ECG and physical examination.
- Toxicity according to the latest version of NCI CTCAE (currently V4.03, refer to Table 2) for AEs and clinical laboratory profile as follows:
  - Screening: record and report screening results, however not considered treatment emergent AEs.
  - Throughout the study: record and report all AEs and SAEs according to GCP.

2.2.2 Efficacy Endpoints

Efficacy endpoints will be secondary endpoints for this study. The following secondary endpoints will be assessed:

- Response rates as assessed at final BM evaluation based on Cheson 2003 criteria [4] (Appendix C):
  - Complete response (CR)
  - Complete response with incomplete hematological recovery of platelets or neutrophils (CRi)
  - Partial response (PR)
  - Overall response defined as the sum of CR, CRi and PR.
  - Complete Response composite (CRc) defined as the sum of CR and CRi.

- Change in leukemic cell apoptosis in PB and BM.
- Kinetics of mobilization of leukemic blasts from BM to PB.
- Overall survival (OS) during the long-term follow-up defined as time from enrollment to death from any cause.

2.2.3 Pharmacokinetic Endpoint

- PK analysis of multiple injections of BL-8040.
- For PK analyses, blood samples will be collected on Days 1, 3 and 7 at pre-dose, 0.25, 0.5, 1, 2, 4, 8 and 24 hrs post BL-8040 administration. Additional samples will be collected on Day 5 at pre-dose and 0.5 hr post BL-8040 administration.
- Non-compartmental PK parameters for BL-8040 (see below) will be derived from the individual concentration obtained at each of the PK time-points. Additional PK parameters may be derived if considered necessary:
    - C_{max} - maximum BL-8040 plasma concentration
    - T_{max} - time to reach the maximum BL-8040 plasma concentration
    - AUC_{0-t} - Area under the BL-8040 plasma concentration-time curve from time of administration up to the last time point with a measurable concentration post dosing, calculated by linear up-logarithmic down trapezoidal summation
    - $AUC_{0-\infty}$ - Area under the BL-8040 plasma concentration-time curve extrapolated to infinity, calculated as: $AUC_{0-\infty} = AUC_{0-t} + C_{last}/\lambda_z$, where C_{last} is the last measurable concentration
    - λ_z - elimination rate constant, determined by linear regression of the terminal points of the ln-linear plasma concentration-time curve
    - $t_{1/2}$ - terminal elimination half-life, defined as $0.693/\lambda_z$

2.2.4 Exploratory Endpoints

- CXCR4 receptor occupancy
- Additional pharmacodynamic endpoints relevant to CXCR4 inhibition
- Anti-BL-8040 antibody titers

3 STUDY DESIGN

This will be an open-label, multicenter, phase IIa, dose escalating study in subjects with relapsed/refractory AML, defined according to WHO criteria [(1)] (Appendix B) including subjects who failed chemotherapy only and those who failed previous Autologous Stem Cell Transplantation (ASCT)/ Allogeneic Stem Cell Transplantation (AlloSCT), provided at least 6 months have passed from transplant.

Eligible subjects will receive SC injections of BL-8040 alone ("monotherapy period") over two days (one dose per day that may be administered into one or more injection sites at the discretion of the Investigator) followed by concurrent administration of BL-8040 with standard salvage chemotherapy ("combined period") over 5 days. During the "combined period," BL-8040 will be administered 4 hours prior to chemotherapy. The chemotherapy

will consist of cytarabine (Ara-C) 1.5 or 3 g/m^2/d per dose (based on age), administered IV over 3 hours, for 5 days[a] and will not be escalated.

The first part of the study (Part 1) will include escalating dose groups and be considered the **'escalation phase'**. Six potential dose levels (see Table 1) will be investigated starting at dose level 1. Patients will be accrued in a conventional 3+3 design. Applying this study design, the first cohort of 3 patients will be treated at dose level 1 and evaluated for dose escalation.

If at dose level 1 and beyond, 0 out of 3 patients experience DLT, then the next cohort of 3 patients will be treated at the next dose level. If 1 out of 3 patients develop DLT, an additional 3 patients will be treated at the same dose level. If no more DLT develops at that dose, i.e. 1 out of a total of 6 patients develops DLT, the dose escalation continues to the next dose level. At any given dose, if greater than 1 out of 3 patients or 1 out of 6 patients experience DLT, the dose level exceeds the MTD. In this situation, 3 more patients will be treated at the next lower dose if there are less than 6 patients already treated at that dose. MTD is defined as the highest dose level in which 6 patients have been treated with less than 2 instances of DLT.

The decision to proceed to the next higher dose level will be made by an independent DMC[b] after review of relevant safety data collected up to and including Day 30 (± 2 days; Day 28 ± 2 of chemotherapy) of the last subject of the previous dose group. The DMC may recommend evaluation of intermediate doses (or doses lower than the starting dose of 0.5 mg/kg) of BL-8040 in combination with Ara-C. The decision process for dose escalation is outlined in Figure 1.

Dose escalation will be permitted until the MTD is established and protocol specific stopping rules for toxicity are met. If no MTD is reached, dose escalation will continue up to dose level 6 (2.0 mg/kg). It is anticipated that up to 36 eligible patients will be required for the dose escalation.

At the discretion of the Sponsor, additional subjects may be enrolled into a selected dose group to confirm safety, efficacy and pharmacokinetic (PK) profile for the selected dose, bringing the study up to approximately 70 subjects in total. This portion of the study will be considered the **'expansion phase'** (Part 2). The DMC, in consultation with the Sponsor and Investigators, will decide on the selected dose level for expansion based on safety data, MTD, other relevant toxicity considerations, and all available PK and correlative PD data.

During Part 2 of the study, at the Investigator's discretion and after discussion with the Sponsor, subjects may be treated with a second cycle of BL-8040 in combination with Ara-C if they are considered to have had clinical benefit during the first treatment cycle, but failed to achieve CR or CRi. In the event that subjects receive a second treatment cycle, the dosing regimen will be identical to that in the first treatment cycle. The second treatment cycle will start after clinical response assessment has been completed for the first treatment cycle, i.e., no sooner than Day 30 (± 2 days; Day 28 ± 2 of chemotherapy).

[a] Subjects ≤ 60 years will receive Ara-C **3** g/m^2/d, and those > 60 years will receive Ara-C **1.5** g/m^2/d: each dose over 3 hours, for 5 consecutive days.

[b] Data Monitoring Committee will be comprised of 3 members appointed by the Sponsor including at least one clinician, and persons knowledgeable of the investigational drug.

During Part 2 of the study, any DLT occurring at a frequency of > 30% will stop accrual. In this situation, the DMC, in consultation with the Sponsor and Investigators, may recommend a lower dose level for the expanded cohort.

The study will comprise a screening period, a treatment period (monotherapy and combined treatment) and a follow-up period. For each dose group, visit scheduling and assessments will be similar (see Section 5 and Appendix A).

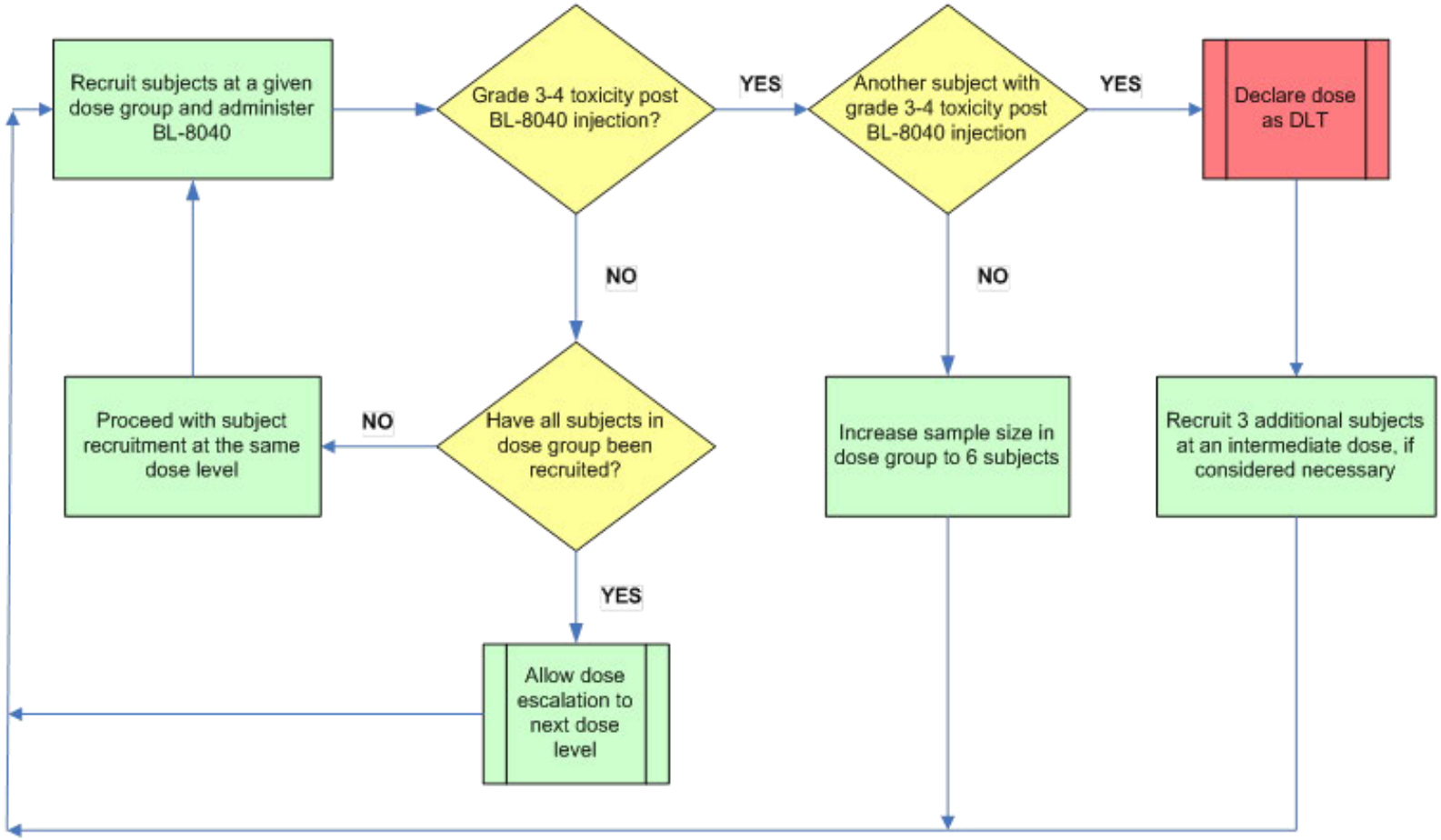

Figure 1 BL-8040 Dose escalation decision tree

4 STUDY POPULATION

This study will be conducted in subjects aged 18 to 75 years diagnosed with relapsed/refractory AML. The exact number of subjects enrolled will depend on the toxicity observed in each dose group and the number of dose groups required to reach MTD.

4.1 INCLUSION CRITERIA

1. Adult men and women subjects aged 18 to 75, inclusive.
2. Confirmed diagnosis of relapsed/refractory AML (WHO criteria [1]; Appendix B).
   - Refractory subjects after up to 2 cycles of induction therapy[a] or first complete response (CR1) duration ≤ 90 days.
   - Relapse occurring > 90 days and ≤ 24 months since CR1[b].
3. AML relapse > 6 months since autologous or allogeneic stem cell transplantation, provided they are in first relapse and:
   - No active graft-versus-host disease (GVHD > grade 1).
   - No treatment with high dose steroids for GVHD (up to 20 mg Prednisolone or equivalent, Appendix G).
   - No treatment with immunosuppressive drugs with the exception of low dose cyclosporine and tacrolimus (blood levels of 0.5-0.6 µg/mL).
4. Clinical laboratory values should be as follows:
   - WBC < 30,000/µL
   - Blasts in PB < 20,000. Treatment with Hydroxyurea is permitted up to 24 hrs prior to BL-8040 administration to achieve blast counts < 20,000 prior to enrollment.
   - Creatinine < 1.3 mg/dL; if Creatinine is > 1 mg/dL the Creatinine clearance should be > 40 mL/min as calculated using the Cockcroft-Gault formula.
5. Women of childbearing potential and all men must agree to use an approved form of contraception (e.g. oral, transdermal patch, implanted contraceptives, intrauterine device, diaphragm, condom, abstinence or surgical sterility) prior to study entry and for the duration of study participation through 30 days after the last dose of BL-8040. Confirmation that female subjects are not pregnant must be established by a negative serum β-human chorionic gonadotropin (β-hCG) pregnancy test result obtained during screening. Pregnancy testing is not required for post-menopausal or surgically sterilized women.
6. Subject is able and willing to comply with the requirements of the protocol.
7. Subject is able to voluntarily provide written informed consent.

[a] Subjects who have failed to respond to up to 2 prior induction treatment regimens will be considered eligible,. Prior induction therapy must include at least 1 cycle of an anthracycline (e.g., at least 45 mg/m^2/dose daunorubicin or at least 9 mg/m^2/dose idarubicin) or anthracenedione (e.g., at least 10 mg/m^2/dose mitoxantrone) and cytarabine-based regimen.

[b] Relapsed subjects must have achieved a CR or CRi lasting > 90 days, resulting from no more than 2 cycles of induction cytotoxic chemotherapy including at least 1 cycle of an anthracycline (e.g., at least 45 mg/m^2/dose daunorubicin or at least 9 mg/m^2/dose idarubicin) or anthracenedione (e.g., at least 10 mg/m^2/dose mitoxantrone) and cytarabine-based regimen. An unlimited number of consolidation cycles following CR1 are allowed..

4.2 EXCLUSION CRITERIA

1. Administration of conventional chemotherapy within 2 weeks of enrollment date. In the event that subjects have received chemotherapy > 2 weeks from the date of enrollment, they may be included provided they have recovered from the associated non-hematological toxicities to ≤ grade 1.
2. Life expectancy of ≤ 2 months.
3. Known allergy or hypersensitivity to any of the test compounds, materials or contraindication to test product.
4. Use of investigational device or agents within 2 weeks of enrollment date.
5. Low Performance Status (ECOG[a] > 2; Appendix E).
6. O_2 saturation < 92% (on room air), evidence of TLS > grade 2 (according to the Cairo-Bishop criteria [3]; Appendix D) or leukostasis [2].
7. Abnormal liver function tests:
   - Serum aspartate transaminase (AST/SGOT) or alanine transaminase (ALT/SGPT) 2 x upper limit of normal (ULN).
   - Serum bilirubin. Total bilirubin > 2.0 mg/dL (34 µmol/L), conjugated bilirubin > 0.8 mg/dL.
8. Left ventricular ejection fraction < 40 %.
9. History of myocardial infarction or cerebrovascular accident within 6 months of enrollment date.
10. Presence of active, uncontrolled infection.
11. Known central nervous system disease (e.g., Alzheimer's disease).
12. Acute promyelocytic leukemia.
13. Exposure to high dose Ara-C within 6 months of enrollment.
14. Subject has concurrent, uncontrolled medical condition, laboratory abnormality, or psychiatric illness which could place him/her at unacceptable risk, including, but not limited to:
    - Subject has been diagnosed or treated for another malignancy within 3 years of enrolment, except in situ malignancy, or low-risk prostate, skin or cervix cancer after curative therapy
    - A co-morbid condition which, in the view of the Investigators, renders the subject at high risk from treatment complications.
15. Female subjects who are pregnant or breastfeeding.
16. Prior clinically significant grade 3-4 non-hematological toxicity to high dose Ara-C or grade ≥ 2 of neurological toxicity.
17. Seropositive for HIV antibodies (HIV1 and HIV2), Hepatitis C antibody (Hep C Ab) or a Hepatitis B carrier (positive for Hepatitis B surface antigen [HBsAg]).
18. Unable to comply with study requirements in the opinion of the investigator.
19. Extramedullary AML involvement (including CNS involvement).

[a] ECOG = Eastern Cooperative Oncology Group

4.3 SUBJECT IDENTIFICATION

At screening, all subjects who signed informed consent will be identified by a subject number, initials and birth date; subject number will be used throughout the study.

4.4 SCREENING FAILURES

Subjects who fail to meet the entrance criteria at any stage during the screening period are defined as screen failures. All screen failures will be documented on the screening log, which documents the subject number, subject's initials, birth date and reason(s) for screen failure. The screening log will be kept in the Investigator's Site File.

Screen failure subjects will be withdrawn from the study and receive standard of care performed at the site.

4.5 REMOVAL, REPLACEMENT, OR EARLY WITHDRAWAL OF SUBJECTS FROM THERAPY OR ASSESSMENT

Subjects are free to discontinue their participation in the study at any time and without prejudice to further treatment. The Investigator must withdraw any subject from the study if that subject requests to be withdrawn, or if it is determined that continuing in the study would result in a significant safety risk to the subject.

Subjects withdrawn from the study prior to baseline visit or prior to first BL-8040 injection will be replaced by the Investigator to achieve the appropriate number of subjects per dose group, regardless of the reason for withdrawal.

The subject's participation in this study may be discontinued due to the following reasons:

- Request of regulatory agency or Sponsor or primary care physician or Investigator
- Withdrawal of consent by subject
- Any subject who develops intolerance to treatment.
- Female subject who becomes pregnant.
- Any subject who requires concomitant medication which could confound evaluation of the study drug.
- Subject is unwilling or unable to continue the study or is lost to follow-up
- Subject is non-compliant with study procedures / study protocol
- Investigator decides that withdrawal from the study is in the best interest of the subject
- Subject meets one of the stopping rules criteria during the study (see Section 6.2.3).

4.6 HANDLING OF WITHDRAWALS

If a subject is withdrawn from the study, either at his or her request or at the Investigator's discretion or if requested by the Sponsor, primary care physician or regulatory agency, or fails to return, every effort should be made to determine the reason. This information will be recorded on the subject's case report form (CRF). All subjects who withdraw from the study prematurely, regardless of cause, should undergo all Early Discontinuation Study Visit (see Section 5.4). It is vital to obtain follow-up data for any subject withdrawn because of an AE or abnormal laboratory test finding. In any case, every effort must be made to undertake safety follow-up procedures.

Premature withdrawal may occur for any of the following reasons:

1. Death
2. Disease progression/relapse
3. Pregnancy
4. AE
5. Subject request
6. Investigator request
7. Sponsor request
8. Other party's request

If withdrawal is caused by an AE that the Investigator considers may be related to the study drug, it will be reported to the Internal Safety Committee, institutional review board/independent ethics committee (IRB/IEC) and Sponsor.

Any serious AE (SAE) must be reported to the Sponsor or Sponsor's designee by telephone or fax within 24 hours of becoming aware of the event and to the IRB/IEC according to local regulations (for SAE notification procedures, refer to Section 7.5).

In the event of any AEs considered to be clinically significant by the investigator, subjects will be followed up with appropriate medical management until the outcome is determined or stabilized, according to the Investigator's clinical judgment. All follow-up information will be recorded in the subject's CRF until resolution of the AE. Subsequent follow-up will be documented in the subject's personal file.

4.7 SPONSOR'S TERMINATION OF STUDY

The Sponsor reserves the right to discontinue the study at any time at the participating centers for any reason.

Regulatory Authorities also have the right to terminate the study for any reason.

5 STUDY PROCEDURES AND ASSESSMENTS

Schedule of events for this study are shown in Appendix A. No protocol related procedures should be performed before subjects provide written informed consent. Study related events and activities including specific instructions, procedures, concomitant medications, dispensing of study medication, and descriptions of AEs should be recorded in the appropriate source documents and CRF.

5.1 SCREENING PERIOD (VISIT 1, DAY -7 TO DAY 0)

At Visit 1, the purpose and procedures of the study will be fully explained to participants. Those wishing to enroll in the study will sign a written informed consent prior to initiating any evaluations or study-related procedures. Following signing of informed consent, adult male and female subjects aged ≥18 years will be screened for study eligibility by assessment of inclusion and exclusion criteria.

The following assessments should be done at screening visit 1:

- Confirmation of relapsed/refractory AML within 2 weeks prior to screening based on BM biopsy or aspiration or PB results.
- Collection of demographic data and medical history.
- Physical examination (including height and weight measurements and assessment of cerebellar function).

- Vital signs (blood pressure, pulse rate, oral temperature, O_2 saturation levels and respiration rate).
- ECOG performance status (Appendix E).
- 12-lead electrocardiogram (ECG).
- Echocardiogram (ECHO)/Multiple Gated Acquisition (MUGA).
- Chest X-ray.
- Safety laboratory assessments including hematology, biochemistry, coagulation (PT and aPTT) and serum pregnancy test (for women of child bearing potential).
- HIV, HCV and HBV serology.
- Clinical evaluation of leukostasis [(2)] related symptoms (visual symptoms, shortness of breath and decreased oxygen saturation in blood measured by pulse oximetry) and TLS (according to Cairo–Bishop criteria [(3)]; Appendix D).
- BM biopsy and aspirate will be conducted within 7 days prior to commencement of the treatment for baseline assessment of leukemic cell numbers and apoptosis by caspase-3 staining. CXCR4 levels and other relevant parameters will be measured in BM by IHC and/or other techniques and will be analyzed for correlation to efficacy. In subjects who receive cytoreductive therapy, BM samples will be collected post therapy and prior to BL8040 administration.

If any of the assessments listed above were performed within 3 weeks prior to the screening visit, a repeat assessment will not be required at screening and the data will be acceptable for study purposes.

5.2 TREATMENT PERIOD (VISITS 2-8 AND 10-16, DAY 1 TO DAY 7)[a]

Treatment period is comprised of BL-8040 monotherapy (2 days) followed by combined therapy period (5 days) as follows:

Monotherapy period – On Day 1 (Baseline, enrollment day) and Day 2, eligible subjects will receive BL-8040 monotherapy administered by SC injection(s), once daily in the morning. Subjects considered suitable for a second treatment cycle during the expansion phase will receive BL-8040 monotherapy on Days 1 and 2 of the additional cycle as described above.

Combined therapy period – On Days 3-7, subjects will be treated once daily in the morning with BL-8040 SC injection(s) followed by chemotherapy 4 (± 0.5) hours later. The chemotherapy will consist of Ara-C 1.5 or 3 g/m^2 administered IV over 3 hours (**3** g/m^2/d for subjects ≤ 60 years, **1.5** g/m^2/d for subjects > 60 years).

Subjects considered suitable for a second treatment cycle during the expansion phase will receive BL-8040 in combination with Ara-C on Days 3-7 of the additional cycle as described above.

The following assessments will be conducted at the treatment visits:

- Laboratory safety evaluations[b]:

[a] Treatment Period refers to Visits 2-8 and also Visits 10-16 for expansion phase subjects who receive a second treatment cycle...

[b] Subjects considered suitable for a second treatment cycle during the expansion phase will undergo the same laboratory safety evaluations during the second cycle with the exception of coagulation and partial biochemistry.

  - Hematology (CBC) and biochemistry samples will be collected daily on Days 1-7 prior to administration of BL-8040.
  - Coagulation (PT and aPTT) will be evaluated on Day 1 pre-dose and 24 hrs post-dose, and on Day 7 at 24 hrs post-dose.
  - WBC counts, including differential and leukemic cell count, will be measured on Days 1, 2, 3 and 7 at 4 and 8 hrs post BL-8040 injection.
  - Partial biochemistry samples (electrolytes and kidney function) will be collected on Days 1, 2, 3 and 7 at 4 and 8 hrs post BL-8040 injection.
  - Additional hematology, biochemistry and coagulation samples may be collected at the discretion of the Investigator or upon Sponsor's request.
- Anti-drug antibody (ADA) and complement activation:
  - Blood samples for assessment of ADA and complement activation will be collected pre-dose and at 4 hrs post BL-8040 administration on Days 1 and 7. On Day 3 an ADA sample will be collected pre-dose only.
- PK sampling[a]:
  - Blood samples for BL-8040 PK analysis will be collected on Days 1, 3 and 7 at pre-dose, 0.25, 0.5, 1, 2, 4, 8 and 24 hrs post BL-8040 administration.
  - Samples will also be collected on Day 5 at pre-dose and 0.5 hr post BL-8040 administration.
  - PK sampling may be discontinued during the expansion phase at the discretion of the Sponsor. The Sponsor will notify sites when PK sample collection can be halted.
- 12-lead ECGs:
  - 12-lead ECGs will be recorded on Days 1, 3 and 7 at pre-dose, 0.5, 1, 2, 4, 8 and 24 hrs post BL-8040 administration.
  - For subjects receiving a second treatment cycle during the expansion phase, ECGs will only be recorded on Days 1 and 7 of the second cycle at pre-dose and 4 hrs post BL-8040 administration.
  - Additional ECGs may be recorded at the discretion of the Investigator or upon Sponsor's request.
- BM biopsy and/or aspirate[b]:
  - Bone marrow biopsy and/or aspiration will be performed on Day 3 (prior to BL-8040 injection) for quantitative assessment of leukemic blast number and apoptosis of leukemic cells in the BM[c] using caspase-3 staining.
- FACS analysis[d]:
  - Leukemic blasts in peripheral blood (PB) will be assessed by analysis of surface markers on Days 1 and 3 at pre-dose, 4[e] and 24 hrs post BL-8040

[a] PK sampling will only be performed during the first treatment cycle for subjects in the expansion phase.

[b] Day 3 BM sampling will only be performed during the first treatment cycle for subjects in the expansion phase.

[c] Subjects who do not undergo BM evaluation on Day 3 will still be included in the safety and efficacy evaluation.

[d] FACS analysis will only be performed during the first treatment cycle for subjects in the expansion phase.

[e] 4 hr post-dose samples on Day 3 to be taken prior to administration of Ara-C.

injection. Additional signaling pathway proteins may be assessed at the discretion of the Sponsor.

- Leukemic cell apoptosis in PB will be assessed by Annexin V and Propidium iodide (PI) analysis on Days 1 and 3 at pre-dose, 4[a] and 24 hrs post BL-8040 injection.
- CXCR4 occupancy will be measured in the PB of dose escalation phase subjects, using the CXCR4 antibodies 12G5 and 1D9, on Days 1 and 3 at pre-dose, 4[a] and 24 hrs post BL-8040 injection.

- FISH analysis[b]:
  - In the expansion phase of the study, subjects with identifiable chromosomal abnormalities at baseline will be assessed by FISH in PB and/or BM aspirate collected on Days 1 and 3 at pre-dose, 4[a] and 24 hrs post BL-8040 injection.
- Clinical evaluations:
  - Vital signs, physical examination, including assessment of cerebellar function and recording of adverse events (AEs) and concomitant medications will be performed daily on Days 1-7 prior to administration of BL-8040. For expansion phase subjects receiving a second treatment cycle, the same assessments will be performed daily on Days 1-7 prior to administration of BL-8040.
  - Clinical evaluation of leukostasis [(2)] related symptoms (visual symptoms, shortness of breath and decreased oxygen saturation in blood measured by pulse oximetry) and TLS (according to Cairo–Bishop criteria [(3)]; Appendix D) will be assessed on Day 1 and upon commencement of such symptoms or when WBC ≥ 30,000/µL.

5.3 FOLLOW-UP PERIOD (VISITS 9 AND 17)[c]

The follow-up period will start after completion of Ara-C chemotherapy and continue for up to 6 weeks after initiation of salvage chemotherapy with Ara-C, i.e., up to Day 44. Expansion phase subjects who receive a second treatment cycle will also be followed for up to 6 weeks after initiation of Ara-C during the second cycle, i.e., up to Day 44 of the second cycle.

Bone marrow biopsy and aspiration will be performed on Day 30 (± 2 days; 28 ± 2 days from initiation of salvage chemotherapy) unless, in the opinion of the Investigator, earlier biopsy/aspiration is indicated based on early appearance of blast cells in PB. The follow-up period will end when a BM biopsy and/or aspirate, performed between Day 20 – 44, provides definite assessment of response to therapy. Bone marrow aspirate collected during this time frame will be examined by FACS analysis for final assessment of leukemic cell numbers.

In subjects who do not show sufficient BM recovery by Day 30 (in the absence of leukemic cells), BM biopsy and aspiration will be repeated 2 weeks later (Day 44) to exclude aplasia. Additional bone marrow aspirations may be performed at the Investigator's discretion to assess response.

The following assessments will also be performed during the follow-up period:

[a] 4 hr post-dose samples on Day 3 to be taken prior to administration of Ara-C.

[b] FISH analysis will only be performed during the first treatment cycle for patients in the expansion phase.

[c] Follow-up period refers to Visit 9 and Visit 17 for expansion phase subjects who receive a second treatment cycle.

- Haematology and biochemistry tests will be performed at least twice a week for the duration of the follow-up period
- Time to recovery of WBC and platelets
- Recording AEs and concomitant medications.
- Collection of an ADA sample at the end of the follow-up period.

For expansion phase subjects receiving a second treatment cycle, bone marrow biopsy/aspiration and follow-up assessments following the second treatment cycle will be performed as described above. However, ADA sample collection will only take place at the end of the follow-up period following the first treatment cycle.

5.4 LONG-TERM FOLLOW-UP

Subjects participating in the expansion phase will be followed for up to 5 years after completion of the Follow-up period. Sites will contact subjects by telephone at approximately 3 month intervals (± 1 month) after the end of the Follow-up period to determine AML status and survival.

5.5 EARLY DISCONTINUATION STUDY VISIT

An early discontinuation study visit will be performed for subjects who withdraw from the study for the reasons specified in Section 4.5.

All reasons for treatment discontinuation will be documented in the source documents as well as in the CRF. Only one reason (the most severe) for early discontinuation should be recorded in the CRF. If one of the reasons for discontinuation is an AE, this should be chosen as the reason. Every effort should be made to follow-up these subjects for resolution of the AE.

At this visit the activities relating to the study period at which time the subject discontinued will be performed. For example, if the subject discontinues during the Treatment period, the visit activities will be similar to those described in Section 5.2. Activities may include (but not be limited to): AE assessment, concomitant medications, laboratory safety tests, vital signs and physical examination by the Investigator.

This visit may be performed on the same day as an originally scheduled visit or could be conducted separately. Data collection at these visits should primarily be guided according to principles to protect subject safety and wellbeing.

5.6 UNSCHEDULED VISIT

An unscheduled visit may be performed at any time during the study at the subject's request or as deemed necessary by the Investigator. The date and reason for the unscheduled visit will be recorded. AE monitoring and concomitant medication recording will be performed by the Investigator. Other procedures and evaluations will be completed as deemed necessary by the Investigator and may include (but not be limited to) laboratory safety tests, vital signs and physical examination.

5.7 SAFETY ASSESSMENTS

Safety assessments will be based on changes from baseline of clinical signs and symptoms reported by the subject or observed by the Investigator, including AEs, concomitant medication use, treatment compliance, tolerability (e.g. dropouts due to AEs), vital signs, ECGs, physical examination, laboratory safety assessments and clinical evaluation of leukostasis and TLS.

5.7.1 Adverse Events (AEs)

Adverse Events will be assessed at all study visits throughout the study.

Any new systemic AE that occurs between scheduled assessment visits should be brought to the attention of the Investigator and recorded in the subject's medical file and on the appropriate CRF page.

AEs will be reported and graded in accordance with the latest NCI-CTCAE version (currently version 4.03) and coded by Data Management using the latest version of MedDRA (currently version 14.0) (see Section 7.1 for more details).

5.7.2 Concomitant Medications

Concomitant medication use will be recorded from Baseline (Visit 2) through all study visits.

5.7.3 Vital Signs

Vital signs will be measured at Screening (Visit 1) and daily during the Treatment Period (Visits 2-8 and 10-16 for expansion phase subjects who receive a second treatment cycle).

Vital signs will include blood pressure, pulse rate, oral temperature, oxygen saturation and respiration rate after at least 5 minutes rest as per standard practice at the investigational site. Significant findings noticed after the start of study drug which meet the definition of an AE must be recorded on the AE CRF module.

5.7.4 Electrocardiogram

ECG will be performed at Screening (Visit 1) and during the Treatment Period on Days 1, 3 and 7 (Visits 2, 4 and 8). ECG printed recording will be collected at pre-dose, 0.5, 1, 2, 4, 8 and 24 hrs post BL-8040 administration. For subjects receiving a second treatment cycle during the expansion phase, ECGs will be recorded on Days 1 and 7 (Visits 10 and 16) of the second cycle at pre-dose and 4 hrs post BL-8040 administration; additional ECGs post BL-8040 will be performed at the discretion of the Investigator or upon Sponsor's request. The subject should rest for at least 10 minutes before measurement is taken.

ECG printouts will be evaluated by the Investigator or designee, signed and dated and filed in the source documentation file. When potentially clinically significant findings are detected by the Investigator or designee, a cardiologist should be consulted for a definitive interpretation and appropriate treatment, if required. All communications and diagnoses should be filed in the source documentation file. The Investigator/Investigator's designee/local cardiologist is responsible for determining whether the ECG findings are of clinical significance. All abnormalities will be closely monitored until stabilized or resolved.

5.7.5 Physical Examination

Physical examination will be conducted at Screening (Visit 1), and during the Treatment Period (Visits 2-8 and 10-16 for expansion phase subjects who receive a second treatment cycle). Height will be recorded only at Visit 1 (screening).

Physical examination will include weight measurements, assessment of head, lungs, cardiovascular system, abdomen, musculoskeletal system, skin, lymph nodes, neurological system and, where appropriate, other body systems as indicated in the study schedule. Neurological assessment must include examination of cerebellar function.

Information about the physical examination must be present in the source documentation at the study site. Significant findings that are present prior to the start of study drug must be

included in the Relevant Medical History/ Current Medical Conditions CRF. Significant findings made after the start of study drug which meet the definition of an AE must be recorded on the AE CRF module.

5.7.6 Laboratory Safety Assessments

All clinical laboratory safety assessments, listed below, will be performed by local laboratories at the participating sites at Screening (Visit 1), daily during the Treatment Period (Visits 2-8 and 10-16 for expansion phase subjects who receive a second treatment cycle) and at least twice weekly during the follow-up period (Visit 9 and Visit 17 for expansion phase subjects who receive a second treatment cycle).

Laboratory safety sampling will include the parameters listed below. The exact time-points for each one of the tests are specified in Appendix A.

Evaluations	Parameters
Hematology	Red blood cell count, hemoglobin (HGB), hematocrit (HCT), mean cell hemoglobin (MCH), mean cell hemoglobin concentration (MCHC), mean corpuscular volume (MCV), white blood cell (WBC) count and differential (including number of blasts, neutrophils and lymphocytes) and platelet count.
Biochemistry	Electrolytes: sodium, potassium, magnesium, calcium and phosphorus Liver function tests: AST, ALT, ALP, total bilirubin, albumin Kidney function tests: creatinine, BUN Other: glucose, uric acid
Coagulation	Pro-thrombin time (PT)/INR and activated partial thromboplastin time (aPTT)
Serology[a]	HIV antibodies (HIV1 and HIV2), Hepatitis B surface antigen (HBsAg) and Hepatitis C antibody (Hep C Ab).
Other[a]	Pregnancy test - a serum β-HCG pregnancy test for women of childbearing potential

A serum pregnancy test, if applicable, will be collected at screening. The serum pregnancy test will be performed at the local laboratory.

Laboratory safety test abnormalities, which arise after study drug administration, will be repeated as clinically indicated until the values return to normal or until the etiology has been determined and the condition considered stable. Abnormal laboratory test results that are considered to be clinically important by the Investigator will be reported as an AE in the AE CRF module. A laboratory abnormality will not be considered an AE unless:

- Intervention is required
- Changes in dose are required (decrease, discontinued, interrupted)
- Other treatment/therapy is required
- Associated with other diagnoses

Laboratory results will be reported to the Investigator or designee who will review, sign and date abnormal laboratory findings for clinical significance. The Investigator will note any laboratory test results of clinical concern or values that were outside normal ranges and

[a] To be collected at screening only.

provide details of the relationship to investigational product and the action taken. If a change in a laboratory value represents a medical condition, the medical condition will be listed in the AE record. If no correlation is possible, the direction of change (increase or decrease) in addition to the actual value will be recorded.

5.7.7 Anti-drug antibody (ADA) assessment

Blood sampling for assessment of ADA formation and complement activation will be performed pre-dose and at 4 hrs post BL-8040 administration on Days 1 and 7 and at the end of the follow-up period. On Day 3 an ADA sample will be collected pre-dose only (Visits 2, 4, 8 and 9)[a].

5.7.8 Leukostasis and Tumor Lysis Syndrome (TLS)

Clinical evaluation of leukostasis and TLS will be performed at Screening (Visit 1), baseline (Day 1, Visit 2 and Visit 10 for expansion phase subjects who receive a second treatment cycle) and during the Treatment Period upon commencement of symptoms or when WBC ≥ 30,000/µL.

Leukostasis [(2)] related symptoms include visual symptoms, shortness of breath and decreased oxygen saturation in blood measured by pulse oximetry.

TLS will be evaluated using the Cairo-Bishop criteria [(3)] (Appendix D).

5.8 EFFICACY ASSESSMENTS

5.8.1 Response rate

Response rate will be evaluated at the final BM evaluation[b] based on Cheson 2003 criteria [(4)] (Appendix C):

- Complete response (CR)
- Complete response with incomplete hematological recovery of platelets or neutrophils (CRi)
- Partial response (PR)
- Overall response defined as the sum of CR, CRi and PR.
- Complete response composite (CRc) defined as the sum of CR and CRi.

5.8.2 Leukemic cells apoptosis in PB

Assessment of leukemic cell apoptosis in PB will be performed on Days 1 and 3 (Visits 2 and 4) at pre-dose, 4[c] and 24 hrs post BL-8040 injection. Apoptosis will be assessed by immunocytochemistry and flow cytometry, using Annexin V and propidium iodide (PI) apoptosis detection kits according to the manufacturer's instructions.

5.8.3 Leukemic cells apoptosis in BM

Assessment of leukemic cell apoptosis in BM will be conducted within 7 days prior to commencing study treatment (Visit 1) and on Day 3 (pre-dose; Visit 4). Quantitative

[a] Expansion phase subjects who receive a second treatment cycle will have ADA and complement activation samples collected during the first treatment cycle only.

[b] Expansion phase subjects who receive a second treatment cycle will have BM evaluation performed at the end of both treatment cycles. The second BM evaluation will be used to define the subject's clinical response.

[c] 4 hr post-dose samples on Day 3 to be taken prior to administration of Ara-C.

assessment of apoptotic cells in BM biopsies and aspirates will be conducted using caspase-3 staining.

5.8.4 Leukemic blast counts in PB

Leukemic blast count in PB will be assessed by FACS analysis of surface markers on Days 1 and 3 (Visits 2 and 4) at pre-dose, 4[a] and 24 hrs post BL-8040 injection. Additional signalling pathway proteins may be assessed at the discretion of the Sponsor.

5.8.5 Assessment of Chromosomal Abnormalities by FISH

In the expansion phase of the study, subjects with identifiable chromosomal abnormalities at baseline will be further assessed by FISH in PB and/or BM aspirate collected on Days 1 and 3 (at pre-dose, 4[a] and 24 hrs post BL-8040 injection.

5.8.6 CXCR4 receptor occupancy in PB

CXCR4 occupancy will be measured in the PB of dose escalation phase subjects, using the CXCR4 antibodies 12G5 and 1D9, on Days 1 and 3 (Visits 2 and 4) at pre-dose, 4[a] and 24 hrs post BL-8040 injection.

5.9 PK ASSESSMENTS

BL-8040 PK parameters will be determined on the basis of blood samples collected on Days 1, 3, 5 and 7 (Visits 2, 4, 6 and 8).

Blood samples for BL-8040 PK analysis will be collected on Days 1, 3 and 7 at pre-dose, 0.25, 0.5, 1, 2, 4, 8 and 24 hrs post BL-8040 administration. Additional samples will be collected on Day 5 (Visit 6) at pre-dose and 0.5 hr post BL-8040 administration. PK parameters are listed in Section 2.2.3.

No PK blood samples will be collected from expansion phase subjects who receive a second treatment cycle.

PK sampling may be discontinued during the expansion phase at the discretion of the Sponsor. The Sponsor will notify sites when PK sample collection can be halted.

PK analysis will be conducted by a central laboratory using a validated High Performance Liquid Chromatography (HPLC) method.

5.10 BLOOD SAMPLING AND PROCESSING

Samples will be collected for safety and efficacy analysis, ADA titers and determination of BL-8040 plasma concentrations at the time-points indicated in Appendix A.

Instructions for the collection, processing, storage and shipment of samples are detailed in the Laboratory Manual provided by the Sponsor.

5.11 TIME WINDOWS FOR SAFETY, PK AND EFFICACY ASSESSMENTS

The time windows shown below will apply to post-dose safety (ECG and laboratory safety evaluations), efficacy (FACS analysis of leukemic cell mobilisation and apoptosis and CXCR4 receptor occupancy) and PK assessments.

[a] 4 hr post-dose samples on Day 3 to be taken prior to administration of Ara-C.

Time-point	Safety	Efficacy	PK
0.25 hr			± 2 min
0.5 hr	± 5 min		± 5 min
1 hr	± 10 min		± 10 min
2 hrs	± 15 min		± 15 min
4 hrs	± 30 min	± 30 min	± 30 min
8 hrs	± 30 min		± 30 min
24 hrs	± 1 hr	± 1 hr	± 1 hr

6 INVESTIGATIONAL PRODUCT

6.1 IDENTITY OF INVESTIGATIONAL PRODUCT

BL-8040 is a highly selective CXCR4 antagonist co-developed by [redacted] and BioLineRx Ltd. as a novel investigational therapy for the treatment of cancer.

BL-8040, a white to off-white powder synthetic polypeptide, is freely soluble in water and in 0.45% Sodium Chloride (half normal saline). It is manufactured in accordance with cGMP by [redacted]

6.2 STUDY DRUG ADMINISTRATION AND DOSAGE

6.2.1 BL-8040

On Days 1 and 2, subjects will receive once daily SC injections of BL-8040 in the morning according to the dose group to which they are assigned.

Between Days 3 and 7, BL-8040 will be administered once daily by SC injection(s) 4 (+/- 0.5) hrs prior to administration of standard chemotherapy (chemotherapy will be initiated on Day 3). The same instructions are applicable for expansion phase subjects who receive a second treatment cycle.

The BL-8040 injection site will be rotated on Days 1-7, to minimize the severity of any local injection site reactions. At the discretion of the Investigator, a single dose administration may be split and injected into more than one site. The same instructions are applicable for expansion phase subjects who receive a second treatment cycle.

During the expansion phase of the study, subjects with blast values of ≥ 30,000 and < 50,000/µL and/or WBC counts of ≥ 50,000 and < 60,000/µL, 24 hrs following the first BL-8040 injection, will not receive the second injection. Provided there are no signs of leukostasis on detailed physical examination, they will proceed directly to the combination therapy stage (protocol Day 3). In this situation, subjects will not receive BL-8040 prior to the first dose of Ara-C[a], but will receive BL-8040 prior to Ara-C on subsequent days provided blast count is < 30,000/µL and WBC counts is < 50,000/µL.

[a] Subjects who skip Day 2 due to blast counts ≥ 30,000 and < 50,000 and or WBC counts ≥ 50,000 and < 60,000/mL 24 hrs following the 1st dose of BL-8040, will proceed directly to protocol Day 3. All Day 3 assessments and procedures will be performed with the exception of BL-8040 administration and the following **post-dose** assessments: PK profiling, ECG measurements, WBC count (differential and leukemic cells), partial

Similarly, subjects with blast values of ≥ 30,000 and < 50,000/µL and/or WBC counts of ≥ 50,000 and < 60,000/µL 24 hrs following the second BL-8040 injection will be given the first dose of Ara-C without receiving BL-8040[a], provided there are no signs of leukostasis on detailed physical examination, but will receive BL-8040 prior to Ara-C on subsequent days provided blast count is < 30,000/µL and WBC counts is < 50,000/µL.

The planned dose escalation scheme will be as shown in Table 1. Dose modifications may include dose reductions, including doses lower than the starting dose of 0.5 mg/kg, and intermediate doses, but the maximum dose to be tested will not exceed 2.0 mg/kg.

6.2.2 Chemotherapy

Chemotherapy will consist of Ara-C **3** g/m^2/day for subjects ≤ 60 years (performance status permitting) and **1.5** g/m^2/day for subjects > 60 years administered IV over 3 hours.

6.2.3 Stopping Rules and Dose Limiting Toxicities

Dose-limiting toxicity (DLT)[b] is defined as a clinically significant adverse event or abnormal laboratory value assessed as unrelated to disease progression, intercurrent illness or concomitant medications and occurring during the safety period (30 days[c]) that meets any of the following criteria (refer to Table 2 for CTCAE severity grading):

- CTCAE grade 3 AST (SGOT) or ALT (SGPT) or bilirubin for ≥ 7 days
- CTCAE grade 4 AST (SGOT) or ALT (SGPT) of any duration
- All other clinically significant, non-hematological NCI common terminology criteria that are CTCAE grade 3 or 4

To be considered a DLT such toxicity must be possibly, probably or definitely related to BL-8040.

An adverse event must be clinically significant to define DLT e.g. nausea and vomiting, alopecia, study drug-related fever, electrolyte abnormalities (including K, Na, Cl, HCO_3, Mg, Ca, bilirubin) that are ≤ grade 3 will not constitute DLT. Myelosuppression and cytopenias are expected outcomes of leukemia treatment and per se will not constitute DLT. Only prolonged myelosuppression, as defined by the NCI criteria specific for leukemia, i.e. marrow cellularity < 5% on Day 42 or later (6 weeks) from start of therapy without evidence of leukemia, will be considered in defining MTD and DLT.

Subjects experiencing ≥ grade 3 BL-8040 related toxicity, either in the monotherapy or combined treatment period (excluding hematological toxicity), will be withdrawn from the

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biochemistry and assessment of CXCR4 receptor occupancy, leukemic blast apoptosis and mobilization (FACS and FISH). BM biopsy and/or aspiration must be performed prior to Ara-C administration.

[a] Subjects with blast counts ≥ 30,000 and < 50,000 and/or WBC counts ≥ 50,000 and < 60,000/µL 24 hrs following the 2nd dose of BL-8040, will undergo all Day 3 assessments and procedures with the exception of BL-8040 administration and the following **post-dose** assessments: PK profiling, ECG measurements, WBC count (differential and leukemic cells), partial biochemistry and assessment of CXCR4 receptor occupancy, leukemic blast apoptosis and mobilization (FACS and FISH). BM biopsy and/or aspiration must be performed prior to Ara-C administration.

[b] Only BL-8040 related or possibly related, grade 3-4 toxicities define DLT. For example, bone pain at grade 3/4 will not necessarily be defined as DLT, based on physician's decision and accounting for other administered drugs.

[c] In case of prolonged BM recovery it will be evaluated again at 6 weeks and considered part of the DLT assessment.

study, but followed for toxicity. Subjects who experience toxicity, which is not related to BL-8040, either during monotherapy or within the combination therapy period, will be allowed to continue BL-8040 treatment at the Investigator's discretion.

BL-8040 injections will be stopped in case of a significant increase in WBC and/or blasts (WBC ≥ 60,000/µL and/or blasts ≥ 50,000/µL, respectively) measured prior to administration of the next BL-8040 injection and/or evidence of leukostasis, TLS or grade 3-4 allergic reaction. These subjects will be withdrawn from the study and will be followed-up for safety for up to 6 weeks. In addition, during the **escalation phase**, subjects with blast values of ≥ 30,000 and < 50,000/µL and/or WBC counts of ≥ 50,000 and < 60,000/µL 24 hrs following BL-8040 injection on Days 1-6, will be withdrawn from the study and replaced.

During the expansion phase of the study, subjects with blast values of ≥ 30,000 and < 50,000/µL and/or WBC counts of ≥ 50,000 and < 60,000/µL, 24 hrs following the first BL-8040 injection, will not receive the second injection. Provided there are no signs of leukostasis on detailed physical examination, they will proceed directly to the combination therapy stage (protocol Day 3). In this situation, subjects will not receive BL-8040 prior to the first dose of Ara-C[a], but will receive BL-8040 prior to Ara-C on subsequent days provided blast count is < 30,000/µL and WBC counts is < 50,000/µL.

Similarly, subjects with blast values of ≥ 30,000 and < 50,000/µL and/or WBC counts of ≥ 50,000 and < 60,000/µL 24 hrs following the second BL-8040 injection will be given the first dose of Ara-C without receiving BL-8040[b], provided there are no signs of leukostasis on detailed physical examination, but will receive BL-8040 prior to Ara-C on subsequent days provided blast count is < 30,000/µL and WBC counts is < 50,000/µL.

Subjects who do not receive BL-8040 on Days 2 and/or 3, will not provide the full data set required for assessment of secondary endpoints relating to leukemic blast apoptosis and mobilization. However, they will be considered eligible for assessment of the secondary efficacy endpoint relating to response rate.

During the combination therapy, if blast values are ≥ 30,000/µL, BL-8040 administration will be discontinued.

6.2.4 Rescue medication

Leukostasis

Initiation of chemotherapy will be expedited in subjects experiencing leukostasis. Additionally, leukopharesis should be considered. Subjects developing shortness of breath with reduced saturation should be carefully monitored and receive oxygen.

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[a] Subjects who skip Day 2 due to blast counts ≥ 30,000 and < 50,000 and or WBC counts ≥ 50,000 and < 60,000/µL 24 hrs following the 1st dose of BL-8040, will proceed directly to protocol Day 3. All Day 3 assessments and procedures will be performed with the exception of BL-8040 administration and the following **post-dose** assessments: PK profiling, ECG measurements, WBC count (differential and leukemic cells), partial biochemistry and assessment of CXCR4 receptor occupancy, leukemic blast apoptosis and mobilization (FACS and FISH). BM biopsy and/or aspiration must be performed prior to Ara-C administration.

[b] Subjects with blast counts ≥ 30,000 and < 50,000 and/or WBC counts ≥ 50,000 and < 60,000/µL 24 hrs following the 2nd dose of BL-8040, will undergo all Day 3 assessments and procedures with the exception of BL-8040 administration and the following **post-dose** assessments: PK profiling, ECG measurements, WBC count (differential and leukemic cells), partial biochemistry and assessment of CXCR4 receptor occupancy, leukemic blast apoptosis and mobilization (FACS and FISH). BM biopsy and/or aspiration must be performed prior to Ara-C administration.

Tumour Lysis Syndrome

Subjects should be hydrated vigorously (urine output and fluid input should be monitored). Allopurinol and Rasburicase should be considered.

6.3 MANUFACTURING OF STUDY MEDICATION

BL-8040 drug substance (4F-benzoyl-TN14003 peptide) is a white or off-white powder synthetic polypeptide, freely soluble in water and in 0.45% Sodium Chloride (half normal saline). It is manufactured in accordance with current good manufacturing practice (cGMP) requirements by [redacted] Reconstitution and administration instructions will be provided in a separate study manual.

6.4 PACKAGING AND LABELING OF STUDY MEDICATION

The study drug is packaged in a USP Type 1 clear glass, single-use, 6 mL vial. The packaging and labeling will be performed by:

[redacted]

6.5 DISTRIBUTION AND SHIPMENT OF STUDY MEDICATION

The investigational medicinal product will be packed and shipped in appropriate boxes. If, upon arrival at the clinical investigation site, study drug supplies appear to be damaged, the study monitor should be contacted immediately.

Each shipment of study drug supplies for the study will be accompanied by a shipment form describing the contents of the shipment, product certificate of analysis, acknowledgement of receipt and other appropriate documentation. The shipment form will assist in maintaining current and accurate inventory records. The study staff will confirm the receipt of clinical supply to the study monitor.

All study supplies should arrive at the Pharmacy/Investigational site in sufficient quantity and in time to enable dosing as scheduled. The Sponsor or its representative must notify the Principal Investigator's designee prior to dispatch of drug supplies, with the anticipated date of their arrival.

6.6 STORAGE, DISPENSING AND RETURN OF THE INVESTIGATIONAL MEDICINAL PRODUCT

Vials of BL-8040 for injection should be stored in the refrigerator (2-8°C) in its original packaging, protected from light.

Records should also be kept by the Investigator or designee as to how much study drug was dispensed to each subject. The study monitors must periodically check the study drug supplied to ensure expiry date and sufficient amount of study drug, and be sure that drug accountability is being performed at each visit, and the drug accountability logs are maintained.

All investigational products must be kept in a secure area with access to the study drug limited to designated study personnel.

Only trained personnel under the supervision of either the Investigator or the local pharmacist are authorized to dispense and administer study drug to participating subjects.

Further details and instructions will be provided in the Pharmacy Manual.

6.7 ACCOUNTABILITY AND COMPLIANCE OF INVESTIGATIONAL MEDICINAL PRODUCT

Each delivery must be acknowledged by the hospital pharmacist (or authorized study team member responsible for the investigational medicinal product) by filling in the receipt record form and returning it by fax/email to the Sponsor or designee. Accurate, complete and timely documentation of study drug distribution will be maintained by the pharmacy and the study staff of the investigational site which may include confirmation of receipts of clinical supply, drug accountability logs and other forms.

The medical center pharmacist (or authorized study team member responsible for the investigational medicinal product) is responsible for ensuring the supervision of the storage and allocation of these supplies, which will be forwarded to the Investigator at the appropriate time before administration. The Investigator may dispense investigational drug only to subjects enrolled in the study.

Drug accountability records must be maintained by the clinical investigation site at all times. At the last study visit, all used and unused investigational drug will be collected and drug accountability performed by the study staff. The study monitor will check these regularly during monitoring visits.

The subject number, the date, batch number/pack number and quantity of study drug used by the subject will be checked for correctness and recorded on the appropriate accountability forms. Unused drug supplies will be returned to the Sponsor. At the end of the study, all clinical supplies and the corresponding accountability forms must be returned to the Sponsor, the study monitor, or designee for reconciliation or destruction. A photocopy of these records must be kept at the clinical investigation site.

The inventory will be made available to the study monitor who will verify accountability and verify dose during the course of the study.

Study drug orders, records of study drug receipts, dispensing records and inventory forms located at the site will be examined and reconciled by the study monitor periodically during and at the end of the study.

6.8 CONCOMITANT THERAPY

At the screening visit, relevant treatments currently received by the subject will be recorded in the subject's CRF including treatment's name, indication, dose, total daily dose and start and stop dates.

Any medications (including prescription, over-the-counter, herbal supplements and other health store-type products) to be taken during the study must be approved by the Investigator.

Concomitant medication use will be recorded from Baseline (Visit 2) through end of the Treatment Period (Visit 8 / Day 7). The following information should be recorded: treatment's name (generic, if possible), indication, dose and start and stop dates.

6.8.1 Allowed Medications

The following concomitant medications/therapies will be allowed during the treatment period:

- Allopurinol up to 300 mg/day (with adjustment to kidney function) and/or Rasburicase (up to 0.2 mg/kg/day, for up to 5 days).
- Clinically appropriate measures in case of BL-8040-related local injection site reactions (e.g., corticosteroids, anti-histamines, local treatments etc.) and preventive treatment before subsequent doses; also relevant for subjects with systemic reactions.
- Systemic and allergic treatment for chemotherapy-related allergic reactions.
- Antiemetic drugs (e.g., Ondansetron) as required clinically based on local guidelines for patients experiencing nausea while treated with BL-8040 only, and as a preventive approach during the combined treatment period.
- Gastrointestinal and kidney protective medications, routinely used in patients receiving chemotherapy, aiming to avoid peptic pain and TLS respectively (Losec, allopurinol, respectively).
- Prophylactic antibiotics (e.g., quinolone or cephalosporin), antifungals (e.g., voriconazole) and antivirals (e.g., valacyclovir).
- Blood products, commonly required in patients receiving chemotherapy for AML.
- Low-dose steroids (100 mg hydrocortisone or equivalent) are allowed as pre-medication for blood transfusion or with IV anti-fungals.
- B6 – provided to avoid neurotoxicity.
- Steroid eye drops - to prevent Ara-C induced inflammation.

Additional medications/therapies to manage treatment or disease emergent conditions will be allowed at the discretion of the Investigator in consultation with the Sponsor, in advance where possible. In case there is a change in therapy related to an AE, the Sponsor or Investigator may decide to withdraw the subject (refer to Section 4.6).

7 SAFETY AND PHARMACOVIGILANCE

7.1 ADVERSE EVENT (AE)

An AE is defined in ICH E6 as "any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product."

An abnormal result of diagnostic procedures including abnormal laboratory findings will be considered an AE if it fulfills one or more of the following:

- Results in subject's withdrawal by the Investigator
- Is associated with an SAE
- Is associated with clinical signs or symptoms
- Is considered by the physician to be of clinical significance

A new condition or the worsening of a pre-existing condition will be considered an AE.

AEs do not include the following:

- Medical/surgical procedures are not AEs (e.g., surgery, endoscopy, tooth extraction, transfusion). The condition that leads to the procedure is an AE if the procedure was not planned at screening visit.

- Overdose of concomitant medication without any signs or symptoms unless the subject is hospitalized for observation.
- Hospitalization for elective surgery planned prior to study (situation where an untoward medical occurrence has not occurred).
- Disease progression

All AEs, whether observed by the Investigator or designee or volunteered by or elicited from the subject, should be recorded individually on an AE CRF page with the following information: the specific event or condition, whether the event was present pre-baseline or not, the dates and times (using the 24 hour clock, where midnight is 00:00 and noon is 12:00) of occurrence, duration, severity, relationship to study medication, action taken to study drug, outcome, and whether considered non-serious or serious, drug-related or not.

Once the subject has signed the Informed Consent Form (ICF), AEs will be recorded until the end of the Follow-up period. The severity of the AE will be assessed by the investigating physician in accordance with the definitions below. A Serious AE must fulfill the requirements listed in Section 7.2.

Adverse Event severity (Table 2) will be recorded and graded according to the latest version of the NCI-CTCAE (currently version 4.03) and coded into the database according to the latest version of MedDRA (currently version 14.0).

Table 2 Severity of Adverse Events According to CTCAE (Version 4.03)

Grade	Description
0	No AE or within normal limits
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental Activities of Daily Living (ADL)
3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL
4	Life-threatening consequences; urgent intervention indicated
5	Death related to AE

A semi-colon indicates 'or' within the description of the grade.
A single dash (-) indicates a grade is not available

The following definitions should be used for toxicities/AEs that are not defined in the CTCAE:

- Mild (Grade 1): The AE is noticeable to the subject but does not interfere with routine activity, no medical intervention is required;
- Moderate (Grade 2): The AE interferes with routine activity but responds to symptomatic therapy or rest;
- Severe (Grade 3): The AE significantly limits the subject's ability to perform routine activities despite symptomatic therapy;
- Life-threatening (Grade 4): The subject is at immediate risk of death.

The Investigator will document his opinion of the relationship of the AE to treatment with investigational product using the criteria outlined in Table 3.

Outcome to Date are classified as follows:

- Recovered: The subject has fully recovered from the AE with no residual effects observable
- Recovered with sequelae: The subject has recovered from the AE with residual effects observable
- Improved: the subject status improved but has not been fully recovered
- Ongoing: AE is not recovered
- Fatal
- Unknown

AEs will be coded by Data Management using the latest version of MedDRA (currently version 14.0) AE dictionary.

All AEs, serious and not serious, will be recorded on the AE Case Report Form, and if relevant, the Concomitant Medications Record in the CRF will be updated. Severity and relationship to study drug will be assessed by the Investigator as described in Table 3. Particular attention should be made to ensure no discrepancies between the AE and the SAE form (i.e. outcome, severity, relationship must be consistent).

Treatment emergent AEs (TEAEs) are defined as AEs observed after 1st dose of study drug.

Table 3 Relationship of Adverse Event to Treatment

Relationship	Criteria
Unrelated	The patient did not receive the study medication. OR The temporal sequence of the AE onset relative to administration of the study medication is not reasonable. OR There is another obvious cause of the AE.
Unlikely	There is evidence of exposure to the study medication. However, it does not follow a reasonable temporal sequence from administration of drug. It does not follow a known response pattern to the suspected drug. It does not re-appear or worsen upon re-challenge. There is another more likely cause of the AE.
Possible	There is evidence of exposure to the study medication. The temporal sequence of the AE onset relative to the administration of the study medication is reasonable. The AE could have been due to another equally likely cause.
Probable	There is evidence of exposure to the study medication. The temporal sequence of the AE onset relative to administration of the study medication is reasonable. The AE is more likely explained by the study medication than by another cause. A direct cause and effect relationship between the suspected drug and the adverse event is likely. It disappears or decreases upon cessation of drug administration or reduction in dose.
Related	There is evidence of exposure to the study medication. The temporal sequence of the AE onset relative to administration of the study medication is reasonable. The AE is more likely explained by the study medication than by another cause. The AE shows a pattern consistent with previous knowledge of the study medication. A direct cause and effect relationship between the suspected drug and the adverse event

	has been demonstrated. It disappears or decreases upon cessation of drug administration or reduction in dose.

7.2 SERIOUS ADVERSE EVENTS (SAEs)

An SAE is any AE occurring at any dose that suggest a significant hazard or side effect, regardless of the Investigator or Sponsor's opinion on the relationship to the investigational medicinal product and that results in, but may not be limited to, any of the following outcomes:

- death (regardless of the cause)
- a life-threatening experience
- inpatient hospitalization or prolongation of existing hospitalization (any inpatient hospital admission that includes a minimum of an overnight stay in a health care facility)
- a persistent or significant disability/incapacity
- a congenital anomaly or birth defect

Important medical events that may not result in death, be life-threatening, or require hospitalization may be **serious** when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

Inpatient hospitalization or prolongation of existing hospitalization means that hospital inpatient admission and/or prolongation of hospital stay were required for treatment of AE, or that they occurred as a consequence of the event.

Hospitalization for elective treatment of a pre-study condition (pre-baseline) that did not worsen while on study and optional hospitalizations not associated with a clinical AE (e.g. elective cosmetic surgery) are not considered SAEs.

Significant medical events are those which may not be immediately life-threatening, but may jeopardize the subject and may require intervention to prevent one of the other serious outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; such an AE will normally be considered serious by this criterion.

A **life-threatening** adverse drug experience is any AE that places the subject, in the view of the Investigator, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death.

Any newly emergent SAEs, after treatment is discontinued or the subject has completed the study, and is considered to be related to the study drug or study participation, should be recorded and reported immediately to Sponsor or delegate.

7.3 DEFINITION OF AN UNEXPECTED ADVERSE EVENT

An **unexpected** adverse drug event is any AE, the specificity or severity of which is not consistent with information in the current Investigator's Brochure for an unapproved investigational product.

Suspected Unexpected Serious Adverse Reaction (SUSAR) is a SAE assessed as unexpected by the Sponsor and that is judged by either the reporting Investigator or the Sponsor to have a reasonable causal relationship to the investigational medicinal product.

7.4 EXCEPTIONS IN THE REPORTING OF SAE

According to EU and FDA detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use, regarding clinical trials in high morbidity or mortality diseases, it is acceptable to define some exceptions in the immediate reporting of specific SAEs. Refer to EU guidance ENTR/CT3, 5.1.9 and FDA guidance "Safety Reporting Requirements for INDs and BA/BE Studies" (Dec 2012).

High dose chemotherapy is a recognized condition with a relatively high morbidity and/or high mortality.

Under these circumstances, it seems appropriate that the SAEs, clearly related to the high dose chemotherapy could be an exception for an immediate systematic reporting.

These AEs will be thoroughly handled and followed up through the CRF (AE form) and will be reviewed monthly by the medical safety officer and could be re-qualified for reporting if necessary.

Each event must be carefully analyzed by the Investigator's designee to decide whether the SAE could be considered as an exception or must be immediately reported.

7.5 NOTIFICATION OF SERIOUS ADVERSE EVENT (SAE)

Initial notification of SAEs

An Initial SAE report form must be completed and sent by **fax/email to the Medical Monitor** within 24 hours of the Investigator's knowledge of the event. **Any fatal or life-threatening event should be reported immediately, by phone, fax or email. Reporting SAEs to regulatory authorities and/or IRBs will comply with local regulations.**

Medical Monitor

[redacted]

The Initial SAE report will be followed within 24 hours by a completed SAE report including a sufficiently detailed narrative to allow for a medical assessment of the case, as well as copies of hospital case reports, results of applicable diagnostic tests, laboratory results, biopsy results, autopsy reports and other documents when requested and applicable.

Minimum criteria for a valid initial SAE case:

For regulatory purposes, initial SAE reports should be submitted to Medical Monitor and/or the Sponsor immediately and should include:

- A suspected investigational medicinal product,
- An identifiable subject (e.g. study subject code number),
- An AE with the Investigator's assessment of seriousness and relationship to study drug,
- An identifiable reporting source (Investigator contact details).

Once sent, the SAE form and accompanying documentation should be placed in the SAE section of the Investigator's site file.

In addition, all SUSARs and relevant SAEs will be reported to the IRB/IEC and regulatory authorities as required by local regulations and ICH-GCP guidelines.

Follow-up of SAEs:

Follow-up of all SAEs that occur during the study will continue until their satisfactory resolution or stabilization. In outstanding cases, it may be defined as "ongoing without further follow-up" if mutually agreed by the Investigator and Sponsor.

A Follow-up SAE Report Form must be completed by the site (marked as "Follow-up report") and sent to the Medical Monitor within a reasonable timeframe (an SAE Follow-up report is required whether or not there is any additional information to the initial report).

The contact information for Follow-up SAE reporting is the same as for initial SAE reports (see above section).

As for the initial SAE report, once sent, the Follow-up SAE report and accompanying documentation should be placed in the SAE section of the Investigator's site file.

8 STATISTICAL ANALYSIS

8.1 SAMPLE SIZE CONSIDERATION

As this is a Phase IIa study, the exact number of subjects enrolled will depend on the toxicity observed in each dose group and the number of dose groups required to reach MTD. If all six dose groups are required and if each dose group is expanded to 6 subjects (see stopping rules Section 6.2.3 and Figure 1), then a total of 36 subjects will be enrolled into the dose escalation part of the study.

Once a dose has been selected for the **expansion phase**, additional subjects may be enrolled in that dose group up to a total of approximately 70 subjects in the study.

8.2 ANALYSIS SETS

Intention-To-Treat (ITT) Analysis Set: All enrolled subjects who receive at least one dose of study medication.

Per-Protocol (PP) Analysis Set: All enrolled subjects who complete the study according to the protocol without major protocol violations.

8.3 STATISTICAL METHODS

All measured variables and derived parameters will be listed individually and, if appropriate, tabulated by descriptive statistics. Summary statistics will be provided for all safety, exploratory and baseline/demographic variables. For categorical variables, frequency tables including percentages will be presented. For continuous variables, descriptive statistics such as number of available observations, mean, median, standard deviation (SD), minimum and maximum will be tabulated. All available data and the tabulation of results will be displayed by initial dose level and with all levels pooled as a whole if applicable.

Dose limiting toxicity will be determined by definition and will be summarized by dose level. The MTD will be determined by study structure and DLTs.

The data will be analyzed as described in the Statistical Analysis Plan.

8.3.1 Safety Analysis

Changes in vital signs and routine laboratory data will be presented with descriptive statistics to demonstrate the trend of change.

Number of subjects with physical abnormality at each scheduled visit will be tabulated by body system and by dose level. ECG examination results will be displayed in descriptive statistics and by dose level with number of subjects with abnormal findings tabulated for each schedule visit.

Adverse event incidence will be summarized descriptively by system organ class and preferred term using the latest version of MedDRA (currently version 14.0) and by dose level. The worst severity grade of AEs, as determined by the latest version of NCI-CTCAE (currently version 4.03), and their relationship to study medication will be analyzed by System Organ Class, preferred term and by original dose level. The action taken and outcome will also be analyzed accordingly.

By subject list of toxicity severity grade will be presented in time-sequence manner using the latest version of NCI-CTCAE (currently version 4.03) with System Organ Class and preferred term. The number and incidence of subjects experiencing toxicity will be tabulated by worst severity grade in each MedDRA term. Subjects experiencing toxicity ≥ grade 3 for each type of toxicity will be calculated and presented by original dose level.

8.3.2 Efficacy Analysis

95% Confidence Interval (CI) will be calculated for proportion of subjects defined [4] (Appendix C) in the secondary efficacy endpoints who achieve:

Complete Response (CR)

Complete Response with incomplete hematological recovery (CRi)

Partial Response (PR)

Overall Response (OR) defined as sum of CR, CRi and PR.

Complete Response composite (CRc) defined as the sum of CR and CRi.

Overall survival (OS) during the long-term follow-up.

8.3.3 PK Analysis

Individual PK parameters and the mean, SD and 95% CI values will be tabulated for each dose group.

Dose proportionality/linearity in relation to C_{max} and AUC will also be assessed if there is sufficient data available in each dose group.

All tests will be two-tailed and a p value of [redacted] or less will be considered statistically significant.

9 ETHICS

9.1 INSTITUTIONAL REVIEW BOARD OR INDEPENDENT ETHICS COMMITTEE

Prior to initiation of the study, the Investigator will submit the study protocol and amendments, Investigator's Brochure and amendments, ICF and any other documents that may be provided to the subject or any other documents requested by the IRB/IEC for review and approval.

The names and affiliations of all members of the IRB/IEC must be provided to the Principal Investigator and BioLineRx. In lieu of this, the IRB/IEC must certify that it has been officially authorized/recognized according to the national legislation.

The IRB/IEC must provide written approval of the study to keep in the Investigator's file. Records of approval of all documents pertaining to this study, including the local regulatory authority, should be filed as such. The Investigator will not begin the study until the protocol, ICF and any other document provided to the subject have been approved by the IRB/IEC. The Investigator must agree to make any required progress reports to the IRB/IEC, as well as reports of SAEs, life-threatening conditions or death. The IRB/IEC will also be notified of Part 1 preliminary results.

9.2 ETHICAL CONDUCT OF THE STUDY

All clinical work conducted under this protocol is subject to ICH GCP (E6) guidelines. This includes an inspection by Sponsor or its designee, health authority or IRB/IEC representatives at any time. The Investigator must agree to the inspection of study-related records by health authority representatives and/or Sponsor or its designee.

The study will be conducted in accordance with Sponsor and/or designee's standards operating procedures and the following guidelines:

- GCP: Consolidated Guideline (International Conference on Harmonization of Technical Requirements for the Registration of Pharmaceuticals for Human Use, May 1996).
- Declaration of Helsinki: Seoul, 2008 (Appendix F).
- US Code of Federal Regulations (Title 21, CFR Part 11, 50, 54, 56 and 312) and/or EU Directives; and/or local country regulations and guidelines.

9.3 SUBJECT INFORMATION AND CONSENT

Prior to screening for the study each subject will be informed in detail about the study drugs to be administered and the nature of the clinical investigation with its risks and discomforts to be expected. The basic elements of informed consent as specified by the FDA (21 CFR 50.25) and ICH-GCP will be followed. The subjects will also be instructed that they are free to withdraw their consent and discontinue their participation in the study at any time without prejudice. Written consent will be obtained from each subject to be involved in the clinical trial by using the IRB/IEC-approved ICF prior to the conduct of any study-related activity. A copy of the ICF will be submitted together with this protocol and must be approved by the IRB/IEC prior to study commencement. Each subject will be given a copy of the written ICF, and each subject's chart will include the signed ICF for study participation. The original subject signed and dated ICFs will be maintained per ICH record retention requirements. Regulatory authorities may check the existence of the signed ICF in this central study folder if not having performed so during the study.

9.4 SUBJECT INSURANCE

A product liability to cover against injury and damages arising from the use of investigational products in this project is provided by the Sponsor for the total duration of the study covering the subjects and Investigators in respect of the risks involved in conducting this study according to this protocol. The insurance policy will be filed in the Investigator's site file or can be made available to the Investigator and to the IRB/IEC upon request.

Subjects will be insured through contract between an insurance company and the Sponsor.

9.5 INFORMING THE GENERAL PRACTITIONER

When required by location regulation, the Investigator will inform the subject's primary care physician of his/her participation in the study, by sending a letter to the physician.

9.6 PERSONAL DATA PROTECTION

The Sponsor will comply with local regulations and with the principle of subject's right to protection against invasion of privacy. Throughout this trial, all subject data will be identified only by a subject identification number and subject initials and date of birth. The data will be blinded in all data analyses. The subject must be informed and consent to authorized personnel of the Sponsor, such as study monitor, auditor, etc. and relevant health regulatory agencies having direct access to personal medical data to assure a high quality standard of the study. At the subject's request, medical information may be given to his or her personal physician or other appropriate medical personnel responsible for his or her welfare.

9.7 DATA AND SAFETY MONITORING

An Internal Safety Committee will be assigned by the Sponsor prior to the beginning of the study. The committee will be comprised of 3 members appointed by the Sponsor including at least one clinician and persons knowledgeable of the investigational drug. The decision to proceed to the next dose group will be made by this committee.

This Internal Safety Committee will assess the progress of the clinical trial, the safety data and will recommend to the Sponsor and to the Investigator whether to continue, modify or stop the trial.

9.8 PROTOCOL EXCEPTIONS AND DEVIATIONS

Departures from the protocol should be avoided, unless required for the safety of the subject. Protocol deviations, and if possible the reason for occurrence, will be documented by the study monitor for visit reports and will be included in the final clinical study report. The Investigator must report any protocol deviations to the Sponsor or the Sponsor's designee, should they occur. If required, the Investigator should also report deviations to the IRB/IEC in accordance with local regulations and within a reasonable time. No prospective waivers will be allowed for patients who do not fulfill the inclusion/exclusion criteria.

9.9 PROTOCOL AMENDMENTS

Changes to the protocol may be made only by the Sponsor (with or without consultation with the Investigator). All protocol modifications must be submitted to the site IRB/IEC in accordance with local requirements and, if required, to the Regulatory Authority, either as an amendment or a notification. Approval for amendments must be received before any changes can be implemented, except for changes necessary to eliminate an immediate hazard to trial subjects, or when the changes involve only logistical or administrative aspects of the trial. No approval is required for notifications.

10 QUALITY CONTROL AND QUALITY ASSURANCE

The study will be conducted according to GCP as outlined by ICH Topic E6 step 5 guidelines. The CRO's SOPs will be followed to ensure that clinical trials are conducted and data are generated, documented and reported in compliance with the protocol, GCP and applicable regulatory requirements.

10.1 AUDITS AND INSPECTIONS

The study may be audited according to the Sponsor's or its designee's QA inspection program. The purpose of the audit is to determine whether or not the study is being conducted and monitored in compliance with the study protocol and ICH GCP guidelines. Audit visit(s) will be arranged in advance with site personnel at a mutually acceptable time.

The Investigator should understand that source documents for this trial should be made available to appropriately qualified personnel from the Sponsor or its designees or the regulatory authority inspectors after appropriate notification. The verification of the CRF data must be made by direct inspection of source documents. The auditor may ask to visit the facilities where laboratory samples are collected, where the investigational product is stored and prepared and any other facility used during the study. These audits or inspections may take place at any time, during or after the study, and are based on the national regulations, as well as ICH guidelines.

10.2 STUDY MONITORING

Monitoring of the study is the responsibility of the Sponsor and may be delegated to a CRO. The study monitor will advise the Investigator regarding the practical conduct of the study and maintaining compliance with the protocol, GCP and all applicable regulatory requirements.

Before study initiation, at the site initiation visit or at an Investigator's meeting, a Sponsor or CRO representative will review the protocol and CRFs with the Investigator and his staff. The Sponsor/CRO will also be responsible for training study personnel in the study specific procedures.

Throughout the course of the study, the study monitor will oversee the conduct and the progress of the study by frequent contacts with the Investigator and his staff. This will include telephone calls and on-site visits. During the on-site visits, the CRF will be reviewed for completeness and accuracy with corresponding source documents. As part of the data audit, source documents will be made available for review by the study monitor. The study monitor will also perform drug accountability checks and will periodically review the Investigator study file to ensure completeness of documentation in all respects of clinical study conduct.

Periodically, some or all of the facilities used in the study (e.g., local laboratory, pharmacy) may be reviewed. Monitoring visits will be arranged in advance with site personnel at a mutually acceptable time. Sufficient time must be allowed by the site personnel for the monitor to review CRFs and relevant source documents. The Investigator should be available to answer questions or resolve data clarifications. The Investigator or appointed delegate will receive the study monitor during these on-site visits, cooperate in providing the documents for inspection and respond to enquiries.

The Investigator will ensure that the study participants are aware of and consent to their personal information being scrutinized during the data verification process, as part of study-related monitoring, inspection and/or auditing, by properly authorized persons associated with Sponsor or by domestic and/or foreign regulatory authorities. However, the subject's participation and personal information will be treated as strictly confidential to the extent that the applicable law permits and will not be made publicly available.

Upon completion of the study, the study monitor will arrange for a final review of the study files after which the files should be secured for the appropriate time period.

10.3 QUALITY LABORATORY STANDARDS

Laboratory tests or evaluations described in this protocol will be conducted in accordance with quality laboratory standards as described in the SOPs of the central and local institution laboratories.

Before the study begins, the laboratories to be used in the study will provide a list of the reference ranges for all laboratory tests to be undertaken and details of the method used for quality control. These will be held in the Investigator Site File and the Trial Master File. The methods employed for each assay should be available on request. Any change in the laboratory, its procedures, references, values, etc. during the study must be notified promptly to the Sponsor.

10.4 STUDY DOCUMENTATION

Study documents will include the following:

- Signed ICFs
- Source documents (e.g. subject files, medical notes)
- Investigator copies of the CRFs and SAE reports
- Investigator site file + contents
- Study manual (if applicable)
- Study Pharmacy manual (includes instructions for use)
- Investigator meeting binder and or other training materials

Upon completion of the study, the study monitor will arrange for a final review of the study files after which the files should be secured for the appropriate time period.

10.4.1 Source Document

The Investigator will permit study-related monitoring, audits by or on behalf of the Sponsor, IRB/IEC review and regulatory inspections providing direct access to source data documents. Source documents are original records in which raw data are first recorded. These may be office/clinic/hospital records, charts, diaries, x-rays, laboratory results, printouts, pharmacy records, care records or completed scales for each study participant. Source documents should be kept in a secure and limited access area. All source documents must be accurate, clear, unambiguous, permanent and capable of being audited. They should be made using a permanent form of recording (ink, typing, printing, optical disc etc). They should not be obscured by correcting fluid or have temporary attachments (such as removable self-stick notes). Source documents that are computer generated and stored electronically must be printed, signed and dated by the Investigator.

Source data for subjects registered to the study should indicate the date the ICF was signed, participation in a clinical trial with the clinical protocol number and title, treatment number and evidence that inclusion/exclusion criteria have been met.

10.4.2 Recording of Data on Case Report Form (CRF)

The development of the CRF will be the responsibility of the Sponsor or its designee.

All the pertinent data will be recorded on an electronic Case Report Form (eCRF). All eCRFs will be completed in English and will be reviewed by study monitors for accuracy and completeness. The eCRFs should be completed at the time of the subject's visit, with the exception of results of tests performed outside the Investigator’s office. The Investigator is

responsible for verifying that all data entries in the eCRFs are accurate and correct. The Principal Investigator must sign the completed CRF prior to its submission to the Sponsor.

A representative of the Sponsor or designee will instruct the Investigator and his/her staff prior to the enrollment of the first patient and will train them on recording the findings into the electronic data capture (EDC) system.

(EDC) system on the electronic CRFs (eCRFs):

After the enrollment of the first patient, a study monitor will periodically monitor the progress of the study by conducting onsite visits. This study monitor will also have the ability to review query statuses remotely which may warrant more frequent contact with the Investigator and his/her staff. The Investigator will make available to the study monitor the computer that accesses the eCRFs, source documents, signed consent forms and all other study related documents. The Investigator will be responsible for reviewing eCRFs, providing resolution to data queries generated by the study monitor via the EDC system, providing missing or corrected data, and approving all changes performed on his/her data, and endorsing the patient data within the EDC system. This approval method will include applying an electronic signature, a uniquely assigned username and a password, that together would represent a traditional handwritten signature.

The Investigator will agree to the inspection of study-related records by the Sponsor, external auditor and/or health authority representatives.

10.4.3 Investigator Site File

All documents required for the conduct of the study as specified in the ICH-GCP guidelines will be maintained by the Investigator in an orderly manner and made available for monitoring and/or auditing by the Sponsor/or designee and regulatory agencies.

10.5 CLINICAL TRIAL SUPPLIES

The Sponsor or designee will be responsible for supplying clinical trial supplies to the sites. The Principal Investigator will be responsible for the administration, inventory and accountability of all clinical trial supplies provided to the site, exercising accepted medical and pharmaceutical practices. An accurate and timely record of the disposition of all clinical supplies must be maintained. The supplies and inventory record must be made available for inspection upon request. Upon completion or termination of the study, the Investigator will return the remaining clinical supplies along with a copy of the inventory record and a record of the clinical supplies returned. A copy of these records should be maintained in the site study files. **Under no circumstances will the Investigator allow the study drugs to be used other than as directed by this protocol.**

Clinical trial supplies include, but are not limited to: CRFs, lab supplies, rescue medications and study drugs.

10.6 DATA MANAGEMENT

Data Management services will be provided by the Sponsor or designee. The data management system will be specified in the Data Management Plan.

After the data have been entered and verified, various edit checks will be performed for the purpose of ensuring the accuracy, integrity and validity of the database. These edit checks may include:

- Missing value checks

- Range checks
- Consistency checks
- Sequence checks
- Protocol adherence checks

Queries generated from these checks will be sent to the investigational site for resolution, and the database will be updated to reflect query resolutions as appropriate.

Adverse events will be coded using the latest version of MedDRA (currently version 14.0). Prior and concomitant medications will be coded according to the World Health Organization (WHO) Drug Dictionary.

11 STUDY ADMINISTRATION

11.1 PARTICIPATING CENTERS

Approximately 5 sites in the USA and 5 sites in Israel are planned.

Additional sites may be added in the event of slow recruitment.

11.2 REQUIRED DOCUMENTS PRIOR TO STUDY INITIATION

Prior to the start of this study, all pre-investigational requirements must be met by the Investigator and study site. These may include:

- Appropriate local health authority documentation properly signed and dated by the required Investigator (i.e., documents required for submission to the local IRB/IECs or applicable regulatory authorities).
- Signed copy (original) of the approved protocol
- Completed and signed statement of Investigator
- A signed Clinical Trial Agreement
- Curriculum vitae for the Investigator and sub-Investigator (can be collected at site initiation visit)
- IRB/IEC name and address; and membership list (can be collected at site initiation visit)
- Letter of approval from the IRB/IEC for both protocol (identified by protocol title and number) and ICF (identified by protocol title and number)
- Copy of the IRB/IEC-approved written ICF to be used in the study (that has also been approved by the Sponsor)
- Provisions for direct access to source/data documents if necessary for trial-related monitoring, audits, IRB/IEC review and regulatory inspection
- Name and location of the laboratory utilized for laboratory assays and other facilities conducting tests, as well as a copy of the laboratory certificate and list of normal laboratory values (can be collected at site initiation visit)

In case a laboratory certification is not available, a written statement as to how the laboratory complies with quality assurance should be provided.

Upon satisfactory receipt of all required regulatory documents, the Sponsor will arrange for study drugs to be delivered to the study site. Supply of all other study materials will be the

responsibility of the Sponsor and/or designee. Subject entry should not begin until after the required regulatory documents are confirmed as received and the Investigator Meeting/Initiation Meeting has occurred. All personnel expected to be involved in the conduct of the study will undergo study initiation to include review of study protocol, instructions for CRF completion, AE reporting and overall responsibilities including those for drug accountability and study file maintenance.

The Investigator and/or designee (study monitor) will be provided with an Investigator's File. This file should be used for all trial related documents. The Investigator will be responsible for keeping the Investigator's file updated and ensuring that all required documents are filed. The file will be inspected during monitoring visits.

11.3 STUDY COMPLETION

This study is expected to end when all required subjects have been enrolled and the last subject has completed the study and all query resolutions have been completed.

Data and materials that are required before the study can be considered complete and/or terminated include, but are not limited to:

- Laboratory findings, clinical data and all special test results from screening through the end of the follow-up period
- CRF properly completed by appropriate study personnel and electronically signed by the Investigator
- Completed Drug Accountability Records
- Statement of outcome for each SAE reported
- Copies of protocol amendments and IRB/IEC as well as relevant health authority approval/notification (if applicable)
- Retention of Study Documents Statement

11.4 CLINICAL STUDY REPORT

A clinical study report will be developed by the Sponsor on completion of data analysis. This report will be a clinical and statistical integrated report, according to the ICH E3 guidelines.

11.5 RETENTION OF STUDY RECORDS

The Investigator will retain copies of the approved protocol, completed CRF, signed ICFs, relevant source documents and all other supporting documentation related to the project as defined in ICH-E6 section 8 related to the project per ICH-E6 record retention requirements for at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product in a secure and safe facility with limited access. If the Investigator is unable to retain the study documents for the required amount of time, the Sponsor or designee must be informed of the individual who will be assuming this responsibility.

The Sponsor will notify, in writing, the Investigator when the clinical study data may be discarded. The Investigator will take measures to prevent accidental or premature destruction of these documents.

These files must be made available for inspection upon reasonable request by authorized representatives of the Sponsor and/or the relevant regulatory agencies.

11.6 CONFIDENTIALITY AND PUBLICATION OF STUDY RESULTS

11.6.1 General

All data and information supplied by or on behalf of the Sponsor or otherwise acquired or obtained by any Research Institution, the Principal Investigator and other Investigators ("Recipients") in any manner, in connection with or in performance of this study, is considered "Confidential Information". This Confidential Information includes, but is not limited to, the Investigator's brochure, this protocol and any information relating thereto, CRFs and other scientific data, information relating to Sponsor's Investigational Product and treatment methodology and information relating to Sponsor's (or its affiliates') commercial, technical and financial information, research technology, products, inventions, trade secrets and research and development. The results produced in performance of the study and any data, information or other material collected, developed, generated or prepared during and in the course of performing the study shall be promptly disclosed to Sponsor in full in writing, and are also considered Confidential Information. This Confidential Information shall be and remain the sole property of the Sponsor. Except for Publishable Results (defined below) to the extent it may be published under Section 11.6.2, throughout the duration of the study and after its completion, Recipients shall (i) not disclose Confidential Information to others without the written consent of the Sponsor, except to those of its employees who have a need to know the Confidential Information in order to Recipients' obligations hereunder, and where such employees are bound by written contractual obligations covering Confidential Information that are no less restrictive or protective than those contained herein, provided that Recipients shall remain liable for any disclosure or use of Confidential Information by such employees, (ii) use the same degree of care to preserve confidentiality of Confidential Information as they use for their own information of like nature, which shall not be less than reasonable degree of care, and (iii) not use Confidential Information for any purpose except in the performance of this study. Promptly at Sponsor's request, or upon completion of the study, Recipients will discontinue use and return to Sponsor or destroy, in accordance with Sponsor's instructions, all copies or other manifestations of Confidential Information that may be in their possession or control, except to the extent expressly required hereunder and to comply with Applicable Laws (defined below). Should a Recipient be required to disclose Confidential Information pursuant to law, regulation, judicial or administrative order or request by a governmental or other entity authorized by law to make such request, Recipient shall (i) promptly notify Sponsor prior to such disclosure, (ii) cooperate with Sponsor and provide assistance in seeking a protective order or other suitable protection with respect to the Confidential Information, and (iii) only disclose such Confidential Information to the extent pursuant to said law, regulation, judicial or administrative order, or request by a governmental or other authorized entity.

At the subject's request, medical information may be given to his or her personal physician or other appropriate medical personnel responsible for his or her welfare. The personal physician will be notified by site personnel of subject participation in the study.

11.6.2 Published Data

The object of the study will be to publish the results of the complete study ("Publishable Results") in an appropriate peer-reviewed journal after the conclusion of the study ("Publication"). A formal Publication of the Publishable Results is planned and will be considered a joint publication by the Principal Investigator, other Investigators, Sponsor and the appropriate Sponsor personnel (and Research Institutions) (*Subject to internal review)*. Publication must be undertaken in a responsible and ethical manner, taking into account

relevant external standards regarding the manner and content of scientific, technical and medical publications and in subject to applicable laws, rules, regulations, policies and guidelines ("Applicable Laws"). Authorship will be determined by mutual agreement between Sponsor and Principal Investigator. Sponsor shall be mentioned in all Publications unless contrary instruction is given by Sponsor. Review and comment by Sponsor authorized personnel on draft abstracts and manuscripts for Publication or presentation is required prior to publication or presentation. Authors shall submit a copy of any abstracts, manuscripts or other material proposed for publication or presentation ("**Draft Publications**") to the Sponsor for its approval no fewer than sixty (60) days prior to the intended date of submission of such Draft Publications to any journal, publisher, and/or third party. The Sponsor has the right, at its discretion (a) to evaluate Draft Publications for accuracy and concurrence regarding data, evaluations, and conclusions, (b) to provide an opportunity for Sponsor to share with the Investigator(s) any new or unpublished information of which he or she may be unaware, (c) to ensure that no Confidential Information or other Sponsor proprietary information is being utilized and has been included, and (d) evaluate Draft Publications to determine if patent applications need to be filed on any information disclosed therein.

If the Sponsor determines that such Draft Publication contains Confidential Information or could otherwise be detrimental to Sponsor's intellectual property interest or have other adverse effects on its business, and notifies Principal Investigator of its determination, the Principal Investigator, Research Institutions and other Investigators/authors shall remove such Confidential Information from the Draft Publication or at Sponsor's election, modify it to remove language that is detrimental to Sponsor's intellectual property or other interests, and refrain from submitting such Draft Publication to a journal, publisher and/or other third party for additional ninety (90) days from Sponsor's notification to allow for filing of patent applications or the taking of such other measures as Sponsor deems appropriate to establish, preserve and protect its intellectual property or other interests. Principal Investigator, other Investigators and Research Institutions further agree to redact or modify those sections of the draft Publication which Sponsor in good faith determines falls within (a) to (d) above.

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13 APPENDICES

APPENDIX A SCHEDULE OF ASSESSMENTS

Study Procedures	**Screening Period**	**Treatment Period[23]**							**Follow-up Period[1, 24, 26]**
		Monotherapy Period		**Combined Therapy Period**					
Study Day	**Day -7- to Day 0**	**Day 1/BL**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**	**Up to Day 44**
Study Visit	**1**	**2 / 10**	**3 / 11**	**4 / 12**	**5 / 13**	**6 / 14**	**7 / 15**	**8 / 16**	**9 / 17**
Informed consent	X								
Inclusion/exclusion criteria	X								
Demographic & medical history	X								
Physical examination[2, 3]	X[4]	X	X	X	X	X	X	X	
Vital signs[3, 5]	X	X	X	X	X	X	X	X	
ECOG Performance Status	X								
ECG[6]	X	X		X[16, 17] (Visit 4 only)				X	
ECHO/MUGA & Chest X-ray	X								
Hematology[3]	X	X	X	X	X	X	X	X	X[7]
White blood cell (WBC) count[8]		X	X	X[16, 17]				X	
Biochemistry[3]	X	X	X	X	X	X	X	X	X[7]
Partial biochemistry[9]		X	X	X[16, 17]				X	
Coagulation[10]	X	X						X	
Anti-drug antibody assessment[25]		X (Visit 2 only)		X (Visit 4 only)				X (Visit 8 only)	X (Visit 9 only)
Serum β-hCG	X								
HIV, HBV, HCV serology	X								
Clinical evaluation of leukostasis and TLS	X	X	upon commencement of symptoms or when WBC > 30,000/µL						
Bone Marrow (BM) biopsy/aspirate	X[11,22] (within 7 days prior to BL-8040)			X[20,22] (pre BL-8040 Visit 4 only)					X[12, 13, 22]
CXCR4 expression and occupancy in PB[14] and BM (**dose escalation phase subjects only**)	X[15]	X		X[16, 17]					
BL-8040 SC injections		X	X[16]	X[16, 17]	X	X	X	X	
Ara-C Chemotherapy[18]				X	X	X	X	X	
Pharmacokinetic (PK) sampling[19]		X		X[16, 17]		X		X	
Leukemic cell apoptosis in BM (Caspase-3 staining/Annexin V analysis)	X			X[16, 17] (Visit 4 only)					
Leukemic blasts (FACS and FISH)[20]		X		X[16, 17]					

Study Procedures	Screening Period	Treatment Period[23]							Follow-up Period[1, 24, 26]
		Monotherapy Period		Combined Therapy Period					
Study Day	**Day -7- to Day 0**	**Day 1/BL**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**	**Up to Day 44**
Study Visit	**1**	**2 / 10**	**3 / 11**	**4 / 12**	**5 / 13**	**6 / 14**	**7 / 15**	**8 / 16**	**9 / 17**
Leukemic cell apoptosis in PB (Annexin V and PI analysis)[21]		X		X[16, 17]					
Adverse events	←	—	—	—	—	—	—	—	→
Concomitant medications	←	—	—	—	—	—	—	—	→

BL= Baseline, ECG = electrocardiogram, ECHO/MUGA = echocardiogram/Multiple Gated Acquisition, ECOG – Eastern Cooperative Oncology Group, TLS = tumor lysis syndrome

1. The follow-up period will start after completion of Ara-C chemotherapy and continue for up to 6 weeks after initiation of salvage chemotherapy with Ara-C, i.e., up to Day 44. The follow-up period will end when a BM biopsy and/or aspirate, performed between Day 20 – 44, provides definite assessment of response to therapy.
2. Physical examination, including weight measurement.
3. To be performed before BL-8040 administration on Days 1-7.
4. Height will be measured at screening only.
5. Vital signs will include blood pressure, pulse rate, oral temperature, O_2 saturation levels and respiration rate. To be performed daily before BL-8040 administration on Days 1-7.
6. Single 12-lead ECG recording at screening. On Days 1, 3 and 7 printed recordings will be collected at pre-dose, 0.5, 1, 2, 4, 8 and 24 hrs post BL-8040 administration. Expansion phase subjects who receive a second treatment cycle will only have ECG recordings on Days 1 and 7, i.e., visits 10 and 16 of the second cycle at pre-dose and 4 hrs post BL-8040 administration..
7. Haematology and biochemistry tests will be performed at least twice per week for the duration of the follow-up period.
8. WBC count (differential and leukemic cell count) will be measured at 4 and 8 hrs post BL-8040 injection.
9. Partial biochemistry (electrolytes and kidney function) will be measured at 4 and 8 hrs post BL-8040 injection. **Sampling for partial biochemistry is not required for expansion phase subjects who receive a second treatment cycle, i.e., on visits 10, 11, 12 and 16.**
10. Coagulation will be evaluated at screening, on Day 1 pre-dose and 24 hrs post-dose, and on Day 7 at 24 hrs post-dose. **Sampling for coagulation is not required for expansion phase subjects who receive a second treatment cycle, i.e., on visits 10 and 16.**
11. In subjects who receive cytoreductive therapy, BM samples will be collected post therapy and prior to BL8040 administration.
12. Bone marrow biopsy and aspiration will be performed on Day 30 (28 days from initiation of salvage chemotherapy) unless, in the opinion of the Investigator, earlier biopsy/aspiration is indicated based on early appearance of blast cells in PB.
13. In subjects who do not show sufficient BM recovery by Day 30 (in absence of leukemia), BM biopsy and aspiration will be repeated 2 weeks later (Day 44) to exclude aplasia.
14. CXCR4 receptor occupancy will be measured in the PB on Days 1 and 3 at pre-dose, 4 and 24 hrs post BL-8040.
15. CXCR4 levels will be measured by IHC in pre- BL-8040 BM biopsy samples and will be analyzed for correlation to efficacy.
16. Subjects participating in the **expansion phase only** will skip Day 2 if their blast counts are ≥ 30,000 and < 50,000/µL and/or their WBC counts are ≥ 50,000 and < 60,000/µL 24 hrs following the 1st dose of BL-8040 and will proceed directly to protocol Day 3. All Day 3 assessments and procedures will be performed with the exception of BL-8040 administration and the following **post-dose** assessments: PK profiling, ECG measurements, WBC count (differential and leukemic cells), partial biochemistry and assessment of CXCR4 receptor occupancy, leukemic blast apoptosis and mobilization. **BM biopsy and/or aspiration must be performed prior to Ara-C administration.**

17. Subjects participating in the **expansion phase only** with blast counts ≥ 30,000 and < 50,000/μL and/or their WBC counts are ≥ 50,000 and < 60,000/μL 24 hrs following the 2nd dose of BL-8040, will undergo all Day 3 assessments and procedures with the exception of BL-8040 administration and the following **post-dose** assessments: PK profiling, ECG measurements, WBC count (differential and leukemic cells), partial biochemistry and assessment of CXCR4 receptor occupancy, leukemic blast apoptosis and mobilization. **BM biopsy and/or aspiration must be performed prior to Ara-C administration.**
18. Chemotherapy will consist of Ara-C **3** g/m^2/day for subjects ≤ 60 years and **1.5** g/m^2/day for subjects > 60 years administered intravenously over 3 hrs, 4 hrs (+/- 1 hr) after BL-8040 administration.
19. Blood samples for BL-8040 PK analysis will be collected on Days 1, 3 and 7 at pre-dose, 0.25, 0.5, 1, 2, 4, 8 and 24 hrs post BL-8040 administration. Samples will also be collected on Day 5 at pre-dose and 0.5 hrs post BL-8040 administration. **PK sampling is not required for expansion phase subjects who receive a second treatment cycle, i.e., on visits 10, 12, 14 and 16.**
20. Leukemic blasts in PB and/or BM aspirate will be assessed by FACS and FISH (subjects with identifiable chromosomal abnormalities in the expansion phase only) analysis on samples collected on Days 1 and 3 (Visits 2 and 4) at pre-dose, 4 and 24 hrs post BL-8040. **Sampling for FACS and FISH analysis is not required for expansion phase subjects who receive a second treatment cycle, i.e., on visits 10 and 12.**
21. Leukemic cell apoptosis will be assessed from PB samples collected on Days 1 and 3 at pre-dose, 4 and 24 hrs post BL-8040. **Sampling for leukemic cell apoptosis is not required for expansion phase subjects who receive a second treatment cycle, i.e., on visits 10 and 12.**
22. Bone marrow biopsies/aspirates will be examined by H&E and FACS analysis for assessment of leukemic cell numbers.
23. At the Investigator's discretion, subjects participating in the expansion phase may be treated with a second treatment cycle if they are considered to have had clinical benefit, but not achieved CR or CRi (Study Visits 10-17). The second treatment cycle will start after clinical response assessment has been completed for the first treatment cycle, i.e., no sooner than Day 30 (± 2 days; Day 28 ± 2 of chemotherapy).
24. Subjects participating in the expansion phase will be followed for up to 5 years after completion of the follow-up period. Sites will contact subjects by telephone at approximately 3 month intervals (± 1 month) after the end of the follow-up period to determine AML status and survival.
25. Blood samples for ADA and complement activation will be collected pre-dose and at 4 hrs post BL-8040 administration on Days 1 and 7. On Day 3 an ADA sample will be collected pre-dose only. In addition, an ADA sample will be collected at the end of the follow-up period (Visit 9). Expansion phase subjects who receive a second treatment cycle will have ADA samples collected during the first treatment cycle only.
26. For expansion phase subjects receiving a second treatment cycle, bone marrow biopsy/aspiration and follow-up assessments following the second treatment cycle will be the same as those following the first treatment cycle (with the exception of sampling for ADA – see footnote 25). Both follow-up periods (Visits 9 and 17) will end when a BM biopsy and/or aspirate, performed between Day 20 – 44 of the relevant cycle, provides definite assessment of response to therapy.

APPENDIX B AML DIAGNOSIS CRITERIA

AML diagnosis is based on WHO classification of myeloid neoplasm and acute [1].

Myeloproliferative neoplasms (MPN)
- Chronic myelogenous leukemia, *BCR-ABL1*–positive
- Chronic neutrophilic leukemia
- Polycythemia vera
- Primary myelofibrosis
- Essential thrombocythemia
- Chronic eosinophilic leukemia, not otherwise specified
- Mastocytosis
- Myeloproliferative neoplasms, unclassifiable

Myeloid and lymphoid neoplasms associated with eosinophilia and abnormalities of *PDGFRA*, *PDGFRB*, or *FGFR1*
- Myeloid and lymphoid neoplasms associated with *PDGFRA* rearrangement
- Myeloid neoplasms associated with *PDGFRB* rearrangement
- Myeloid and lymphoid neoplasms associated with *FGFR1* abnormalities

Myelodysplastic/myeloproliferative neoplasms (MDS/MPN)
- Chronic myelomonocytic leukemia
- Atypical chronic myeloid leukemia, *BCR-ABL1*–negative
- Juvenile myelomonocytic leukemia
- Myelodysplastic/myeloproliferative neoplasm, unclassifiable
- *Provisional entity: refractory anemia with ring sideroblasts and thrombocytosis*

Myelodysplastic syndrome (MDS)
- Refractory cytopenia with unilineage dysplasia
  - Refractory anemia
  - Refractory neutropenia
  - Refractory thrombocytopenia
- Refractory anemia with ring sideroblasts
- Refractory cytopenia with multilineage dysplasia
- Refractory anemia with excess blasts
- Myelodysplastic syndrome with isolated del(5q)
- Myelodysplastic syndrome, unclassifiable
- Childhood myelodysplastic syndrome
- *Provisional entity: refractory cytopenia of childhood*

Acute myeloid leukemia and related neoplasms
- Acute myeloid leukemia with recurrent genetic abnormalities
  - AML with t(8;21)(q22;q22); *RUNX1-RUNX1T1*
  - AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11*
  - APL with t(15;17)(q22;q12); *PML-RARA*
  - AML with t(9;11)(p22;q23); *MLLT3-MLL*
  - AML with t(6;9)(p23;q34); *DEK-NUP214*
  - AML with inv(3)(q21q26.2) or t(3;3)(q21;q26.2); *RPN1-EVI1*
  - AML (megakaryoblastic) with t(1;22)(p13;q13); *RBM15-MKL1*
  - *Provisional entity: AML with mutated NPM1*
  - *Provisional entity: AML with mutated CEBPA*
- Acute myeloid leukemia with myelodysplasia-related changes
- Therapy-related myeloid neoplasms
- Acute myeloid leukemia, not otherwise specified
  - AML with minimal differentiation
  - AML without maturation
  - AML with maturation
  - Acute myelomonocytic leukemia
  - Acute monoblastic/monocytic leukemia
  - Acute erythroid leukemia
    - Pure erythroid leukemia
    - Erythroleukemia, erythroid/myeloid
  - Acute megakaryoblastic leukemia
  - Acute basophilic leukemia
  - Acute panmyelosis with myelofibrosis
- Myeloid sarcoma
- Myeloid proliferations related to Down syndrome
  - Transient abnormal myelopoiesis
  - Myeloid leukemia associated with Down syndrome
- Blastic plasmacytoid dendritic cell neoplasm

Acute leukemias of ambiguous lineage
- Acute undifferentiated leukemia
- Mixed phenotype acute leukemia with t(9;22)(q34;q11.2); *BCR-ABL1*
- Mixed phenotype acute leukemia with t(v;11q23); *MLL* rearranged
- Mixed phenotype acute leukemia, B-myeloid, NOS
- Mixed phenotype acute leukemia, T-myeloid, NOS
- *Provisional entity: natural killer (NK) cell lymphoblastic leukemia/lymphoma*

B lymphoblastic leukemia/lymphoma
- B lymphoblastic leukemia/lymphoma, NOS
- B lymphoblastic leukemia/lymphoma with recurrent genetic abnormalities
  - B lymphoblastic leukemia/lymphoma with t(9;22)(q34;q11.2);*BCR-ABL 1*
  - B lymphoblastic leukemia/lymphoma with t(v;11q23);*MLL* rearranged
  - B lymphoblastic leukemia/lymphoma with t(12;21)(p13;q22) *TEL-AML1 (ETV6-RUNX1)*
  - B lymphoblastic leukemia/lymphoma with hyperdiploidy
  - B lymphoblastic leukemia/lymphoma with hypodiploidy
  - B lymphoblastic leukemia/lymphoma with t(5;14)(q31;q32) *IL3-IGH*
  - B lymphoblastic leukemia/lymphoma with t(1;19)(q23;p13.3);*TCF3-PBX1*

T lymphoblastic leukemia/lymphoma

APPENDIX C AML RESPONSE DEFINITION FOR CLINICAL TRIALS

Responses to AML treatment have been defined using the following criteria developed by an International Working Group [4; 30; 31]:

Category	Definition[a]
Complete remission (CR)[b]	Bone marrow blasts < 5%; absence of blasts with Auer rods; absence of extramedullary disease; absolute neutrophil count > 1.0 x 10^9/L (1000/µL); platelet count > 100 x 10^9/L (100,000/µL); independence of red cell transfusions.
CR with incomplete recovery (CRi)[c]	All CR criteria except for: residual neutropenia (< 1.0 x 10^9/L [1000/µL]) or thrombocytopenia (< 100 x 10^9/L [100,000/µL])
Partial remission (PR)	Relevant in the setting of phase 1 and 2 clinical trials only; all hematologic criteria of CR; decrease of bone marrow blast percentage to 5% to 25%; and decrease of pretreatment bone marrow blast percentage by at least 50%

[a] Definitions of response criteria are based primarily on Cheson 2003 criteria [4].

[b] All criteria need to be fulfilled; marrow evaluation should be based on a count of 200 nucleated cells in an aspirate with spicules; if ambiguous, consider repeat exam after 5 to 7 days; flow cytometric evaluation may help to distinguish between persistent leukemia and regenerating normal marrow; a marrow biopsy should be performed in cases of dry tap, or if no spicules are obtained; no minimum duration of response required.

[c] The criterion of CRi is of value in protocols using intensified induction or double induction strategies, in which hematologic recovery is not awaited, but intensive therapy will be continued. In such protocols, CR may even not be achieved in the course of the entire treatment plan. In these instances, the overall remission rate should include CR and CRi patients. Some patients may not achieve complete hematologic recovery upon longer observation times.

APPENDIX D CAIRO-BISHOP CRITERIA FOR DIAGNOSIS OF TUMOR LYSIS SYNDROME (TLS)

Table 3. Cairo-Bishop Criteria for Diagnosis of Tumor Lysis Syndrome (TLS)

Laboratory TLS
2 or more of the following criteria occurring within 3 days before or 7 days after initiation of chemotherapy in a well-hydrated patient who is receiving a hypouricemic agent:
Uric acid ≥ 8 mg/dL (476 μmol/L) or 25% increase from baseline
Phosphate ≥ 4.5 mg/dL or 25% increase from baseline
Potassium ≥ 6 mEq/L or 25% increase from baseline
Calcium ≤ 7 mg/dL or 25% decrease from baseline
Clinical TLS
Includes the diagnosis of laboratory TLS plus 1 or more of the following findings:
Increased serum creatinine (1.5 times the upper limit of normal)
Cardiac arrhythmia or sudden death
New-onset seizures

Adapted with permission from Cairo MS, Bishop M. Tumour lysis syndrome: new therapeutic strategies and classification. Br J Haematol 2004;127:3–11.

APPENDIX E EASTERN COOPERATIVE ONCOLOGY GROUP PERFORMANCE STATUS

Eastern Cooperative Oncology Group (Zubrod-ECOG)[1,2]	
Description	**Grade**
Fully active, able to carry on all pre-disease activities without restriction.	0
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.	1
Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.	2
Capable of only limited self-care, confirmed to bed or chair more than 50% of waking hours.	3
Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	4

[1]Zubrod, C.G., et al. *Appraisal of Methods for the Study of Chemotherapy of Cancer in Man*. Journal of Chronic Diseases, 11:7-33, 1960.
[2]Oken, M.M., et al. *Toxicity and response criteria of the Eastern Cooperative Oncology Group*. Am J Clin Oncol (CCT) 5: 649-655, 1982

APPENDIX F DECLARATION OF HELSINKI (2008)

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI

Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53th WMA General Assembly, Washington 2002 (Note of Clarification on paragraph 29 added)
55th WMA General Assembly, Tokyo 2004 (Note of Clarification on Paragraph 30 added)
59th WMA General Assembly, Seoul, October 2008

A. INTRODUCTION

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

   The Declaration is intended to be read as a whole and each of its constituent paragraphs should not be applied without consideration of all other relevant paragraphs.

2. Although the Declaration is addressed primarily to physicians, the WMA encourages other participants in medical research involving human subjects to adopt these principles.

3. It is the duty of the physician to promote and safeguard the health of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.

4. The Declaration of Geneva of the WMA binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."

5. Medical progress is based on research that ultimately must include studies involving human subjects. Populations that are underrepresented in medical research should be provided appropriate access to participation in research.

6. In medical research involving human subjects, the well-being of the individual research subject must take precedence over all other interests.

7. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best current interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

8. In medical practice and in medical research, most interventions involve risks and burdens.

9. Medical research is subject to ethical standards that promote respect for all human subjects and protect their health and rights. Some research populations are particularly vulnerable and need special protection. These include those who cannot give or refuse consent for themselves and those who may be vulnerable to coercion or undue influence.
10. Physicians should consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

B. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

11. It is the duty of physicians who participate in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects.
12. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.
13. Appropriate caution must be exercised in the conduct of medical research that may harm the environment.
14. The design and performance of each research study involving human subjects must be clearly described in a research protocol. The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest, incentives for subjects and provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study. The protocol should describe arrangements for post-study access by study subjects to interventions identified as beneficial in the study or access to other appropriate care or benefits.
15. The research protocol must be submitted for consideration, comment, guidance and approval to a research ethics committee before the study begins. This committee must be independent of the researcher, the sponsor and any other undue influence. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration. The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No change to the protocol may be made without consideration and approval by the committee.
16. Medical research involving human subjects must be conducted only by individuals with the appropriate scientific training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional. The responsibility for the protection of research subjects must always rest with the

physician or other health care professional and never the research subjects, even though they have given consent.

17. Medical research involving a disadvantaged or vulnerable population or community is only justified if the research is responsive to the health needs and priorities of this population or community and if there is a reasonable likelihood that this population or community stands to benefit from the results of the research.
18. Every medical research study involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and communities involved in the research in comparison with foreseeable benefits to them and to other individuals or communities affected by the condition under investigation.
19. Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject.
20. Physicians may not participate in a research study involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians must immediately stop a study when the risks are found to outweigh the potential benefits or when there is conclusive proof of positive and beneficial results.
21. Medical research involving human subjects may only be conducted if the importance of the objective outweighs the inherent risks and burdens to the research subjects.
22. Participation by competent individuals as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no competent individual may be enrolled in a research study unless he or she freely agrees.
23. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information and to minimize the impact of the study on their physical, mental and social integrity.
24. In medical research involving competent human subjects, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information. After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.
25. For medical research using identifiable human material or data, physicians must normally seek consent for the collection, analysis, storage and/or reuse. There may be situations where consent would be impossible or impractical to obtain for such research or would pose a threat to the validity of the research.

In such situations the research may be done only after consideration and approval of a research ethics committee.

26. When seeking informed consent for participation in a research study the physician should be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent should be sought by an appropriately qualified individual who is completely independent of this relationship.

27. For a potential research subject who is incompetent, the physician must seek informed consent from the legally authorized representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the population represented by the potential subject, the research cannot instead be performed with competent persons, and the research entails only minimal risk and minimal burden.

28. When a potential research subject who is deemed incompetent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential subject's dissent should be respected.

29. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research population. In such circumstances the physician should seek informed consent from the legally authorized representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research should be obtained as soon as possible from the subject or a legally authorized representative.

30. Authors, editors and publishers all have ethical obligations with regard to the publication of the results of research. Authors have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. They should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results should be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest should be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

31. The physician may combine medical research with medical care only to the extent that the research is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

32. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention, except in the following circumstances:
    - The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists; or
    - Where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm. Extreme care must be taken to avoid abuse of this option.
33. At the conclusion of the study, patients entered into the study are entitled to be informed about the outcome of the study and to share any benefits that result from it, for example, access to interventions identified as beneficial in the study or to other appropriate care or benefits.
34. The physician must fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never interfere with the patient-physician relationship.
35. In the treatment of a patient, where proven interventions do not exist or have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgment it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, this intervention should be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information should be recorded and, where appropriate, made publicly available.

22.10.2008

APPENDIX G CORTICOSTEROID COMPARISON CHART

Corticosteroid Comparison Chart

	Equivalent Glucocorticoid Dose (mg)	Potency relative to Hydrocortisone: Anti-Inflammatory	Potency relative to Hydrocortisone: Mineral-Corticoid	Half-Life: Plasma (minutes)	Half-Life: Duration of Action (hours)
Short Acting					
Hydrocortisone (Cortef, Cortisol)	20	1	1	90	8-12
Cortisone Acetate	25	0.8	0.8	30	8-12
Intermediate Acting					
Prednisone	5	4	0.8	60	12-36
Prednisolone	5	4	0.8	200	12-36
Triamcinolone	4	5	0	300	12-36
Methylprednisolone	4	5	0.5	180	12-36
Long Acting					
Dexamethasone	0.75	30	0	200	36-54
Betamethasone	.6	30	0	300	36-54
Mineralocorticoid					
Fludrocortisone	0	15	150	240	24-36
Aldosterone	0	0	400 +	20	- -

Reference: Adrenal Cortical Steroids. In Drug Facts and Comparisons. 5th ed. St. Louis, Facts and Comparisons, Inc.:122-128, 1997

Commonly Prescribed Replacement Steroid Equivalents

Prednisone		Cortisone		Dexamethasone		Hydrocortisone (Cortef)
5 mg	=	25 mg	=	0.75 mg	=	20 mg