MENARINI RICERCHE

CLINICAL STUDY PROTOCOL

A Phase I/II Study of SEL24 in Patients with Acute Myeloid Leukemia

DIAMOND-01

DUAL-KINASES INHIBITOR AGAINST PIM/FLT3 WITH ORAL INTERVENTION IN ACUTE MYELOID LEUKEMIA

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Protocol Version Summary:

Protocol Version:	Version Date:	Comments:
Version 12	**20 April 2021**	**Submitted to FDA and all RAs and ECs/IRB. Approved by AIFA and ISS, URPL, AEMPS and FDA.**
Version 11.3	**1 July 2020**	**Submitted to FDA on 13Jul2020 (SN 0033, no comments received) and to US sites. Approved by AIFA and ISS and Italian sites**
Version 11.2	**10 June 2020**	**Approved by URPL, AEMPS and Polish/Spanish sites**
Version 11.1	**24 March 2020**	**Submitted to FDA on 2Apr2020 (SN 0032), AIFA, ISS, URPL, AEMPS and to all sites**
Version 11.0	**21 February 2020**	**FDA only; *this version was not submitted to the investigative sites***
Version 10.2	**05 August 2019**	**Submitted to FDA on 9Aug2019 (SN 0028) and to all sites**
Version 10.1	**14 June 2019**	**FDA only; *this version was not submitted to the investigative sites***
Version 10.0	**21 May 2019**	**FDA only; *this version was not submitted to the investigative sites***
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Version 8.0	**26 April 2018**	**Submitted to FDA on 11May2018 (SN 0011) and to all sites**
Version 7.0	**06 December 2017**	**Approved by the FDA on 15Dec2017 and submitted to all sites**
Version 6.0	**21 November 2017**	**FDA only; *this version was not submitted to the investigative sites.***
Version 5.0	**19 April 2017**	**Version issued to amend exclusion criteria and prohibited medication, submitted to all sites**
Version 4.0	**27 July 2016**	**The initial protocol submitted to all sites, under which patient enrollment commenced in March 2017.**

PROTOCOL APPROVAL SIGNATURES

Sponsor's Approval:
This study will be conducted in compliance with International Conference on Harmonisation (ICH) guidelines on Good Clinical Practice (GCP), the Declaration of Helsinki (with amendments), and in accordance with local legal and regulatory requirements.

This protocol has been approved by Menarini Ricerche S.p.A.

Signature:[redacted]..... **Date**:....[redacted]

[redacted]
Menarini Ricerche S.p.A.

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Investigator's Approval:
I have read this protocol and agree that it contains all the necessary details for carrying out this study. I will conduct the study as described and will complete the study within the time designated. I verify that I am suitably qualified by education, scientific and medical training and experience to conduct the study. Documentation of my qualifications and professional affiliations are contained in my up-to-date curriculum vitae provided to the Sponsor.

I will provide the supplied copies of the protocol, including future protocol amendments, and all information relating to non-clinical, and clinical experience when available (e.g. in updated editions of the Investigator's Brochure), to all staff in my unit involved in the conduct of this study. I will discuss this material with them to ensure that they are fully conversant with the investigational medicinal product and study design, and that they will handle the data and information generated in the study confidentially.

I will conduct the study in accordance with Good Clinical Practice, the Declaration of Helsinki, and the moral, ethical and scientific principles that justify medical research. The study will be conducted in accordance with the relevant laws and regulations relating to clinical studies and the protection of patients. All patients will be informed comprehensively about the nature of the study and will give their written consent to participate before entry into the study. They will be informed that they may withdraw from the study at any time. I will use only the information sheet and consent form approved by the Sponsor and the Ethics Committee/Institutional Review Board for this study. I will supply the Sponsor with any material written by myself (e.g. summary of study) which is given to the Ethics Committee/Institutional Review Board in support of the application.

Where applicable, the patient information contained in clinic records, reports and manuscripts will be transcribed to the case report forms (the case report form may be the original source document for specified items). Either I or an appointed person will attest to the authenticity of the data and accuracy and completeness of the transcription by signing the case report form. I agree to the audit and monitoring procedures that involve verification of such study records against original records. Should it be requested by government regulatory agencies, I will make available additional background data from my records, and where allowed, from the hospital or institution where the study was conducted.

I understand that the case report forms and other data pertinent to this study are the property of Menarini Ricerche S.p.A. and are confidential. I will supply Menarini Ricerche S.p.A. (or their delegates) with the study data in such a way that the patient cannot be personally identified.

Investigator: _____ _____
Signature Date

Print Name: _____

Institution Name: _____

Institution Address: _____

OTHER CONTACT INFORMATION

Full contact details for each Investigational site, the Sponsor (including appropriate medical monitor contact number), and key coordinating and operational personnel will be maintained in the Trial Master File (TMF) and in each Site Study File.

PROTOCOL SYNOPSIS

Protocol No:
CLI24-001

Study Title:
A Phase I/II Study of SEL24 in Patients with Acute Myeloid Leukemia

SEL24/MEN1703 Investigational Product:
SEL24/MEN1703 will be supplied as drug substance powder in a gelatin capsule (non-formulated API in capsule), as well as formulated drug product in a gelatin capsule. Details of the Investigational Product provided during Part 1 are reported in Table 3. Formulated drug only will be provided for Part 2.

Phase of Development:
Phase I/II

Number of Sites:
Five sites in Part 1. Approximately additional 10-15 sites may be added as required to meet the recruitment needs of the study in Part 2.

Number of Patients:
Twenty-five evaluable patients were enrolled in Part 1 (dose escalation).
In Part 2, the first expansion cohort ("all-comers") 23 unselected relapsed or refractory AML patients have been enrolled. An additional expansion cohort ("IDH mutants") will enroll approximately 20 relapsed or refractory AML patients harboring an IDH mutation (either IDH1 or IDH2).

Table 1: Part 1 Study Objectives and Endpoint (Assessment)

Objective	Endpoint (Assessments)
Primary:	
• To estimate the MTD or MAD and determine the RD of SEL24/MEN1703 for Part 2	• DLT evaluation at the end of one treatment cycle for each dose level
Secondary:	
• To assess the safety and tolerability of SEL24/MEN1703	• The number and frequency of AEs, safety laboratory, vital signs and ECG assessments
• To assess anti-leukemic activity of SEL24/MEN1703	• Assessment of bone marrow and peripheral blast % and other assessments of clinical benefit including ORR (CR, CRi, CRh and MLFS), PR rate, DoR, RFS, EFS and OS
• To evaluate the PK profile of SEL24/MEN1703 and its metabolites as appropriate	• Assessment of PK variables, including C_{max}, AUC and t½
Exploratory:	
• To assess the PD activity of SEL24/MEN1703 • To assess the genetic profile of AML cells	• Flow cytometry assessment of relevant biomarkers (e.g. pS6)

Objective	Endpoint (Assessments)
	• Analysis of relevant mutations in peripheral blasts and bone marrow by using Next Generation Sequencing and/or qRT-PCR

Table 2: Part 2 Study Objectives and Endpoint (Assessment)

Objective	Endpoint (Assessments)
Primary:	
• To further characterize the safety profile of single agent SEL24/MEN1703	• The number and frequency of AE, safety laboratory, vital signs and ECG assessments
Secondary:	
• To assess anti-leukemic activity of single agent SEL24/MEN1703	• Assessment of bone marrow and peripheral blast % and other assessments of clinical benefit including ORR (CR, CRi, CRh and MLFS), PR rate, DoR, RFS, EFS, OS , transfusion conversion rate, transfusion maintenance rate, HSCT rate
• To evaluate the PK profile of SEL24/MEN1703 and its metabolites, as appropriate	• Assessment of PK variables, including C_{max}, AUC and t½
Exploratory:	
• To assess the PD activity of SEL24/MEN1703 • To assess the genetic profile of AML cells	• Flow cytometry assessment of relevant biomarkers (e.g. pS6) • Analysis of relevant mutations in peripheral blasts and bone marrow by using Next Generation Sequencing and/or qRT-PCR

Study Design:
This is a Phase I/II, open-label, multi-center, dose escalation study to estimate the MTD (or MAD) of SEL24/MEN1703 in patients with AML. At the end of Part 1 a RD of SEL24/MEN1703 has to be selected for further evaluation in Part 2. In Part 2 the safety and anti-leukemic activity of SEL24/MEN1703 will be further assessed in the study population.
SEL24/MEN1703 is taken orally once daily (QD) for 14 consecutive days over a 21-day treatment cycle.

NOTE: At the time this protocol Version 12.0 is running, Part 1 has been completed. Procedures to be followed along Part 1 are reported below for completeness

Part 1 was initially designed with an accelerated titration design (ATD) for the first 4 cohorts. The study design has then been revised to follow a 3+3 design from Cohort 2 (50mg) onwards in order to assess for DLT, adverse events and adequate PK profile data from at least 3 patients in each dose level (see Table 3). Patients will be enrolled to cohorts in a sequential fashion following the dosing regimen and will be observed for safety and tolerability during Cycle 1, prior to permitting dose escalation to the next dose level (cohort). From Cohort 4 onwards there will be a mandated recruitment interval of at least 7 days for each patient enrolled.

Should a patient experience a toxicity which qualifies as a DLT during Cycle 1 in any cohort, that cohort will be expanded to enroll up to a maximum of 6 patients to further assess for toxicity prior to considering the next dosing step.

Cohort 4 (100mg) repeated twice due to the introduction of a new formulated SEL24/MEN1703 IMP. To distinguish between the original cohort and the repeat cohort at the same dose level, the repeat cohort is named Cohort 4F.

No recruitment interval is applied in the Cohort 4F where formulated SEL24/MEN1703 IMP is introduced, as this dose level has already been explored with the non-formulated SEL24/MEN1703 API in capsules. Upon the successful completion of the repeat Cohort 4F with the formulated IMP, the study will progress to the next Cohort 4b and onwards, according to the study design, using SEL24/MEN1703 formulated IMP only. In particular it has been shown that, overall, PK disposition of SEL24/MEN1703 (absorption, distribution and elimination) following the administration of formulated IMP is in line with that observed with non-formulated IMP. This evidence further supports that no dose adjustment is warranted with formulated IMP.

Patients who commenced dosing with the non-formulated SEL24/MEN1703 API in capsules and who are still on treatment, will continue receiving this formulation until treatment withdrawal per protocol.

Recruitment and dose escalation for each cohort in Part 1 is described in Table 3.

Table 3: Patients exposure along Dose Escalation Steps

Cohort	Dose Level	Patients treated with non-formulated IMP	Patients treated with Formulated IMP	Patients who experienced DLT
1	25 mg	2*	0	1
2	50 mg	3	0	0
3	75 mg	3	0	0
4	100 mg	3	0	0
4F	100 mg	0	3	0
4b	125 mg	0	7*	1
5	150 mg	3	1	3

* One patient not DLT evaluable

In Part 1, according to a 3+3 design, the MTD is defined as the highest dose at which no more than 1 in up to 6 patients experience a DLT during Cycle 1. In Cohort 5, provided the MTD is not exceed with 125 mg and to further characterize the safety profile of MEN1703, up to 4 additional patients will be treated at 150 mg formulated IMP according to a Bayesian modified toxicity probability interval (mTPI) with a target toxicity rate ≤ 25%. Should none of these 4 patients experience a DLT, higher dose levels may be considered and will be subject to a protocol amendment.

The DMC consisting of the Principal Investigator at each site, plus the Medical Monitor and Sponsor representatives, will review all safety data available during Cycle 1 for each cohort and assess for DLT during Part 1 of the study. Experts in the evaluation of PK and PD data may participate in the DMC meetings to help inform the next dose escalation step. Further details of DMC procedures/participants in the different parts of the study are reported in the ad-hoc charter.

The dose escalation rules to be followed during Part 1 of the study are described in Table 4.

Table 4: Part 1 Dose Escalation Rules

No. of evaluable patients with DLT at a given dose level	Dose escalation rules
0	Proceed to next dose level
≥2	Dose escalation will be stopped. This dose level will be declared the MAD (highest dose administered). Additional patients will be entered at the **previously highest** dose level with <33% DLTs, to a maximum of 6, if less than 6 patients were treated previously at that dose. NOTE: at the 150 mg dose, additional 4 patients will be tested targeting ≤ 25% toxicity rate as described above.
1	Proceed to enter 6 patients at the dose level: - if no further patients experience DLT, proceed to the next dose level - if 1 or more of the additional patients enrolled suffer DLT, then dose escalation is stopped, and this dose is declared the MAD which has exceeded the MTD. Additional patients will be entered at the **previously highest** dose level with <33% DLTs, to a maximum of 6, if less than 6 patients were treated previously at that dose - confirmation that a dose level exceeds the MTD may be obtained before completing enrollment of 6 patients
≤1 out of 6 at highest dose level administered	This is generally the MTD/RD. At least 6 patients must be entered at the proposed recommended dose level for Part 2.

In addition to DLT evaluation, there will be ongoing assessment of all adverse events (AEs) and serious adverse events (SAEs), changes in laboratory values (clinical chemistry, hematology, coagulation, lipid profile, and urinalysis) and electrocardiograms as further measures of safety and tolerability. All safety parameters will continue to be assessed beyond Cycle 1. Note that where the DMC is concerned about any safety signal in the study e.g. a trend in Grade 2 events, they may recommend a cohort is expanded to evaluate up to 6 patients, in order to explore this safety signal further.

The highest SEL24/MEN1703 dose level considered to be well tolerated, and to have optimal PK and PD characteristics, will be called the RD and will be selected for further evaluation in Part 2.

Part 2 foresees the enrollment of patients to be treated at the RD (identified in Part 1 based on recommendation by the DMC) in the expansion cohorts defined below:

- The expansion cohort in 20 unselected relapsed or refractory AML patients patients ("***all-comers***")

NOTE: At the time this protocol version 12.0 is running, the expansion cohort in *"all-comers"*AML patients has been already completed with 23 patients enrolled.

- An additional expansion cohort ("***IDH mutants"***) will enroll approximately 20 relapsed or refractory AML patients harboring an IDH mutation (either IDH1 or IDH2).

The evaluable patients treated at the RD in Part 1 or in Part 2 may be also retrospectively included in exploratory safety/efficacy pooled analysis, including patients with comparable inclusion criteria.

Considering that IDH inhibitors are approved/available only in some of the participating countries, it is anticipated that the study will enroll both IDH inhibitor pre-treated and IDH inhibitor naïve patients. For this reason, the recruitment will aim to have a balanced distribution across the two sub-populations to explore the differences in SEL24/MEN1703 activity between pre-treated and IDH inhibitor naïve patients, if any.

Retrospective correlations between the clinical activity of SEL24/MEN1703 and relevant disease markers (e.g. CD25 expression, FLT3 mutational status, IDH1/IDH2 mutational status, others) may be included in the statistical analysis plan.

In both Parts of the study, the criteria for retreatment described in Section 4.4 must be met prior to proceeding to administer a further cycle of treatment.

Dose Limiting Toxicity:
DLT events for dose escalation decisions will be assessed to the end of Cycle 1 for each patient in each cohort, except in the case of protracted neutropenia in the absence of active AML, where evaluation of the event must be conducted over 42 days. Ongoing safety events beyond Cycle 1 will be reviewed across all cohorts during the study to help inform dose escalation decisions.

AEs will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) V4.03. The AEs listed below will be considered as DLT unless they are clearly and incontrovertibly attributable to the underlying disease or to an extraneous cause:

- Grade 5 toxicity
- Grade 4 neutropenia lasting ≥42 days from the start of the therapy cycle in absence of evidence of active AML (<5% blasts)
- Grade 3 or 4 non-hematologic toxicity, except:
  - Alopecia;

- Grade 3 fatigue, asthenia, anorexia, fever, or constipation;
- Grade 3 nausea, vomiting, or diarrhea not requiring tube feeding, TPN, or hospitalization;
- Infection, bleeding, or other expected direct complications of cytopenia due to active leukemia;
- Grade 3 or 4 electrolyte imbalances that respond to correction i.e. return to ≤Grade 2, within 48 hours (h) from correction's onset;
- Grade 3 increase in aspartate aminotransferase (AST) and/or, alanine aminotransferase (ALT) and/or alkaline phosphatase (ALP) recovering ≤Grade 2 within 7 days.

Only **clinically significant** abnormalities in laboratory findings, physical examination, vital signs, weight or ECG (see Section 7.2) will be considered for DLT assessment, according to the protocol definition.

Inclusion/Exclusion Criteria:

Inclusion Criteria

Patients are eligible to be included in study if they meet all of the following criteria:

1. Patient with diagnosis of AML (i.e. ≥20% blasts in bone marrow or peripheral blood) harboring IDH1 or IDH2 mutation (as per local assessment).
2. Provide written informed consent prior to Screening.
3. Male or female patients, age ≥18 years old.
4. Patient has no standard therapeutic options available (including IDH inhibitors where approved) and has:
   a) Relapsed AML unsuitable for intensive chemotherapy;
   b) Primary refractory AML unsuitable for intensive chemotherapy;

   Clarification note: Patients naïve to IDH inhibitor are eligible ONLY if no IDH inhibitors are approved/available in the country/site where they are enrolled.

5. ECOG Performance Status 0, 1 or 2.
6. Adequate organ function at Screening, including:
   a) Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤2.5X the upper limit of normal (ULN);
   b) Total bilirubin ≤2X ULN;
   c) Creatinine clearance ≥40 mL/min (Cockcroft-Gault formula) (see Appendix B);
   d) Left ventricular ejection fracture (LVEF) ≥40% as per local assessment practice.
7. A female of childbearing potential, defined as any female who has experienced menarche and who has not undergone successful surgical sterilization or is not postmenopausal (i.e. has serum follicle stimulating hormone level ≥30 IU/L in the absence of hormone replacement therapy, or complete absence of menses for at least 12 consecutive months which is not due to medication), must have a negative pregnancy test within 7 days prior to receiving study drug.
8. Sexually active male or female patients of childbearing potential are eligible providing that:

Female:

- Agrees to use an effective method of birth control as applicable per local law that both results in a Pearl index < 1 and is considered highly effective as defined by the Clinical Trial Facilitation Group (e.g. combined estrogen and progestogen containing hormonal contraception, progestogen-only hormonal contraception, intrauterine device, intrauterine hormone-releasing system, vasectomized partner, total sexual abstinence or bilateral tubal occlusion)*.
- Undergoes a pregnancy test at Day 1 of each treatment cycle with a final test to be taken when no relevant drug systemic exposure is expected (i.e. 30 days from the last study drug administration).

Male:

- Agrees to use an effective contraceptive method (condom) during treatment and until the end of relevant systemic exposure. Females of childbearing potential that are partners of male study participants have to observe the same birth control indications that apply to female participants.

** Hormonal contraceptives are allowed as pre-clinical evaluation of SEL24/MEN1703 confirmed a low interaction between SEL24/MEN1703 and the most common active principles used for this purpose.*

Exclusion Criteria

Patients are not eligible to be included in study if they meet any of the following criteria:

1. Received anti-cancer treatments (including cytotoxic chemotherapy, radiotherapy, hormonal therapy, biologic, immunotherapy or investigational drugs) within 14 days or 5 half-lives (whichever is longer) before the first dose of study drug.
2. Prior treatment with a PIM inhibitor.
3. Hyperleukocytosis (leukocytes >30 x10^9/L) immediately prior to the first dose of study drug and/or clinical concerns of leukostasis.
   Note: *Patients may undergo leukapheresis according to routine practice before the first dose of study drug; where hydroxyurea is used prior to receiving study drug, it may be continued up to Cycle 1, Day 21, although Investigators are asked to stop treatment prior to the first dose of study drug or before Day 7, wherever possible.*
4. Clinically significant active central nervous system (CNS) leukemia.
   Note: *Previously treated and controlled CNS leukemia and ongoing standard CNS prophylaxis (e.g. with intrathecal cytarabine) is acceptable.*
5. Patients who have undergone major surgery within 1 month prior to first dose of study drug.
6. Hematopoietic stem cell transplant within 4 months of first dose of study drug.
7. Requires systemic immune-modulating therapy (regardless of dose) for the prophylaxis or treatment of GVHD.
8. Evidence of ongoing and uncontrolled systemic bacterial, fungal, or viral infection, with the exception of patients with documented Grade CTCAE ≤2 infections with evidence of improvement or without evidence of worsening infection.

9. Known positive serology for human immunodeficiency virus (HIV).
10. Ongoing drug-induced liver injury, known chronic active hepatitis C (HCV) infection, known chronic active hepatitis B (HBV) infection, alcoholic liver disease, non-alcoholic steatohepatitis, primary biliary cirrhosis, extrahepatic obstruction cause by cholelithiasis, cirrhosis of the liver, or portal hypertension. Participants with history of chronic HBV and HCV infection are eligible if disease is stable and sufficiently controlled as per investigator's judgment.
11. Ongoing drug-induced pneumonitis.
12. Ongoing inflammatory bowel disease.
13. Pregnancy or breastfeeding.
14. Concurrent participation in another therapeutic clinical study.
15. Ongoing toxicity from any prior anti-cancer therapy that has not resolved to Grade 1 or less prior to the first dose of study drug.
16. Received an agent known to be a sensitive CYP2D6 substrate or a CYP2D6 substrate with a narrow therapeutic range, a strong or moderate CYP2D6 inhibitor, or a BCRP inhibitor within 7 days or a period corresponding to 4-5 half-lives of the agent, prior to the first dose of study drug.
17. Cardiac dysfunction defined as myocardial infarction within 6 months of study entry, New York Heart Association (NYHA) Class III or IV heart failure, uncontrolled dysrhythmias or poorly controlled angina.
18. Are receiving any active treatment for thrombosis.
19. History of serious ventricular arrhythmia (e.g. VT or VF, ≥3 beats in a row), or QT interval corrected for heart rate (QTc) ≥480 ms.
    Note: *QTc values up to 500 ms will be acceptable where patient's medical history e.g. bundle branch block, is known to cause mild QTc prolongation and the condition is well controlled.*
20. Any disease, syndrome or condition which may affect significantly drug intake via oral route.
21. Any other prior or current medical condition, intercurrent illness, surgical history, physical or 12-lead electrocardiogram (ECG) findings, laboratory abnormalities, or extenuating circumstance (e.g. alcohol or drug addiction) that, in the investigator's opinion, could jeopardize patient safety or interfere with the objectives of the study.

IMP Administration and Duration of Treatment:
SEL24/MEN1703 will be taken orally once daily for 14 consecutive days over a 21-day treatment cycle.

Patients must be informed that a SEL24/MEN1703 photosensitivity/phototoxicity effect cannot be excluded. For this reason, patients should minimize or avoid exposure to natural or artificial sunlight (tanning beds or UVA/B treatment) during the entire study period. If patients need to be outdoors when taking SEL24/MEN1703, they should wear loose-fitting clothes that protect skin from sun exposure and discuss other sun protection measures with the investigator. If a sunburn like reaction or skin eruption occurs, patients should contact the investigator.

Throughout the study, treatment with SEL24/MEN1703 may continue until the occurrence of one of the following events, whichever comes first:

- Patient withdrawal of consent.
- Disease progression.
  Note: *Patients with disease progression may continue to receive SEL24/MEN1703, if in the opinion of the Investigator, they remain clinically stable and may be deriving potential clinical benefit from SEL24/MEN1703 and it is not considered detrimental to the patient to continue study treatment.*
- Treatment delay of more than 2 weeks for reasons other than toxicity (see Section 4.4).
- Occurrence of an unacceptable toxicity (see Section 4.4).
- Requirement for treatment with prohibited medication (see Section 6.9.2).
- Treatment non-compliance.
  Note: *Treatment non-compliance will be based on patient enquiry and SEL24/MEN1703 capsule count on return of used IMP to pharmacy. In Part 1, it will be defined as missing more than 2 doses in a 14-day dosing schedule in Cycle 1. After Cycle 1 and throughout Part 2, treatment compliance will be assessed on a case-by-case basis.*
- Study non-compliance.
  Note: *Each patient's continued willingness to attend study visits and undergo study assessments will be assessed on a case-by-case basis.*
- Investigator decision that it is in the patient's best interest to withdraw from the study.

Continuation of the study treatment may be discussed between the Investigator and the Sponsor on a case by case basis. The DMC may also advise on the suitability of an individual patient to continue to receive study treatment.

Study Assessments:

Safety

Adverse events, clinical chemistry, hematological, coagulation, lipid profile and urinalysis parameters will be assessed. All clinical AEs and laboratory abnormalities will be graded according to NCI CTCAE V4.03. DLT, SAEs and AEs leading to treatment discontinuations will be determined.

Patients will also undergo regular physical examination, vital sign, ECG and urinalysis assessments.

Disease assessment

Disease assessment will involve evaluation of leukemic blast proportion in the bone marrow. Hematologic parameters from the routine local assessments including blast percentage (where applicable), absolute neutrophil count (ANC), platelet count, and other relevant parameters such as transfusion dependence will also contribute to this assessment. Evaluation of disease status will be performed at the time-points described in the Schedule of Study Assessment (Table 5). To note, disease assessment must be performed as soon as the peripheral lab results become consistent with an objective response. Disease assessment will also include an aliquot of bone marrow aspirate/biopsy that will be centrally stored for future analysis (e.g. minimal residual disease), if any.

In case bone marrow aspirate/biopsy is consistent with CRi or better response, but still a minimal percentage of peripheral blasts is detected, the response assessment can be postponed up to 2 weeks and will be based on repeated peripheral blood results and last bone marrow aspiration results.

Transfusion conversion rate and transfusion maintenance rate

Starting from Protocol V12.0, information about transfusion dependency will be collected and evaluated among study endpoints. For the purpose of defining transfusion conversion rate and transfusion maintenance rate, transfusion status (independent Vs. dependent) at baseline period and post-baseline period are defined as follows for subjects who took at least one dose of study drug:

Baseline transfusion status:

- Baseline period is defined as the period from 28 days prior to the first dose to 28 days post first dose (C2D7). For subjects who are on treatment <28 days, baseline period is from 28 days prior to the first dose (in the event that this information is not available the ICF signature date will be exploited as baseline period start) until the end of treatment.
- Subjects are classified as baseline transfusion independent if there is no red blood cells (RBC) or platelet transfusions within the baseline period; otherwise, the subject is to be considered as baseline transfusion dependent.

Post-baseline transfusion status:

- Post-baseline period is defined as the period from 29 days post first dose (day after C2D7) until last dose.
- For subjects who are on treatment ≥84 days (C5D1 or more), subjects are classified post-baseline transfusion independent if there is one consecutive 56 days period without any RBC or platelet transfusion in the post-baseline period.
- For subjects who are on treatment >28 days (beyond C2D7) but <84 days (up to C4D21), post-baseline transfusion status is not evaluable.
- Otherwise, the subject is considered post-baseline transfusion dependent.

Both transfusion conversion rate and maintenance rate apply to subjects who have evaluable post-baseline transfusion status.

Transfusion conversion rate is defined as the number of subjects who were transfusion dependent at baseline period but become transfusion independent at post-baseline period divided by the total number of subjects who were transfusion dependent at baseline period. Transfusion maintenance rate is defined as the number of subjects who were transfusion independent at baseline period and still maintain transfusion independent at post-baseline period divided by the total number of subjects who were transfusion independent at baseline period.

Allogeneic hematopoietic stem cell transplant (HSCT) rate

Allogeneic HSCT rate is defined as the percentage of subjects undergoing allo-SCT during the study period. MRD status will be recorded immediately prior to the transplant and after the procedure whenever a bone marrow aspirate/biopsy will be collected (recommended every 2 months unless differently indicated by the treating physician based on actual patient's parameters).

In the event a patient undergoes allogeneic HSCT, the following information will be recorded: a) date of transplant; b) HLA match type (HLA-identical sibling, syngeneic, HLA-matched other relative, HLA-

mismatched relative, Unrelated donor); c) source of stem cells (Bone marrow, peripheral blood, cord blood, others); d) conditioning regimen (myeloablative, non-myeloablative).

Pharmacokinetics

The PK profile of SEL24/MEN1703 and its metabolites (as appropriate) will be evaluated by analysis of concentration levels in plasma. Evaluation of CYP2D6 phenotyping will be carried out. Results will be reported separately. Blood sampling will be performed as described in the Schedule of Study Assessment (Table 5). Left over sample aliquots may be analyzed for metabolite identification purposes. The results of the metabolite identification analysis will be reported separately.

Pharmacodynamics

The PD activity of SEL24/MEN1703 will be assessed by changes between pre- and post-treatment levels of relevant biomarkers e.g. pS6 in peripheral blood by using flow cytometry. Blood sampling for this assessment will be performed as described in the Schedule of Study Assessment (Table 5). Left over sample aliquots may be used for future biomarker analysis which is relevant to the development of SEL24/MEN1703 in AML.

Genetic profile of AML cells

The genetic profile of AML cells of each patient will be performed at the time-points described in the Schedule of Study Assessment (Table 5) by using Next Generation Sequencing and/or qRT-PCR. The mutational status of patients before and after treatment with SEL24/MEN1703 will be assessed by the analysis of a panel of relevant AML mutated genes in bone marrow. Left over sample aliquots and aliquots of bone marrow aspirates/biopsy may be used for future biomarker analysis which is relevant to the development of SEL24/MEN1703 in AML.

Statistical Methods:

This is a preliminary study with a limited number of patients, which is being performed primarily to assess safety. The sample size for this study was determined for both clinical and statistical study design considerations.

Part 1 of the study ran according to the standard "3+3" design.[1,2]. At the 150 mg dose cohort, up to 4 additional patients were to be treated with formulated IMP according to a Bayesian modified toxicity probability interval (mTPI) with a target toxicity rate ≤ 25%. Safety data have been reviewed prior to progress with additional cohort at higher dose and wereto be subject to a protocol amendment.

Part 2 permits further evaluation of the safety and tolerability of the RD of SEL24/MEN1703 in the expansion cohorts defined above.

Statistical analysis will be performed through descriptive statistics only and separately for the two different cohorts *("all-comers"* and *"IDH-mutant"*).

The evaluable patients treated at the RD in Part 1 or in Part 2 may be also retrospectively included in exploratory safety/efficacy pooled analysis, including patients with comparable inclusion criteria.

On-going safety will be assessed regularly by the DMC during Part 2 and at a minimum when 6 new patients have been dosed (to end Cycle 1) or every 2 months, whichever comes first. No dose escalation steps will be permitted in Part 2.

Demographic data will be displayed, and summary statistics will be used to describe the study population.

Safety data will be tabulated for all patients. Laboratory parameters and adverse events will be included. Adverse events will be tabulated by body system, severity and relation to therapy.

Anti-leukemia activity data will be tabulated.

Table 5: Schedule of Study Assessments (14 days SEL24/MEN1703 treatment in 21-day cycles)

Cycle	Screening ≤28-days	Cycle 1								Cycle 2			Cycle 3 onwards		Final Study Visit[17]	Follow Up[18]
Visit		**D1**	**D2**	**D3&4**	**D7 (±1)**	**D14 (±1)**	**D15**	**D17**	**D19**	**D1 (±2)**	**D7 (±1)**	**D14 (±1)**	**D1 (±2)**	**D14 (±1)**		
Demographics	X															
Medical history	X															
Inclusion/exclusion checks	X															
FSH and/or Pregnancy test[1]	X	X								X			X		X	
ECOG PS	X									X			X		X	
Vital signs[2]	X	X								X			X		X	
Physical examination[3]	X	X								X			X		X	
Clinical chemistry[4]	X	X	X	X	X	X				X	X	X	X	X	X	
Hematology[4]	X	X	X	X	X	X				X	X	X	X	X	X	
Coagulation[4]	X	X	X	X	X	X				X	X	X	X		X	
Lipid profile[4]	X	X				X				X		X	X		X	
Peripheral blasts[5]	X	X				X						X		X	X	
Urinalysis	X	X								X			X		X	
Electrocardiogram[6]	X	X			X					X			X		X	
Echocardiogram (or MUGA scan)	X															
Bone marrow aspirate/biopsy[7]	X												(X)§		(X)	
Disease evaluation[8]													(X)§		(X)	
The genetic profile of AML cells[9]	X												(X)§		(X)	
PD biomarker blood sampling[10]	X	X				X				X		X	X§	X§		
CYP2D6 phenotyping[11]	X															
CD25 Expression[12]	X															
Mutational Status[13]	X															
AML Karyotypic analysis	X															
Adverse events		X	X	X	X	X				X	X	X	X	X	X	
Concomitant medication	X	X	X	X	X	X				X	X	X	X	X	X	
Transfusion status	X	X	X	X	X	X				X	X	X	X	X	X	
SEL24/MEN1703 administration[14]		X - once daily dosing for 14 consecutive days in 21-day cycles														
PK sampling (blood)[15]		X	X		X	X	X	X	X	X	X	X	X	X		
PK (urine collection)[16]		X	X													
Follow-up assessments																X

General instructions:

- Informed Consent must be obtained using the current version of the PIS/ICF prior to commencing Screening.

- On dosing days, assessments should be performed prior to SEL24/MEN1703 dosing unless specified otherwise; tolerance windows for specific assessments are described below.
- (X) denotes an optional sample; please refer to Footnotes.
- X[§] denotes a sample not taken at every cycle; please refer to Footnotes.
- Additional assessments may be performed as clinically indicated.

Footnotes:

1 A pregnancy test is required within 7 days prior to receiving study drug. Pregnancy test may be alternatively carried out at C1D1 visit prior to first SEL24/MEN1703 administration; results of the test should be available prior to receiving study drug. Additionally, a pregnancy test is required on the first day of each study cycle and at the Final Study Visit. If the Final Study Visit is performed before 30 days has elapsed from the last study drug administration, the pregnancy test shall be postponed when 30 days (+7 d tolerance) from the last study drug intake is elapsed (i.e. when no relevant drug systemic exposure is expected). A negative pregnancy test may be confirmed by urine or blood test. Where a urine test is positive or equivocal, a blood test must be performed to confirm the result. Patients requiring confirmation of post-menopausal status will have FSH levels assessed at Screening.

2 Vital signs include temperature, systolic blood pressure, diastolic blood pressure, heart rate and respiratory rate.

3 Physical examination includes height and weight at Screening and only weight at the start of each cycle. After Screening, further assessments may be symptom-directed.

4 For complete list of Clinical chemistry, Hematology, Coagulation, and Lipid profile parameters please refer to Appendix E. Coagulation parameters may be assessed from the Hematology sample. Should a patient develop coagulation abnormalities at any point during the study, a comprehensive evaluation of coagulation abnormalities will be performed immediately which may include, but not be limited to repeat PT/INR, APTT, fibrinogen, D-dimer, plus a peripheral blood smear, thrombin time, to be evaluated by the Investigator in conjunction with the patient's medical history, a physical examination and concomitant medication review. Repeat testing may be performed as clinically indicated, which may include additional parameters or time-points (please also refer to Appendix E).

5 Assessment of blasts in peripheral blood will be carried out at Screening, C1 D1 pre-dose, C1 onwards at D14 (or last day of dosing in each cycle; -2 d tolerance from C3 onwards), and FSV. This assessment may be performed from the Hematology sample.

6 At C1 D1, the electrocardiogram assessment will be carried out pre-dose and at 4-6 h post dose.

7 Bone marrow aspirate/biopsy shall be taken at the following time points: at Screening, either as soon as peripheral lab results become consistent with an objective response or at C3 D1 whichever comes first, at a recommended frequency of every 2 cycles thereafter e.g. C5 D1, C7 D1, etc. (-2 d tolerance) or as clinically indicated, at relapse and FSV. In case of AML relapse following response to SEL24/MEN1703, a bone marrow aspirate/biopsy is highly recommended, whenever possible. Time-points described as (X)[§] are recommended every 2 cycles, but not mandatory. Patients may not have the FSV assessment performed where they already have had a bone marrow assessment in the last month or have progressive disease. A bone marrow differential will be performed locally. An aliquot of bone marrow aspirate/biopsy will be centrally stored for future analysis (e.g. minimal residual disease), if any. Please refer to the Lab Manual for full details on bone marrow aspirates/biopsy collection, time-points, processing, storage and shipment.

8 Disease evaluation will be performed at every time-point (excluding Screening) where a bone marrow aspirate/biopsy is taken.

9 Bone marrow aspirate/biopsy taken during the study will be tested centrally for the genetic profile of AML cells. Please refer to the Lab Manual for full details on sample collection, time-points, processing, storage and shipment.

10 Blood sampling for PD biomarker assessments will be taken at Screening, C1 D1 pre-dose, C1 D1 2-6h post-dose, C1 D14 2-6h post-dose, C2 D1 pre-dose, C2 D14 2-6h post-dose, C3 D1 pre-dose, C3 D14 2-6h post-dose. All sample times are approximate and every effort should be made to take the samples as close to the specified time given and, where relevant, contemporaneously with blood sampling for PK assessments. For the C1 D1and D14 a ±30 min window is allowed. Please refer to the Lab Manual for full details on PD biomarker sample collection, time-points, processing, storage and shipment.

11 CYP2D6 phenotyping will be assessed centrally on a blood sample collected at Screening.
12 CD25 expression will be assessed centrally on an aliquot of blood sample for PD biomarker assessment taken at Screening.
13 Mutational status (including at least FLT3 and IDH mutations) will be assessed locally at Screening.
14 SEL24/MEN1703 will be given once daily on D1-14 over 21-day treatment cycles. Doses shall be taken on an empty stomach (at least 2 hours after and 1 hour before eating).
15 Blood samples for plasma PK analysis will be taken at C1 D1 pre-dose, 0.5, 1, 2, 4, 6, 8, 10-14 and 24 h (C1 D2 pre-dose), C1 D7 at 4 and 8 h post dose, C1 D14 (or last day of dosing in cycle) pre-dose, 0.5, 1, 2, 4, 6, 8, 10-14 and 24 h (C1 D15), 72 h (C1 D17), 120 h (C1 D19), C2 D1 pre-dose (-1 d tolerance), D7 and 14 (or last day of dosing in cycle) at 2-6 h post dose, C3 onwards D1 pre-dose (-1 d tolerance) and D14 (or last day of dosing in each cycle) at 2-6 h post dose (-2 d tolerance). All sample times are approximate, and every effort should be made to take the samples as close to the specified time given and, where relevant, contemporaneously with blood sampling for PD biomarker assessments. For the C1 D1, D2, D7 and D14 a ±5 min window is allowed, for the C1 last day of dosing 24 h (C1D15), 72 h (C1D17) and 120 h (C1D19) samples, a ±2 h window is allowed. Please refer to the Lab Manual for full details on sample collection, time-points, processing, storage and shipment.
16 Part 1 only. Urine collection for PK analysis will be collected from the first dose of SEL24/MEN1703 until immediately prior to the second dose. Please refer to the Lab Manual for full details on sample collection, time-points, processing, storage and shipment.
17 Final study assessments to be conducted up to 30 d (+/-2 d) from last dose of SEL24/MEN1703. Adverse events and concomitant medications must be assessed to 30 d from last dose of SEL24/MEN1703. Other assessments may be carried out between 7-30 d from last dose.
18 An assessment of each patient's disease status and AML-related medications administered will be made approximately every 3 months from last dose of SEL24/MEN1703 for up to 1 year (or until End of Study, whichever occurs first) regardless of the initiation of additional treatments to determine date of progression (where appropriate) and survival status.

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LIST OF ABBREVIATIONS

AE	adverse event
ADHD	attention deficit hyperactivity disorder
ALT	alanine aminotransferase
AML	acute myeloid leukemia
ANC	absolute neutrophil count
API	active pharmaceutical ingredient
AST	aspartate aminotransferase
ATC	anatomical therapeutic chemical
AUC	area under the curve
$AUC_{0-\infty}$	AUC from time zero to infinity
AUC_{0-t}	AUC from time zero to time t
BID	twice daily dosing
BCRP	breast cancer resistance protein
BSA	body surface area
BUN	blood urea nitrogen
CD25	cluster of differentiation 25; gene coding for the alpha chain of Interleukin 2 receptor protein
cDNA	complementary deoxyribonucleic acid
cGMP	current Good Manufacturing Practice
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CL	plasma clearance
C_{max}	maximum plasma concentration
CNS	central nervous system
COVID-19	Coronavirus disease 2019
CR	complete response/remission
CRA	Clinical Research Associate
CRF	Case Report Form
CRi	complete remission with incomplete blood count recovery
CRh	complete remission with partial hematologic recovery
CRO	contract research organization
CTCAE	common terminology criteria for adverse events
DLT	dose limiting toxicity
DMC	Data Monitoring Committee
DoR	duration of response
EC	European Community
EC	Ethics Committee
ECG	electrocardiogram
ECI	events of clinical interest
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EGFR	epidermal growth factor receptor
EDC	electronic data capture

EFS	event-free survival
EU	European Union
FDA	(US) Food and Drug Administration
FIH	first-in-human
FLT3	Fms-like tyrosine kinase 3; a gene coding for FMS-like tyrosine kinase-3
FPI	first patient in
FSH	follicle-stimulating hormone
FSV	final study visit
GALT	gut associated lymphoid tissue
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
GPCR	G-protein-coupled receptors
GVHD	Graft versus Host Disease
HBV	hepatitis B virus
HCV	hepatitis C virus
hERG	human ether-a-go-go-related gene
HIV	human immunodeficiency virus
HMA	hypomethylating agents
HNSTD	highest non-severely toxic dose
HSCT	hematopoietic stem cell transplant
I.V.	intravenous(ly)
IB	Investigator's Brochure
IC50	half maximal inhibitory concentration
ICF	informed consent form
ICH	International Conference on Harmonisation
IDH	Isocitrate DeHydrogenase
IMP	investigational medicinal product
IND	investigational new drug
IRB	Institutional Review Board
ITD	internal tandem duplication
IWRS	interactive web response system
LDH	lactate dehydrogenase
LPO	last patient out
LVEF	left ventricular ejection fraction
MAD	maximum administered dose
MRD	minimal residual disease
MLFS	morphologic leukemic-free state
ms	millisecond(s)
MTD	maximum tolerated dose
MUGA	multi-gated acquisition
NCI	National Cancer Institute
NOAEL	no observed adverse effect level
NYHA	New York Heart Association
ORR	objective (or overall) response rate
OS	overall survival

PBMC	peripheral blood mononuclear cells
PD	pharmacodynamic(s)
PD	progressive disease
PIM	proviral integration site for Moloney murine leukemia virus; a serine/threonine protein kinase (a proto-oncogene)
PIS	patient information sheet
PK	pharmacokinetic(s)
PS	performance score
QD	once daily
QTc	corrected Q wave T wave interval
RD	recommended dose
RFS	relapse-free survival
s.c.	subcutaneous(ly)
SAE	serious adverse event
SAP	Statistical Analysis Plan
SEL24/MEN1703	a dual kinase inhibitor targeting PIM (PIM1, PIM2, PIM3) and FLT3 kinases; also referred to as SEL24-B489 or SEL24-1289 (free base forms) and SEL24-B489A and SEL24-1289A (hydrochloride salt of SEL24-B489 or SEL24-1289)
SSRI	selective serotonin reuptake inhibitor
SDSU	Study Drug Safety Unit
SUSAR	suspected unexpected serious adverse reaction
$t_{½}$	half-life
t_{max}	time to reach maximum concentration
TMF	Trial Master File
TPN	total parenteral nutrition
ULN	upper limit of normal
USA	United States of America
VF	ventricular fibrillation
V_{ss}	volume of distribution at steady state
VT	ventricular tachycardia
λ_z	individual estimate of the terminal elimination rate constant

1. INTRODUCTION

1.1. Acute Myeloid Leukemia

Acute myeloid leukemia (AML), a malignancy of a myeloid precursor cell, is an extremely aggressive malignancy; patients treated with supportive care alone have a median survival of 2.5 months[1]. In the United States it was estimated that there would be approximately 14,500 new cases of AML in 2013[2], in the European Union (EU), annual incidence is on the order of 20,000 new cases[3]. AML represents approximately 25% of all adult leukemias as measured by the incidence rate[4]. Despite significant recent advances in the treatment of many cancers, the mainstay of initial treatment of AML was developed nearly 40 years ago as a combination of cytosine arabinoside (ara-C or cytarabine) with an anthracycline (this combination is known as '7+3'), and remains the standard of care. Approximately 60% to 70% of adults with AML can be expected to attain a CR following appropriate induction therapy; however, over half of these patients will subsequently relapse and only about 25% of adults with AML can be expected to survive 3 or more years and be cured. Patients who fail to achieve a CR with current standard therapy have very poor prognosis. In patients who relapse within 6 months of attaining CR (regardless of age), the prognosis remains particularly poor. Some patients who have had a prolonged period of CR may respond a second time to standard therapy (cytarabine plus an anthracycline, '7+3'), but for patients who are refractory to this regimen, there are no therapies that have been shown to prolong survival.

AML is primarily a disease of older adults and the median age of patients at diagnosis is 65 years. Age plays a key role in the prognosis of AML; 5-year survival of patients younger than 45 is over 50%, but drops to less than 5% for patients older than 65 years[4]. There are several factors that contribute to this survival disparity based on age. Firstly, older patients exhibit a worse performance status than younger patients, often due to intercurrent medical conditions. Secondly, AML in older patients is more frequently associated with unfavorable cytogenetics, which implies a greater degree of genetic damage and drug resistance. Finally, older AML patients exhibit a higher frequency of multi-drug resistance (*mdr*) expression, which also contributes to drug resistance[5]. These aspects of AML in the elderly are reflected in several key outcomes: compared with patients 55 years and younger, patients aged 65 to 75 years have lower rates of CR (39% vs. 64%); higher rates of mortality within 30-days after induction (23% vs. 3%); and lower overall median survival times (6.9 months vs. 18.8 months)[5]. Given these poor outcomes, many older patients are not considered to be candidates for aggressive remission induction therapy, may now receive combination treatments such as low dose cytarabine with either venetoclax or glasdegib or a hypomethylating agent (azacitidine/azacytidine or decitabine) with venetoclax.

Although specific treatments are available for patients with AML harboring specific mutations, relapsed or refractory AML remains one of the largest unmet needs in medicine, particularly in patients that have already failed target salvage options, where any.

1.2. SEL24/MEN1703

Menarini Ricerche S.p.A (hereinafter referred to as Menarini) is developing a dual kinase inhibitor targeting PIM (PIM1, PIM2, PIM3) and FLT3 kinases, named SEL24/MEN1703.

Fms-like tyrosine kinase 3 internal tandem duplication (FLT3-ITD) is one of the most common genetic lesions in AML and is associated with a poor long-term prognosis[6]. Although FLT3 tyrosine kinase inhibitors are now approved for commercial use, the medical need in FLT3 mutated AML patients is still largely unmet, particularly – though not limited - in patients with relapsed or refractory disease. PIM (proviral integration site for Moloney murine leukemia virus) kinases are thought to be major drivers of the resistance phenotype and their inhibition in relapsed samples restores cell sensitivity to FLT3 inhibitors[7]. Thus, simultaneous PIM and FLT3 inhibition represents a promising strategy in AML therapy.

1.3. Non-Clinical Studies with SEL24/MEN1703

SEL24/MEN1703, a potent PIM and FLT3-ITD dual activity inhibitor, demonstrates significantly broader activity in AML cell lines and primary AML blasts, irrespective of FLT3 status, than selective FLT3-ITD or PIM inhibitors.

In vitro studies and *in vivo* nonclinical pharmacology studies in mouse leukemia human xenograft models have been conducted to evaluate the anticancer potential of SEL24/MEN1703. Evaluation of SEL24/MEN1703 by enzymatic assay and biomarker studies shows that it exhibits potent activity on PIM kinase isoforms comparable with AZD1208, and slightly lower activity than quizartinib for the FLT3 mutant.

SEL24/MEN1703 demonstrates strong cytotoxic effects in AML cell lines, independently of FLT3 status, in contrast to quizartinib and AZD1208, which show more narrow therapeutic potential.

The unique mechanism of inhibiting both PIM and FLT3 kinases translates into potent effects in *in vivo* models. SEL24/MEN1703 shows anticancer effects in subcutaneous xenografts AML models and is superior to quizartinib and AZD1208, depending on the genetic background of mutations. Nonclinical pharmacology study results suggest that SEL24/MEN1703 may offer a comprehensive approach to targeting the PIM/FLT3 axis in AML patients and that the activity can be further enhanced by combination with standard chemotherapy.

In vitro and *in vivo* safety pharmacology studies have been conducted. *In vitro* studies included nuclear receptor binding studies, hERG inhibition and hERG tail currents recorded from transfected HEK293 cells. An *in vivo* GLP study has been conducted in male Beagle dogs to evaluate the effects on cardiovascular and neurobehavioral functions.

SEL24/MEN1703 was tested on a panel of G-protein-coupled receptors (GPCRs) and other receptors. The compound was tested at the high concentration of 10 µM. Three receptors were identified as inhibited more than 85% (NK1, 5HT2B, and sigma). Both receptors were tested for agonistic and antagonistic activity of SEL24/MEN1703. No agonistic activity was detected.

Results of evaluation of hERG currents indicated that for SEL24/MEN1703, the hERG IC_{50} was 3.561 µM. For the positive control, E-4031, the mean hERG inhibition was 88.5%. In addition, SEL24/MEN1703 inhibited hERG tail current in HEK293 cells stably transfected with hERG cDNA with an estimated IC_{50} value of 2.5 µM.

In a GLP safety pharmacology study in the dog, the effect of SEL24/MEN1703 at doses of 5, 10 and 20 mg/kg on arterial blood pressure, heart rate, lead II ECG intervals, core body temperature and on neurobehavioral functions was assessed in conscious telemetered Beagle dogs. After the administration of SEL24/MEN1703 at these doses, no effect was noted on arterial blood pressure, heart rate, lead II ECG intervals and core body temperature. The evaluation of neurobehavioral parameters, both direct and remote, did not show changes compared with vehicle at any dose level.

Pharmacokinetic studies have been performed in mouse, rat, and dog. The pharmacokinetic profile of SEL24/MEN1703 obtained *in vivo* in mice, rats and dogs confirmed good bioavailability and a favorable profile for oral administration. *In vivo* efficacious doses as low as 25 mg/kg twice daily (BID) in the mouse leads to complete biomarker response in tumor and spleen including inhibition of phosphorylation of the classical PIM target S6 (Ser235/236 and Ser240/244). According to PK/PD modelling analysis based on MOLM16 cell line xenograft data performed with the aim to investigate the exposure-response relationship between plasma SEL24/MEN1703 concentration and inhibition of S6 (Ser235/236) phosphorylation, the IC50 is expected at a plasma concentration of approximately 800 ng/mL. A dose of 25 mg/kg QD in rat reaches therapeutic plasma levels of biomarker inhibition and administration of 100 mg/kg QD in rat leads to approximately 3 times higher compound concentration in plasma than the predicted therapeutic level. Pharmacokinetic studies confirmed that QD administration is sufficient to maintain therapeutic exposure in rats. In another study, bioavailability was evaluated in fasted as well as non-fasted female Sprague Dawley rats. Good absolute bioavailability (calculated from AUC_{0-t}), i.e., higher than 70%, was shown for both conditions after oral administration in an aqueous solution formulation; however, the non-fasted state showed slightly higher oral bioavailability than the fasted state (76.2% vs. 70.2%).

Non-GLP repeat-dose toxicity studies have been conducted in rat and dog and GLP repeat-dose studies have been carried out in rat and dog. The non-GLP studies confirmed the therapeutic index and lack of any toxicology findings at therapeutic doses by clinical pathology and histopathology. These studies also demonstrated that adverse effects observed at higher doses are completely or partially reversible in a follow-up recovery period.

A non-GLP 10-day twice daily oral gavage toxicity study in rats established that the severely toxic dose resulting in 10% lethality (STD10) for SEL24/MEN1703 administered twice daily (12 h ± 1 h apart) was between 50 and 100 mg/kg/day under those experimental conditions.

In a two-week repeat-dose followed by a two-week recovery period study in rats, the highest dose level of 80 mg/kg/day induced mortality and severe clinical signs after at least 10 days of daily administration in relation to kidney and liver toxicity. At 20 and 40 mg/kg/day given for two weeks, SEL24/MEN1703 induced adverse dose-related degeneration/regeneration (tubulonephrosis) in the kidney, and bile duct hyperplasia in the liver. The dose level of 20 mg/kg/day was expected to be a no observed adverse effect level (NOAEL) with sufficient plasma exposure. However, based on kidney and liver adverse pathological changes observed at all doses in both sexes, no NOAEL or STD10 could be established under these experimental conditions.

A GLP two-cycle study of two-week oral repeat-doses followed by a four-week recovery period was conducted in rats in which SEL24/MEN1703 was administered orally to Crl:CD(SD) rats once

daily for two cycles of 14 days separated by one week of treatment withdrawal. Rats were treated at doses of 0 (vehicle), 10, 25 and 50 mg/kg/day (as parent). At 25 mg/kg/day, SEL24/MEN1703-related findings were observed in the thymus and sternum-bone marrow from males and females, and in the liver, adrenals and mammary gland from males only; at 50 mg/kg/day, SEL24/MEN1703-related findings were observed in thymus, sternum bone-marrow, kidneys, liver and adrenals from both sexes, and in male (prostate and seminal vesicles) and female (ovaries, vagina, cervix and uterus) reproductive tracts. Overall, males were more affected in terms of incidence and severity compared to females, and the liver (degenerative and proliferative changes in the intra and extra-hepatic biliary system), kidney (renal degenerative/ necrotic changes of the proximal tubule), and male/female reproductive tract (endocrine disruption) findings were considered adverse at 50 mg/kg/day. These findings were sometimes associated to clinical pathology and organ weight changes; furthermore, clinical observations (mainly piloerection) and decreases in the body weight/body weight gain and food consumption were also observed at 50 mg/kg/day at the end of each treatment cycle. Based on the pathology findings, the NOAEL is considered to be 25 mg/kg/day, which corresponds to mean C_{max} and AUC_{0-24} values of 570 ng/mL and 8950 ng.hr/mL in males and to mean C_{max} and AUC_{0-24} values of 579 ng/mL and 7920 ng.hr/mL in females after two cycles of 14 days treatment separated by one week of treatment withdrawal.

In a non-GLP dose range-finding and oral repeat-dose toxicity study in the Beagle dog, it was determined that the lowest dose of 10 mg/kg was well-tolerated when administered for 10 days. The next higher dose of 30 mg/kg demonstrated clear toxicity and is considered not suitable for studies of longer duration. The highest dose of 60 mg/kg necessitated early kill of both male and female dogs and was clearly beyond the maximum tolerated dose.

A GLP two-cycle 14-day oral repeat-dose toxicity study was conducted in Beagle dogs followed by a four-week treatment-free recovery period. SEL24/MEN1703 was administered orally to Beagle dogs QD for 2 cycles of 14 days separated by one week of treatment withdrawal at the doses of 0 (vehicle), 5, 10 and 20 mg/kg/day. Treatment resulted in severe clinical signs, marked limp of the right and/or left hind limb, reduction of proprioceptive reflex, reduction in body weight and food consumption in animals at 20 mg/kg/day leading to early termination of one male and two females. Microscopic findings in the gall bladder, liver, stomach, small intestine (duodenum, jejunum, ileum), kidneys, lymphoid organs/tissue (thymus, spleen-white pulp, mandibular and mesenteric lymph nodes, Gut Associated Lymphoid Tissue (GALT)), hematopoietic tissue (sternum-bone marrow) and prostate were variably observed in surviving and premature decedents at 20 mg/kg/day and in the gall bladder, liver, lymphoid organs/tissue (thymus, spleen-white pulp, mandibular and GALT), and male reproductive system (prostate, testes, epididymis) at 10 mg/kg/day with a partial recovery in the gall bladder and liver and with no recovery in the male reproductive system. In one male, after the second cycle treatment, at 10 mg/kg limping of the left hind limb was observed. Based on these results the NOAEL is considered to be 5 mg/kg/day which corresponded to mean C_{max} and AUC_{0--24} values of 485 ng/mL and 5850 ng.hr/mL in males and to mean C_{max} and AUC_{0--t} values of 556 ng/mL and 6730 ng.hr/mL in females after two cycles of 14 days of treatment.

The drug interaction potential of SEL24/MEN1703 has been characterized in detail in an extensive range of *in vitro* drug interaction studies as outlined in the FDA Guidance for Industry: Drug Interaction Studies-Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations (Draft Guidance, February 2012) and in the EMA Guideline on the investigation of drug interactions (June 21, 2012). These studies indicate that SEL24/MEN1703 may inhibit CYP2D6 and act as a substrate for CYP2D6 and BCRP.

Please refer to the current edition of the Investigator's Brochure for further information on the non-clinical studies with SEL24/MEN1703.

1.4. Rationale for SEL24/MEN1703 Starting Dose Selection and Dose Escalation Plan

The first-in-human (FIH) starting dose for the clinical study in patients with AML was derived based on data accumulated from preclinical non-GLP and GLP repeat oral dose toxicology studies with SEL24/MEN1703 conducted in rats and dogs. The dog was the more sensitive species and the observations from the repeat dose dog GLP toxicology study form the basis for the rationale for the FIH starting dose.

This FIH study initially employed an accelerated dose escalation design for the first 4 cohorts, in which the starting dose was 25 mg in the first cohort (1 patient, in the absence of unacceptable toxicity), followed by a dose of 50, 75 and 100 mg in Cohorts 2, 3 and 4, respectively (1 patient per cohort, in the absence of unacceptable toxicity). Thereafter, dose escalation was to proceed according to a conventional 3 + 3 design with successive cohorts having dose increments of 50% or less.

The 25, 50, 75 and 100 mg doses in humans were supported by the non-clinical toxicology findings in animals. Rats and dogs were administered daily doses of SEL24/MEN1703 for two 14-day cycles with one week rest between treatment cycles, followed by a 28-day treatment-free recovery period. This treatment regimen mimics that to be utilized in the first-in-human clinical study in patients with AML.

Doses of 10, 25 and 50 mg/kg (human equivalent dose [HED] of 60, 150 and 300 mg/m^2, respectively) were administered to rats with no significant toxicity findings. Since no MTD was achieved, the rat was considered the less sensitive species.

Doses of 5, 10 and 20 mg/kg (HED of 100, 200 and 400 mg/m^2, respectively) were administered to dogs. The dog was considered the more sensitive species since the 20 mg/kg SEL24/MEN1703 dose resulted in severe clinical signs leading to early termination of 3 out of 12 animals.

Following a four-week recovery period, SEL24/MEN1703-related findings were reversible in all dose groups. Based on the findings in dogs, the NOAEL was 5 mg/kg and the highest non-severely toxic dose (HNSTD) was 10 mg/kg.

As shown in the tables below, the HED of the NOAEL in dogs is 170 mg, based on a human BSA of 1.7 m^2. Per the ICH S9 guidance, an appropriate human starting dose would be 50 mg, which is 1/6th the HNSTD in dogs. This study commenced with a lower starting dose of 25 mg. Doses of 25

mg through 100 mg remain well below the HED of the NOAEL in dogs and are also below the NOAEL and the lowest safe dose tested in rats.

Table 6: Human rationale based on dog toxicology studies

SEL24/MEN1703 dose level in dogs (mg/kg/d)	Human equivalent dose (HED)	HED in mg, based on 1.7 m^2 BSA
5 (NOAEL)	100 mg/m^2/d	170 mg
10 (HNSTD)	200 mg/m^2/d	340 mg
20 (toxic dose)	400 mg/m^2/d	680 mg

Table 7: Human dose rationale based on rat toxicology studies

SEL24/MEN1703 dose level in rats (mg/kg/d)	Human equivalent dose (HED)	HED in mg, based on 1.7 m^2 BSA
10 (safe dose)	60 mg/m^2/d	102 mg
25 (NOAEL)	150 mg/m^2/d	255 mg
50 (safe dose with reversible SEL24/MEN1703-related findings)	300 mg/m^2/d	510 mg

The first patient to be treated with SEL24/MEN1703 commenced dosing on 15 March 2017. As of 06 October 2017, eight patients had been dosed with SEL24/MEN1703 at the dose levels described in Table 8.

Table 8: CLI24-001 Patient Disposition up to clinical hold (all patients treated with non-formulated IMP)

Cohort	1	2	3	4	5
SEL24/MEN1703 Dose Level	25 mg	50 mg	75 mg	100 mg	150 mg
N	2*	1	1	1	3
DLT	1	0	0	0	2

*One patient not included in the dose-determining population

Accelerated titration design had continued through to Cohort 4. At the 150 mg dose level (the first cohort to be enrolled following the 3+3 design), DLTs were reported in 2 patients (another patient experienced a DLT event at 25 mg dose level). The occurrence of these two events meeting the DLT definition at the 150 mg dose level led to an adjustment of the dose escalation plan for this study, whereby SEL24/MEN1703 was more thoroughly evaluated following a “3+3” design.

The subsequent restarting dose level of 50 mg (Cohort 2) following a 3+3 design was selected, also supported by the PK data obtained that far during the CLI24-001 study: the total (AUC) and maximum (C_{max}) exposure of SEL24/MEN1703 observed in the patients were within, or slightly exceeding the toxicological coverage established in dog at the dose of 5 mg/kg, which was defined as the HNSTD. After single and repeat dose administration of SEL24/MEN1703 25 mg and 50 mg, C_{max} and $AUC_{(0-t)}$ observed in human were more than 11 and 9 times lower than those observed in dogs at the HNSTD, respectively. Overall, the PK results obtained that far in human confirmed that SEL24/MEN1703 exposure at 25 mg and 50 mg is below 1/6 of the exposure obtained at the HNSTD defined in dog (i.e. the most sensitive toxicological species). Moreover, it is noted that the dog is a relevant species also from a metabolic point of view, with the M3 metabolite similarly identified as the main metabolite in human and canine plasma. In a dedicated 10-day toxicology study in the dog (treated at 10, 30 and 60 mg/kg), the parent drug and the M3 metabolite were measured in plasma: the presence of M3 metabolite was confirmed and, at 10 mg/kg, it was double and one third compared to parent drug in the male and female animals, respectively.

As of today, 48 patients were dosed with SEL24/MEN1703 at the doses levels described in Table 9, including 30 patients treated at the RD of 125 mg:

Table 9: CLI24-001 Patient Disposition

Cohort	1	2	3	4	4F	4b	5
SEL24/MEN1703 Dose Level	25 mg	50 mg	75 mg	100 mg	100 mg formulated	125 mg	150 mg
Number patients treated with non-formulated IMP	2*	3	3	3	0	0	3
Number patients treated with Formulated IMP	0	0	0	0	3	30*	1
DLT	1	0	0	0	0	1	3

*One patient not included in the dose-determining population

Since 3 patients (out of 4) treated at 150 mg experienced DLT, the 125 mg dose level, already shown to be tolerable in 6 DLT evaluable patients, was determined to be the RD.

1.5. Safety Guidance Information for Investigators

Throughout the study, Investigators should refer to the current edition of the Investigator's Brochure (IB) for a full review of the potential risks associated with treatment with SEL24/MEN1703 and details of expected AEs.

Based on available safety data, administration of SEL24/MEN1703 may be associated with the potential risk of **fatal thrombosis** and **severe hepatotoxicity**. In addition, hypophosphatemia has occurred at the 25, 50, 75, and 150 mg dose levels. Please refer to Section 6.9.1 for further guidance on the management of this latter event.

No other particular risks have been identified for SEL24/MEN1703 according to available clinical data. Nevertheless, results from non-clinical data do not allow to exclude the potential phototoxic effect of MEN1703. To this end, new safety measures - Inclusion of photosensitivity/phototoxicity

preventive measures – have been implemented in previous Clinical Trial Protocol Versions 11.2 and 11.3. Please refer to Section 6.8 for further guidance on the prevention and management of this event.

Risk Benefit Assessment for COVID-19 pandemic

There is currently an outbreak of respiratory disease (COVID-19) caused by a novel coronavirus SARS-CoV-2 that was first detected in Wuhan City, Hubei Province, China in 2019. This new virus has rapidly spread across the globe causing the World Health Organization (WHO) to declare a pandemic situation on March 12, 2020. In response to the pandemic, the health authorities have issued recommendations on the further conduct of clinical studies. Accordingly,
risk assessments of involvement in the trial with added challenges due to COVID-19 and mitigation measures need to be taken into consideration in all clinical studies to protect subjects, site staff and the society as a whole.

In this phase I/II clinical trial for heavily pre-treated relapsed or refractory AML patients the eligibility will be evaluated by the treating physician/PI after individual assessment that the clinical benefit of the investigational product will outweigh the risk of contracting the SARS-CoV-2 infection without compromising the safety of the subjects.

Measures to mitigate the additional risks caused by COVID-19 are:

- Current national laws and local recommendations for prevention of pandemic will be strictly adhered.
- Subjects will be encouraged to strictly follow local mitigation recommendations (e.g. social distancing, use of mask, etc.).
- Access to clinical site will be granted according to local COVID-19 control measures.
- Based on the local circumstances, to be reassessed on an ongoing basis, additional measures will be considered for implementation including:
    - Interruption or slowing down of recruitment of new trial participants;
    - Postponement of activation of sites that have not yet been initiated;
    - Transfer of trial participants to investigational sites away from risk zones, or closer to their home;
    - IMP re-distribution among sites, in case of shortage of study drug;
    - Safety laboratory tests to be performed at local laboratory or participant's home, in case the trial participants cannot reach the site;
    - Remote consent could be collected (when applicable as per local policy).

2. STUDY OBJECTIVES

Table 1: Part 1 Study Objectives and Endpoint (Assessment)

Objective	Endpoint (Assessments)
Primary:	
• To estimate the MTD or MAD and determine the RD of SEL24/MEN1703 for Part 2	• DLT evaluation at the end of one treatment cycle for each dose level
Secondary:	
• To assess the safety and tolerability of SEL24/MEN1703	• The number and frequency of AEs, safety laboratory, vital signs and ECG assessments
• To assess anti-leukemic activity of SEL24/MEN1703	• Assessment of bone marrow and peripheral blast % and other assessments of clinical benefit including ORR (CR, CRi, CRh and MLFS), PR rate, DoR, RFS, EFS and OS
• To evaluate the PK profile of SEL24/MEN1703 and its metabolites as appropriate	• Assessment of PK variables, including C_{max}, AUC and t½
Exploratory:	
• To assess the PD activity of SEL24/MEN1703	• Flow cytometry assessment of relevant biomarkers (e.g. pS6)
• To assess the genetic profile of AML cells	• Analysis of relevant mutations in peripheral blasts and bone marrow by using Next Generation Sequencing and/or qRT-PCR

Table 2: Part 2 Study Objectives and Endpoint (Assessment)

Objective	Endpoint (Assessments)
Primary:	
• To further characterize the safety profile of single agent SEL24/MEN1703	• The number and frequency of AE, safety laboratory, vital signs and ECG assessments
Secondary:	
• To assess anti-leukemic activity of single agent SEL24/MEN1703	• Assessment of bone marrow and peripheral blast % and other assessments of clinical benefit including ORR (CR, CRi, CRh and MLFS), PR rate, DoR, RFS, EFS, OS , transfusion conversion rate, transfusion maintenance rate, HSCT rate
• To evaluate the PK profile of SEL24/MEN1703 and its metabolites, as appropriate	• Assessment of PK variables, including C_{max}, AUC and t½
Exploratory:	
• To assess the PD activity of SEL24/MEN1703	• Flow cytometry assessment of relevant biomarkers (e.g. pS6)

Objective	Endpoint (Assessments)
• To assess the genetic profile of AML cells	• Analysis of relevant mutations in peripheral blasts and bone marrow by using Next Generation Sequencing and/or qRT-PCR

3. SELECTION CRITERIA

3.1. Inclusion Criteria

Patients are eligible to be included in study if they meet all of the following criteria:

1. Patient with diagnosis of AML (i.e. ≥20% blasts in bone marrow or peripheral blood) harboring IDH1 or IDH2 mutation (as per local assessment).
2. Provide written informed consent prior to Screening.
3. Male or female patients, age ≥18 years old.
4. Patient has no standard therapeutic options available (including IDH inhibitors where approved) and has:
   a) Relapsed AML unsuitable for intensive chemotherapy;
   b) Primary refractory AML unsuitable for intensive chemotherapy;

Clarification note: Patients naïve to IDH inhibitors are eligible ONLY if no IDH inhibitors are approved/available in the country/site where they are enrolled.

5. ECOG Performance Status 0, 1 or 2.
6. Adequate organ function at Screening, including:
   e) Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤2.5X the upper limit of normal (ULN);
   f) Total bilirubin ≤2X ULN;
   g) Creatinine clearance ≥40 mL/min (Cockcroft-Gault formula) (see Appendix B);
   h) Left ventricular ejection fracture (LVEF) ≥40% as per local assessment practice.
7. A female of childbearing potential, defined as any female who has experienced menarche and who has not undergone successful surgical sterilization or is not postmenopausal (i.e. has serum follicle stimulating hormone level ≥30 IU/L in the absence of hormone replacement therapy, or complete absence of menses for at least 12 consecutive months which is not due to medication), must have a negative pregnancy test within 7 days prior to receiving study drug.
8. Sexually active male or female patients of childbearing potentialare eligible providing that:

   Female:
   - Agrees to use an effective method of birth control as applicable per local law that both results in a Pearl index < 1 and is considered highly effective as defined by the Clinical Trial Facilitation Group (e.g. combined estrogen and progestogen containing hormonal contraception, progestogen-only hormonal contraception, intrauterine device, intrauterine hormone-releasing system, vasectomized partner, total sexual abstinence or bilateral tubal occlusion)*.
   - Undergoes a pregnancy test at Day 1 of each treatment cycle and after the end of relevant systemic exposure (30 days from the last study drug administration).

   Male:

- Agrees to use an effective contraceptive method (condom) during treatment and until the end of relevant systemic exposure. Females of childbearing potential that are partners of male study participants have to observe the same birth control indications that apply to female participants.

** Hormonal contraceptives are allowed as pre-clinical evaluation of SEL24/MEN1703 confirmed a low interaction between SEL24/MEN1703 and the most common active principles used for this purpose.*

3.2. Exclusion Criteria

Patients are not eligible to be included in study if they meet any of the following criteria:

1. Received anti-cancer treatments (including cytotoxic chemotherapy, radiotherapy, hormonal therapy, biologic, immunotherapy or investigational drugs) within 14 days or 5 half-lives (whichever is longer) before the first dose of study drug.
2. Prior treatment with a PIM inhibitor.
3. Hyperleukocytosis (leukocytes >30 x10^9/L) immediately prior to the first dose of study drug and/or clinical concerns of leukostasis.
   Note: *Patients may undergo leukapheresis according to routine practice before the first dose of study drug; where hydroxyurea is used prior to receiving study drug, it may be continued up to Cycle 1, Day 21, although Investigators are asked to stop treatment prior to the first dose of study drug or before Day 7, wherever possible.*
4. Clinically significant active central nervous system (CNS) leukemia.
   Note: *Previously treated and controlled CNS leukemia and ongoing standard CNS prophylaxis (e.g. with intrathecal cytarabine) is acceptable.*
5. Patients who have undergone major surgery within 1 month prior to first dose of study drug.
6. Hematopoietic stem cell transplant within 4 months of first dose of study drug.
7. Requires systemic immune-modulating therapy (regardless of dose) for the prophylaxis or treatment of GVHD.
8. Evidence of ongoing and uncontrolled systemic bacterial, fungal, or viral infection, with the exception of patients with documented Grade CTCAE ≤2 infections with evidence of improvement or without evidence of worsening infection.
9. Known positive serology for human immunodeficiency virus (HIV).
10. Ongoing drug-induced liver injury, known chronic active hepatitis C (HCV) infection, known chronic active hepatitis B (HBV) infection , alcoholic liver disease, non-alcoholic steatohepatitis, primary biliary cirrhosis, extrahepatic obstruction cause by cholelithiasis, cirrhosis of the liver, or portal hypertension. Participants with history of chronic HBV and HCV infection are eligible if disease is stable and sufficiently controlled as per investigator's judgment.
11. Ongoing drug-induced pneumonitis.
12. Ongoing inflammatory bowel disease.
13. Pregnancy or breastfeeding.
14. Concurrent participation in another therapeutic clinical study.

15. Ongoing toxicity from any prior anti-cancer therapy that has not resolved to Grade 1 or less prior to the first dose of study drug.
16. Received an agent known to be a sensitive CYP2D6 substrate or a CYP2D6 substrate with a narrow therapeutic range, a strong or moderate CYP2D6 inhibitor, or a BCRP inhibitor within 7 days or a period corresponding to 4-5 half-lives of the agent, prior to the first dose of study drug.
17. Cardiac dysfunction defined as myocardial infarction within 6 months of study entry, New York Heart Association (NYHA) Class III or IV heart failure, uncontrolled dysrhythmias or poorly controlled angina.
18. Are receiving any active treatment for thrombosis.
19. History of serious ventricular arrhythmia (e.g. VT or VF, ≥3 beats in a row), or QT interval corrected for heart rate (QTc) ≥480 ms.
    Note: *QTc values up to 500 ms will be acceptable where patient's medical history e.g. bundle branch block, is known to cause mild QTc prolongation and the condition is well controlled.*
20. Any disease, syndrome or condition which may affect significantly drug intake via oral route.
21. Any other prior or current medical condition, intercurrent illness, surgical history, physical or 12-lead electrocardiogram (ECG) findings, laboratory abnormalities, or extenuating circumstance (e.g. alcohol or drug addiction) that, in the investigator's opinion, could jeopardize patient safety or interfere with the objectives of the study.

3.3. Definition of Evaluable Patient and Replacement of Patients

In Part 1 Cycle 1, a patient must have received at least 12 of their 14 doses of SEL24/MEN1703 within the required 14-day treatment period in order to be evaluable. If a patient is withdrawn from the study for reasons other than a DLT-associated event before the end of the first treatment cycle, the patient must be replaced so that the required number of patients in the cohort is evaluable for the dose escalation decision. Patients who withdraw from the study or discontinue treatment after completion of the first treatment cycle will not be replaced.

In Part 2, patients may be replaced if they are not considered evaluable for safety (all patients who received at least a dose of SEL24/MEN1703). Patients in Part 2 may also be replaced if they received one or more administrations of SEL24/MEN1703 without having one post-treatment bone marrow disease assessment.
In this latter event, patients may be replaced only if the hematology assessments performed on peripheral blood shall not indicate a clear disease progression.

3.4. Reasons for Withdrawal of Patient from Study

Throughout the study, treatment with SEL24/MEN1703 may continue until the occurrence of one of the following events, whichever comes first:

- Patient withdrawal of consent.
- Disease progression.
  Note: *Patients with disease progression may continue to receive SEL24/MEN1703, if in the opinion of the Investigator, they remain clinically stable and may be deriving*

potential clinical benefit from SEL24/MEN1703 and it is not considered detrimental to the patient to continue study treatment.

- Treatment delay of more than 2 weeks for reasons other than toxicity (see Section 4.4).
- Occurrence of an unacceptable toxicity (see Section 4.4).
- Requirement for treatment with prohibited medication (see Section 6.9.3).
- Treatment non-compliance.
  Note: *Treatment non-compliance will be based on patient enquiry and SEL24/MEN1703 capsule count on return of used investigational medical product (IMP) to site. In Part 1 it will be defined as missing more than 2 doses in a 14-day dosing schedule in Cycle 1. After Cycle 1 and throughout Part 2, treatment compliance will be assessed on a case-by-case basis (see also Section 4.4).*
- Study non-compliance.
  Note: *Each patient's continued willingness to attend study visits and undergo study assessments will be assessed on a case-by-case basis.*
- Investigator decision that it is in the patient's best interest to withdraw from the study.

Where appropriate (e.g. in the case of disease progression), continuation of the study treatment will be discussed between the Investigator and the Sponsor on a case by case basis. The DMC may also advise on the suitability of an individual patient to continue to receive study treatment.

Patients who experience a DLT will be permitted to receive further treatment with SEL24/MEN1703 according to the dose modification criteria described in Section 4.4.

3.5. Screen-failure patient and procedures for re-screening

Screen-failure patient is defined as any patient who does not meet eligibility criteria required for study participation or for whom the time window between Screening and C1D1 is longer than 28 days.

Any patient who has screen-failed may be re-screened at a later date should it be determined the patient meets eligibility (e.g. out of range lab value). Re-screening patients will be registered in IWRS with a new screening number and they must sign a new consent form if the first dose of study drug is given more than 28 days after having signed the first consent form.

3.6. Procedures for Patient Discontinuation

If a patient withdraws from the study prior to study completion, the reason for withdrawal should be sought and recorded in the patient file and the electronic Case Report Form (eCRF). Every effort will be made to complete the Final Study Visit.

The Final Study Visit will be performed up to 30 days after the last dose of SEL24/MEN1703. Unscheduled assessments showing disease progression and leading to subject's withdrawal can replace the Final Study Visit provided that all assessment/procedures scheduled for this visit are completed.
After the Final Study Visit, all subjects evaluable for efficacy will be followed for survival/disease status according to local practice (a visit or a telephone call) every 3 months from last dose of

SEL24/MEN1703 for up to 1 year (or until End of Study, whichever occurs first), regardless of the initiation of additional treatments.

In the case of a temporary or permanent clinical hold, procedures will be put in place to communicate this to patients and advice provided to sites on how to complete patient eCRFs.

3.7. Study or Site Termination

If the Sponsor or their representatives, Investigator, or Competent Authority officials discover conditions during the study that indicate that the study or site involvement should be terminated, this action may be taken after appropriate consultation with the Sponsor and the Investigator. Conditions that may warrant termination of the study or involvement of a study site include, but are not limited to:

- The discovery of an unexpected, serious, or unacceptable risk to patients enrolled in the study.
- The decision on the part of the Sponsor to suspend or discontinue testing, evaluation, or development of the study drug.
- Failure of the Investigator(s) to comply with pertinent clinical study regulations.
- Submission of knowingly false information from the research facility to the Sponsor, study monitor, or Competent Authority.
- Insufficient adherence to protocol requirements.

In any case, the study will end with the Final Study Visit of the last subject who discontinues the study treatment.. For safety monitoring, all serious adverse events (SAEs) with a suspected causal relationship to the study treatment that occur after the End of Study must be recorded and notified to the Sponsor.

Study termination and follow-up will be performed in accordance with applicable local regulations.

4. STUDY DESIGN

This is a Phase I/II, open-label, multi-center, dose escalation study to estimate the MTD (or MAD) of SEL24/MEN1703 in patients with AML. At the end of Part 1 a RD of SEL24/MEN1703 will be selected for further evaluation in Part 2. In Part 2 the safety and anti-leukemic activity of SEL24/MEN1703 will be further assessed in the study population.
The starting dose will be 25 mg SEL24/MEN1703 taken orally QD for 14 consecutive days over a 21-day treatment cycle. In both parts of the study, the criteria for retreatment described in Section 4.4 must be followed prior to proceeding to administer a further cycle of treatment.

4.1. Part 1

At the time this protocol Version 12.0 is running, Part 1 has been completed; procedures are reported below for completeness.

Part 1 was initially designed with an ATD for the first 4 cohorts. The study design has then been revised to follow a 3+3 design from Cohort 2 (50mg) onwards in order to assess for DLT, adverse events, and adequate PK profile data from at least 3 patients in each dose level (see Table 3).Patients will be enrolled to cohorts in a sequential fashion following the dosing regimen and will be observed for safety and tolerability during Cycle 1, prior to permitting dose escalation to the next dose level (cohort). From Cohort 4 onwards there will be a mandated recruitment interval of at least 7 days for each patient enrolled.

Should a patient experience a toxicity which qualifies as a DLT during Cycle 1 in any cohort, that cohort will be expanded to enroll up to a maximum of 6 patients to further assess for toxicity prior to considering the next dosing step.

Cohort 4 (100mg) is repeated twice due to the introduction of a new formulated SEL24/MEN1703 IMP.

To distinguish between the original cohort and the repeat cohort at the same dose level, the repeat cohort is named Cohort 4F.

No recruitment interval is applied in the cohort 4F where formulated SEL24/MEN1703 IMP is introduced, as this dose level has already been explored with the non-formulated SEL24/MEN1703 API in capsules. Upon the successful completion of the repeat cohort with the formulated IMP, the study will progress to the next Cohort 4b and onwards, according to the study design, using SEL24/MEN1703 formulated IMP only. In particular, it has been shown that, overall, PK disposition of SEL24/MEN1703 (absorption, distribution and elimination) following the administration of formulated IMP is in line with that observed with non-formulated IMP. This evidence further supports that no dose adjustment is warranted with formulated IMP.

Patients who commenced dosing with the non-formulated SEL24/MEN1703 API in capsules and who are still on treatment, will continue receiving this formulation until treatment withdrawal per protocol.

Recruitment and dose escalation for each cohort in Part 1 is described in Table 3.

Table 3: Patients exposure along Dose Escalation Steps

Cohort	Dose Level	Patients treated with non-formulated IMP	Patients treated / to be treated with Formulated IMP	Patients who experienced DLT
1	25 mg	2*	0	1
2	50 mg	3	0	0
3	75 mg	3	0	0
4	100 mg	3	0	0
4F	100 mg	0	3	0
4b	125 mg	0	7*	1
5	150 mg	3	1	3

* One patient not DLT evaluable

In Part 1, according to a 3+3 design, the MTD is defined as the highest dose at which no more than 1 in up to 6 patients experience a DLT during Cycle 1. In Cohort 5, up to 4 additional patients will be treated at 150 mg formulated IMP according to a Bayesian modified toxicity probability interval (mTPI) with a target toxicity rate $\leq 25\%$. Should none of these 4 patients experience a DLT, higher dose levels may be considered and will be subject to a protocol amendment.

The DMC consisting of the Principal Investigator at each site, plus the Medical Monitor and Sponsor representatives, will review all safety data available during Cycle 1 for each cohort and assess for DLT during Part 1 of the study (see Section 4.3). Experts in the evaluation of the PK and PD data may participate in the DMC meetings to help inform the next dose escalation step.

The dose escalation rules to be followed during Part 1 of the study are described in Table 4.

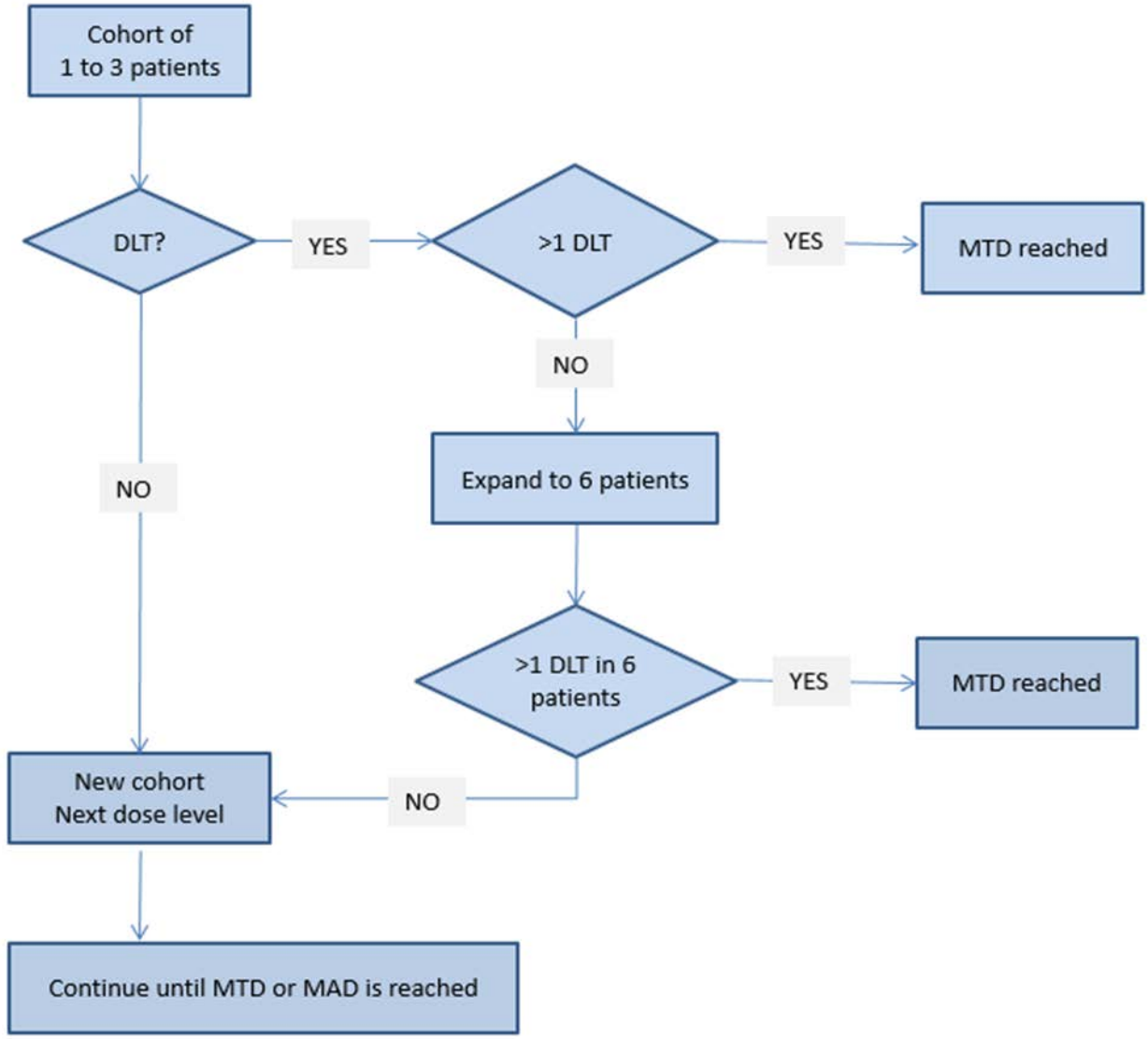
Table 4: Part 1 Dose Escalation Rules

No. of evaluable patients with DLT at a given dose level	Dose escalation rules
0	Proceed to next dose level
≥2	Dose escalation will be stopped. This dose level will be declared the MAD (highest dose administered). Additional patients will be entered at the **previously highest** dose level with <33% DLTs, to a maximum of 6, if less than 6 patients were treated previously at that dose. NOTE: at the 150 mg dose, additional 4 patients will be tested targeting ≤ 25% toxicity rate as described above.
1	Proceed to enter 6 patients at the dose level: - if no further patients experience DLT, proceed to the next dose level - if 1 or more of the additional patients suffer DLT, then dose escalation is stopped, and this dose is declared the MAD which has exceeded the MTD. Additional patients will be entered at the **previously highest** dose level with <33% DLTs, to a maximum of 6, if less than 6 patients were treated previously at that dose - confirmation that a dose level exceeds the MTD may be obtained before completing enrollment of 6 patients
≤1 out of 6 at highest dose level	This is generally the MTD/RD. At least 6 patients must be entered at the recommended dose level for Part 2.

In addition to DLT evaluation, there will be ongoing assessment of all AE and SAEs, changes in laboratory values (clinical chemistry, hematology, urinalysis, lipid profiles) and ECGs as further measures of safety and tolerability. All safety parameters will continue to be assessed beyond Cycle 1. Note that where the DMC is concerned about any safety signal in the study e.g. a trend in Grade 2 events, they may recommend a cohort is expanded to evaluate up to 6 patients, in order to explore this safety signal further.

The schematic below (Figure 1) provides a summary of cohort expansion and dose escalation plan for the protocol based on safety data evaluation.

Figure 1: Cohort expansion and dose escalation plan



The highest SEL24/MEN1703 dose level considered to be well tolerated and to have optimal PK and PD characteristics, will be called the RD and will be selected for further evaluation in Part 2.

4.2. Part 2

Part 2 is designed to enroll patients at the RD identified in Part 1 based on recommendation by the DMC.

Part 2 foresees the enrollment of patients to be treated at the RD (identified in Part 1 based on recommendation by the DMC) in the expansion cohorts defined below:

- The expansion cohort in 20 unselected relapsed or refractory AML patients patients ("***all-comers***")

NOTE: At the time this protocol version 12.0 is running the expansion cohort in "*all-comers*"AML patients has been already completed with 23 patients enrolled.

- An additional expansion cohort ("***IDH mutants")*** will enroll approximately 20 relapsed or refractory AML patients harboring an IDH mutation (either IDH1 or IDH2).

The evaluable patients treated at the RD in Part 1 or in Part 2 may be also retrospectively included in exploratory safety/efficacy pooled analysis, including patients with comparable inclusion criteria.

Considering that IDH inhibitors are approved/available only in some of the participating countries, it is anticipated that the study will enroll both IDH inhibitor pre-treated and IDH inhibitor naïve patients. For this reason, the recruitment will aim to have a balanced distribution across the two sub-populations to explore the differences in SEL24/MEN1703 activity between pre-treated and IDH inhibitor naïve patients, if any.

Retrospective correlations between the clinical activity of SEL24/MEN1703 and relevant disease markers (e.g. CD25 expression, FLT3 mutational status, IDH1/IDH2 mutational status, others) may be included in the statistical analysis plan.

Subjects who have a suitable donor and achieve a response allowing them to undergo hematopoietic stem cell transplant (HSCT) per each institution's assessment can undergo HSCT without leaving the study. However, SEL24/MEN1703 should be stopped and a preHSCT visit should be performed prior to starting the conditioning regimen for HSCT. SEL24/MEN1703 can be resumed after stem cell transplantation if all the following conditions are met:

- Subject is between 30 - 60 days post HSCT
- Subject has had successful engraftment as demonstrated by absolute neutrophil count (ANC) ≥ 500/mm3 and platelets ≥ 20000/mm3 without transfusions
- Subject does not have ≥ grade 2 acute graft-versus-host disease
- Subject is in CR, CRi, CRh

Those subjects resuming treatment will follow the procedures listed under subsequent Cycle 3 Day 1 in the Assessments Schedule. Subjects who do not resume SEL24/MEN1703 will be followed for the applicable endpoints' assessment.
Finally, MRD status will be recorded immediately prior to the transplant and after the procedure whenever a bone marrow aspirate/biopsy will be collected (recommended every 2 months unless differently indicated by the treating physician based on actual patient's parameters).

4.3. DLT Criteria

DLT events for dose escalation decisions will be assessed to the end of Cycle 1 for each patient in each cohort, except in the case of protracted neutropenia in the absence of active AML, where evaluation of the event must be conducted over 42 days. Ongoing safety events beyond Cycle 1 will be reviewed across all cohorts during the study to help inform dose escalation decisions.

AEs will be graded according to the NCI CTCAE V4.03. The AEs listed below will be considered as DLT unless they are clearly and incontrovertibly attributable to the underlying disease or to an extraneous cause:

- Grade 5 toxicity
- Grade 4 neutropenia lasting ≥42 days from the start of the therapy cycle in absence of evidence of active AML (<5% blasts)
- Grade 3 or 4 non-hematologic toxicity, except:
  - Alopecia;
  - Grade 3 fatigue, asthenia, anorexia, fever, or constipation;
  - Grade 3 nausea, vomiting, or diarrhea not requiring tube feeding, TPN, or hospitalization;
  - Infection, bleeding, or other expected direct complications of cytopenias due to active leukemia;
  - Grade 3 or 4 electrolyte imbalances that respond to correction i.e. return to ≤Grade 2, within 48 hours (h) from correction's onset;
  - Grade 3 increase in aspartate aminotransferase (AST) and/or, alanine aminotransferase (ALT) and/or alkaline phosphatase (ALP) recovering ≤Grade 2 within 7 days.

Only **clinically significant** abnormalities in laboratory findings, physical examination, vital signs, weight or ECG (see Section 7.2) will be considered for DLT assessment, according to the protocol definition.

Please refer to Section 7.7.3 for details of how to report DLT events.

4.4. Criteria for Re-treatment and Dose Modification Rules

The following sections describe the requirements for proceeding with treatment with SEL24/MEN1703 from Cycle 2 onwards, and the protocol rules for dose modification due to toxicity.

From Cycle 2 onwards, each patient's liver and renal function tests must return to the values required for entry into the study (Section 3.1) or better, in order to continue treatment in the next cycle. This requirement may be achieved by following a dose delay as described below.

In the case of SEL24/MEN1703-related non-hematologic toxicity, the dose modification rules to be followed in both parts of the study are presented in Table 10. No more than two dose reductions for toxicity will be permitted before withdrawal of study treatment.

Table 10: Dose Modification of SEL24/MEN1703 for Non-hematologic Toxicity

CTCAE Grade	Occurrence of Specified Event	SEL24/MEN1703 Dose Modification
≤Grade 2 (tolerable)	Any	Maintain patient's starting dose if toxicity can be tolerated
Grade 2 intolerable	1st	Delay treatment by up to 2 weeks; - If toxicity resolved, re-start at same dose level - If toxicity not resolved, re-start at dose level below*
	2nd	If at patient's starting dose, delay treatment by up to 2 weeks; - If toxicity resolved, re-start at dose level below* If at dose level below patient's starting dose; - Discontinue permanently
	3rd	Discontinue permanently
Grade 3	1st	Delay treatment by up to 2 weeks; - If toxicity resolved, re-start at dose level below*/** - If toxicity not resolved, permanently discontinue**
	2nd	Discontinue permanently**
Grade 4	Any	Discontinue permanently**

**dose reductions lower than 25 mg are not possible*

***patients with Grade 3 or 4 electrolyte imbalances that respond to correction i.e. return to ≤Grade 2, within 48 h from correction's onset may re-start at the same dose level; if the event occurs a 2nd time, the patient must re-start at the dose level below; if the event occurs a 3rd time, they must be permanently discontinued.*

After Cycle 1, in case of hematologic toxicity the bone marrow status will guide the initiation of the next cycle according to Table 11 (NOTE: bone marrow examination may not be performed in case peripheral labs indicate persistence of disease):

Table 11: Dose Modification of SEL24/MEN1703 for Hematologic Toxicity

Bone marrow status	SEL24/MEN1703 Dose Modification
No remission	Next cycle may commence immediately
Remission	Next cycle may commence once peripheral count recovery has been achieved
Hypocellular (<5% cellularity without evidence of leukemia blasts)	Next cycle may not commence until peripheral counts recover • *Once peripheral counts recover, start SEL24/MEN1703 at same dose level if recovery by Day 42* • *If peripheral count recovery occurs beyond Day 42, then a one dose level reduction of SEL24/MEN1703 for subsequent treatment cycles should be implemented, once peripheral counts recover*
Achieved CR or CRi, with G3 or 4 hematologic toxicity (e.g. febrile neutropenia)	Consider one dose level reduction of SEL24/MEN1703 for subsequent treatment cycles, once peripheral counts recover

The Investigator may determine the resumption of next treatment cycle based on clinical judgement. Deviations from the above guidelines are permitted to ensure safety and serve the best interest of the patient according to the assessment and judgement of the Investigator. The reason for deviating from the guidelines should be documented in source documents.

Dosing may be withheld in the presence of non-drug related Grade 3 or 4 adverse event if the Investigator feels that it is unsafe to continue the administration of SEL24/MEN1703.

In general, a patient who requires more than two dose reductions will be removed from the study unless, in the opinion of the investigator, the patient is experiencing a clinical benefit defined as achieving CR, CRi, CRh, PR or stable disease without unacceptable toxicities. In such cases, a decision regarding the continuation of treatment with SEL24/MEN1703 and further dose reductions will be made on an individual basis in consultation with the medical monitor and the justification will be recorded in the source documents. All dose modifications will be captured in the eCRF.

Patients will be monitored for compliance throughout the study and may be withdrawn if considered to be non-compliant (see Section 3.4). In Part 1 (from Cycle 2 onwards only) and in Part 2, an extended treatment delay e.g. of up to 14 days, may be permitted on one occasion, either before commencing a new treatment cycle or during a treatment cycle, for reasons unrelated to SEL24/MEN1703 toxicity where the Investigator considers the treatment delay to be exceptional and that it remains in the patient's best interests to continue with SEL24/MEN1703.

4.5. Intra-patient Dose Escalation

In Part 1, intra-patient dose escalation will be permitted per patient at the discretion of the Investigator, and in consultation with the DMC. The selected dose for the escalation step must

have been confirmed as well-tolerated (i.e. patients must have been evaluated to the end of Cycle 1, and the dose level does not exceed the MTD). The patients must also have completed 2 or more cycles of treatment at their starting dose without experiencing any DLT or its equivalent. Intra-patient Dose Escalation is not permitted in Part 2.

5. STUDY SCHEDULE

The study consists of a Screening period, Treatment cycles, a Final Study Visit, plus Follow-up Assessments. Informed consent must be obtained using the current version of the Patient Information Sheet (PIS)/Informed Consent Form (ICF) prior to commencing Screening. Patients will attend the clinic for Screening assessments up to a maximum of 28 days before receiving the first dose of SEL24/MEN1703. Due to the nature of the disease being studied, it is likely that Screening assessments will in practice be carried out over a shorter time period. The Final Study Visit assessments will occur up to 30 days after the patient has discontinued SEL24/MEN1703 study treatment. A final AE and concomitant medication review must take place 30 days after the last dose of SEL24/MEN1703. Follow up assessments will be conducted, wherever possible, every 3 months after the Final Study Visit regardless of initiation of additional treatments for up to 1 year (or until End of Study, whichever occurs first).

The following sections provide a detailed listing of study assessments by visit. A summary of this information is also provided in Schedule of the Study Assessment (Table 5).

Patients will be required to visit the study sites for each study visit. Permitted tolerance windows for specific study visits and assessments may apply and are described in the Schedule of Study Assessment (Table 5) and in its footnotes. Where these are applied, the same tolerance windows may also be used for the entire study visit and all other assessments scheduled to be conducted at that visit.

5.1. Schedule of Study Assessments

Each section below provides a summary of study assessments described by visit.
Please also refer to the Schedule of Study Assessments (Table 5) and associated footnotes.
Informed Consent must be obtained using the current version of the PIS/ICF prior to commencing Screening. On dosing days, assessments should be performed prior to SEL24/MEN1703 dosing unless specified otherwise. Additional assessments may be conducted as clinically indicated. Where possible, patients will be followed up every 3 months for up to 1 year from their Final Study Visit regardless of initiation of additional treatments to check for disease progression and survival status. This assessment may be made by telephone interview or performed during the patient's routine clinic visits following completion of participation in the study. If the patient is lost to follow-up public databases can also be searched.

The following list of assessments is based on 14 days of SEL24/MEN1703 treatment in 21-day cycles, further details, including possible exceptions for samples to be collected, are reported in the Schedule of Study Assessments (Table 5) and its footnotes.

Screening (up to a maximum of 28 days prior to first dose of SEL24/MEN1703)

- ~ Demographics
- ~ Medical history
- ~ Inclusion/exclusion check
- ~ FSH/Pregnancy testing (as appropriate; pregnancy test to be conducted within 7 days of the first SEL24/MEN1703 administration)
- ~ ECOG PS

- ~ Vital signs
- ~ Physical examination
- ~ Clinical chemistry
- ~ Hematology
- ~ Coagulation
- ~ Lipid profile
- ~ Peripheral blasts
- ~ Urinalysis
- ~ ECG
- ~ Echocardiogram (or MUGA scan, if this is preferred standard, local cardiac assessment)
- ~ Bone marrow aspirate/biopsy (local bone marrow differential to be performed)
- ~ Genetic profile of AML cells (bone marrow)
  Note: An aliquot of bone marrow aspirates/biopsy will be used
- ~ PD biomarkers (blood)
- ~ CYP2D6 phenotyping (blood)
- ~ CD25 expression (blood)
  Note: An aliquot of blood taken for PD biomarker will be used
- ~ Mutational status
- ~ AML Karyotypic analysis
- ~ Transfusion status
- ~ Concomitant medication

Cycle 1, Day 1

- ~ Vital signs
- ~ FSH/Pregnancy testing
- ~ Physical examination
- ~ Clinical chemistry
- ~ Hematology
- ~ Coagulation
- ~ Lipid profile
- ~ Peripheral blasts
- ~ Urinalysis
- ~ ECG (pre-dose and 4-6 h post dose)
- ~ PD biomarkers (blood; pre-dose, 2-6h post dose)
- ~ Adverse events
- ~ Transfusion status
- ~ Concomitant medication
- ~ PK profile sampling (blood; pre-dose, 0.5, 1, 2, 4, 6, 8, 10-14 h post dose)
- ~ PK (urine; Part 1 only)

Cycle 1, Day 2

- ~ Clinical chemistry
- ~ Hematology

- ~ Coagulation
- ~ Adverse events
- ~ Transfusion status
- ~ Concomitant medication
- ~ PK sampling (blood; 24 h post C1 D1 dose/C1 D2 pre-dose)
- ~ PK (urine; collect to immediately before D2 dose, Part 1 only)

Cycle 1, Days 3 and 4

- ~ Clinical chemistry
- ~ Hematology
- ~ Coagulation
- ~ Adverse events
- ~ Transfusion status
- ~ Concomitant medication

Cycle 1, Day 7

- ~ Clinical chemistry
- ~ Hematology
- ~ Coagulation
- ~ ECG
- ~ Adverse events
- ~ Transfusion status
- ~ Concomitant medication
- ~ PK sampling (blood; 4 h and 8 h post dose)

Cycle 1, Day 14

- ~ Clinical chemistry
- ~ Hematology
- ~ Coagulation
- ~ Lipid profile
- ~ Peripheral blasts
- ~ PD biomarkers (blood; 2-6h post dose)
- ~ Adverse events
- ~ Transfusion status
- ~ Concomitant medication
- ~ PK profile sampling (blood; pre-dose, 0.5, 1, 2, 4, 6, 8, 10-14 h post dose)

Note: PD and PK sampling times are relative to last dose in C1.

Cycle 1, Day 15

- ~ PK sampling (blood; 22-26 h post C1 D14 dose)

Note: PK sampling times are relative to last dose in C1.

Cycle 1, Day 17

~ PK sampling (blood; 70-74 h post C1 D14 dose)

Note: PK sampling time is relative to last dose in C1.

Cycle 1, Day 19

~ PK sampling (blood; 118-122 h post C1 D14 dose)

Note: PK sampling time is relative to last dose in C1.

Cycle 2, Day 1

~ ECOG PS
~ Vital signs
~ FSH/Pregnancy testing
~ Physical examination
~ Clinical chemistry
~ Hematology
~ Coagulation
~ Lipid profile
~ Urinalysis
~ ECG
~ PD biomarkers (blood; pre-dose)
~ Adverse events
~ Transfusion status
~ Concomitant medication
~ PK sampling (blood; pre-dose)

Cycle 2, Day 7

~ Clinical chemistry
~ Hematology
~ Coagulation
~ Adverse events
~ Transfusion status
~ Concomitant medication
~ PK sampling (blood; 2-6 h post dose)

Cycle 2, Day 14

~ Clinical chemistry
~ Hematology
~ Coagulation
~ Lipid profile
~ Peripheral blasts

- ~ PD biomarkers (blood; 2-6 h post dose)
- ~ Adverse events
- ~ Transfusion status
- ~ Concomitant medication
- ~ PK sampling (blood; 2-6 h post dose)

Cycle 3 onwards, Day 1

- ~ ECOG PS
- ~ Vital signs
- ~ FSH/Pregnancy testing
- ~ Physical examination
- ~ Clinical chemistry
- ~ Hematology
- ~ Coagulation
- ~ Lipid profile
- ~ Urinalysis
- ~ ECG
- ~ Bone marrow aspirate/biopsy (mandatory as soon as peripheral lab results become consistent with an objective response and at Cycle 3; recommended every 2 cycles thereafter)
- ~ Disease evaluation (optional; recommended every 2 cycles)
- ~ Genetic profiling (bone marrow, recommended every 2 cycles)
  Note: An aliquot of bone marrow aspirates/biopsy will be used
- ~ PD biomarkers (blood; pre-dose)
- ~ Adverse events
- ~ Transfusion status
- ~ Concomitant medication
- ~ PK sampling (blood; pre-dose)

Cycle 3 onwards, Day 14

- ~ Clinical chemistry
- ~ Hematology
- ~ Peripheral blasts
- ~ PD biomarkers (blood; 2-6 h post dose)
- ~ Adverse events
- ~ Transfusion status
- ~ Concomitant medication
- ~ PK sampling (blood; 2-6 h post dose)

Final Study Visit

- ~ ECOG PS
- ~ Vital signs

- ~ FSH/Pregnancy testing (if Final Study Visit is performed after at least 30 days from last study drug administration; otherwise this test shall be postponed when 30 days have elapsed from last study drug administration
- ~ Physical examination
- ~ Clinical chemistry
- ~ Hematology
- ~ Coagulation
- ~ Lipid profile
- ~ Peripheral blasts
- ~ Urinalysis
- ~ ECG
- ~ Bone marrow aspirate/biopsy (optional; as required)
- ~ Disease evaluation (optional; as required)
- ~ Genetic profiling (bone marrow; optional, as required)
  Note: An aliquot of bone marrow aspirates/biopsy will be used
- ~ Adverse events
- ~ Transfusion status
- ~ Concomitant medication

Follow-Up

~ Follow-up assessments (a visit or a telephone call, as per local practice)

IMPORTANT NOTE: in addition to the optional time points above described, bone marrow aspirate/biopsy is mandatory at Screening and as soon as the peripheral lab results become consistent with an objective response.

5.2. Volume of Blood Sampling

Total blood volumes required during study participation will be provided in PIS/ICF provided to each patient. The Lab Manual will also describe the unit and total blood volumes and provide examples based on various durations on study. Efforts will be made to limit PK and PD blood-letting during the study where on-going data analysis during the study suggests redundancy in sampling. Any such reductions in requirements for PK and PD blood sampling will be described and updated in the Lab Manual.

5.3. Description of Study Interventions and Assessments

Details of the procedures to be followed for specified study assessments are provided. Additional assessments may be carried out as clinically indicated.

5.3.1. Medical history

There will be a baseline assessment of medical history conducted at Screening to confirm eligibility and to record significant medical history and concurrent illnesses in the eCRF. Concurrent illnesses recorded at Screening, that worsen in severity or frequency from this baseline assessment during the study, should be recorded and reported as AEs (see Section 7).

All prior therapy for the treatment of AML must be recorded in eCRF including, but not limited to, start date, stop date and best response.

5.3.2. Pregnancy and FSH test

Female patients of reproductive potential will have a pregnancy test carried out at Screening. This test must be carried out within 7 days prior to first SEL24/MEN1703 administration. Alternatively, pregnancy test may be performed at C1D1 and results should be available prior to receiving study treatment. Additionally, a pregnancy test is required on the first day of each study cycle and after relevant systemic exposure can be reasonably excluded (30 days from the last study drug administration). A urine test is acceptable; however, where a urine test is positive or equivocal, a blood test must be performed to confirm the result. Patients confirmed as pregnant will be excluded from participation in the clinical study.

Please refer to Section 7.7.1 for further instructions on the management of a positive urine test during the study conduct.

Female patients who require documented confirmation of post-menopausal status will have their follicle-stimulating hormone (FSH) levels assessed at Screening. When post-menopausal status is not confirmed, patients will be required to undergo pregnancy testing per protocol to confirm suitability to proceed.

5.3.3. ECOG performance status

ECOG PS will be assessed at the times given in the Schedule of Study Assessment (Table 5). Details of the ECOG PS categories are presented in Appendix A. Patients must be confirmed as ECOG PS 0, 1 or 2 at Screening in order to be eligible for study participation.

5.3.4. Vital signs

Vital sign parameters will be taken at the times given in the Schedule of Study Assessment (Table 5). The date and time of collection will be recorded in the source data and on the eCRF.

Vital sign parameters will consist of measurements of temperature, resting heart rate, seated blood pressure and respiratory rate.

5.3.5. Physical examinations

A physical examination, including measurement of weight, will be taken at the times given in the Schedule of Study Assessment (Table 5). The patient's height will be measured at Screening. The patient's weight will also be assessed at Screening and at the start of every cycle. Height and body weight will be obtained while the patient is wearing light clothing (without shoes).

A full physical examination will include assessment of the following categories: head, eyes, ears, nose, throat, heart, lungs, abdomen, skin, musculoskeletal, extremities, neurological, lymph nodes, and 'other'. After the Screening assessment, the physical examination may be reduced to a symptom-directed assessment.

5.3.6. Clinical chemistry, hematology, coagulation, lipid profile and urinalysis

Blood and urine samples for determination of clinical chemistry, hematology, coagulation, lipid profile and urinalysis parameters will be taken at the times given in the Schedule of Study Assessment (Table 5). The date and time of collection will be recorded in the source data and on the CRF.

All testing will be performed at each site's local laboratory. Patients should be asked to follow local guidance for fasting prior to the lipid profile assessment. At time points where coagulation testing is performed, these parameters may be assessed from the hematology sample. Should a patient develop coagulation abnormalities at any point during the study, a comprehensive evaluation of coagulation abnormalities will be immediately performed which may include, but not be limited to repeat PT/INR, APTT, fibrinogen, D-dimer, plus a peripheral blood smear, thrombin time. These abnormalities have to be evaluated by the Investigator in conjunction with the patient's medical history, physical examination and concomitant medication review. Repeat testing may be performed as clinically indicated, which may include additional parameters or time-points. Additional tests will be performed as required to rule out other etiologies.

Copies of laboratory accreditation certificates and reference ranges will be obtained from each study site prior to the analysis of their first patient sample.

The laboratory variables to be measured are described in Appendix E.

Results from the hematology test panel will contribute to each patient's disease assessment (see Section 5.3.11).

5.3.7. Peripheral blasts

Assessment of peripheral blasts will be part of the hematology panel at the time-points specific in the Schedule of Study Assessment (Table 5).

Results from these assessments will contribute to each patient's disease assessment (see Section 5.3.11).

5.3.8. Electrocardiograms

A resting 12-lead ECG will be performed at the times given in the Schedule of Study Assessment (Table 5).

All 12-lead ECGs should be recorded while the patient is in the supine position. ECGs will be recorded at 25 mm/sec. All efforts should be made to ensure that an identical ECG machine is used to collect traces for individual patients. The Investigator or designated physician will review the ECG results.

5.3.9. Echocardiogram

An echocardiography assessment will be performed at Screening with follow up assessments as clinically indicated. This cardiac assessment may be performed by a MUGA scan if this is the standard, local method used.

5.3.10. Bone marrow assessment

A bone marrow aspirate (or biopsy where obtaining an aspirate is not possible), will be taken at the times specified in the Schedule of Study Assessment (Table 5). A local bone marrow differential assessment, to determine the % of different bone marrow cellular subpopulations, including the % leukemic blasts, will be conducted at Screening. In addition to the optional time points reported in the Schedule of Study Assessment, bone marrow assessment is mandatory at Screening and as soon as the peripheral lab results become consistent with an objective response. Bone marrow aspirates/biopsy will be tested for the genetic profile of AML cells (see Section 5.3.13). An aliquot of bone marrow aspirate/biopsy will be centrally stored for future analysis (e.g. minimal residual disease), if any.

Results from these assessments will contribute to each patient's disease assessment (see Section 5.3.11).

5.3.11. Disease evaluation

Evaluation of disease status will be performed at the time-points described in the Schedule of Study Assessment (Table 5), according to the AML Response Criteria in Appendix D.

Disease assessment will involve evaluation of leukemic blast proportion in the bone marrow. Hematologic parameters from the routine local assessments including blast percentage (where applicable), platelet count, and other relevant parameters such as transfusion dependence will also contribute to this assessment.
To note, disease assessment must be performed as soon as the peripheral lab results become consistent with an objective response. Disease assessment will also include an aliquot of bone marrow aspirate/biopsy that will be centrally stored for future analysis (e.g. minimal residual disease), if any. In case bone marrow aspirate/biopsy is consistent with CRi or better response but still a minimal percentage of peripheral blasts is detected, the response assessment can be postponed up to 2 weeks and will be based on repeated peripheral blood results and last bone marrow aspiration results.

5.3.12. PD biomarkers

Evaluation of PD biomarkers will be performed at the time-points described in Schedule of Study Assessment (Table 5).

The PD activity of SEL24/MEN1703 will be assessed by changes between pre- and post-treatment levels of p-Ser235/6 S6 and other relevant biomarkers as appropriate, in peripheral blood by using flow cytometry.

5.3.13. Genetic profile of AML cells

The genetic profile of AML cells will be performed at the time-points described in the Schedule of Study Assessment (Table 5) by using Next Generation Sequencing and/or qRT-PCR. The mutational status of patients before and after treatment with SEL24/MEN1703 will be assessed by the analysis of a panel of relevant AML mutated genes in bone marrow. Left over sample aliquots

and aliquots of bone marrow aspirates/biopsy may be used for future biomarker analysis which is relevant to the development of SEL24/MEN1703 in AML.
Full details of sample collection and handling for these samples will be described in Lab Manual for the study.

5.3.14. PK sampling

Evaluation of the levels of SEL24/MEN1703 and its metabolites (as appropriate) will be performed at the time-points described in the Schedule of Study Assessment (Table 5). The PK profile of SEL24/MEN1703 and its metabolites, as appropriate, will be evaluated by analysis of concentration levels in plasma. Evaluation of CYP2D6 phenotyping will be carried out (see Section 5.3.15). Results will be reported separately. In Part 1 ONLY, urine samples will also be collected from the first dose of SEL24/MEN1703 until immediately prior to the second dose for PK analysis.

Nominal PK blood sampling times should be adhered to as closely as possible. It is essential that the actual time and date of collection of each blood sample be recorded in the patient's records and in the eCRF.

Full details of sample collection and handling for these samples will be described in the Lab Manual for the study. Left over sample aliquots could be analyzed for metabolite identification purposes. The results of the metabolite identification analysis will be reported separately.

5.3.15. CYP2D6 phenotyping

As SEL24/MEN1703 may both inhibit and act as a substrate for Cytochrome P450 enzyme CYP2D6, patients will be assessed for their CYP2D6 phenotype. A blood sample collected during Screening will be used for this assessment.

5.3.16. CD25 Expression

An aliquot of PD sample collected during Screening will be used for this assessment.

5.3.17. Mutational Status

AML mutational status will be assessed locally at Screening.

5.3.18. AML Karyotypic Analysis

AML Karyotype analysis will be performed locally at Screening.

5.3.19. Transfusion Status

Need for blood transfusion will be recorded as concomitant medication during patient participation to the study. In particular, information on blood transfusion occurred from 28 days prior to the first dose of SEL24/MEN1703 to the Final Study Visit will be collected to define transfusion conversion rate and transfusion maintenance rate.
Transfusion status (independent Vs. dependent) at baseline period and post-baseline period are defined as follows for subjects who took at least one dose of study drug:

Baseline transfusion status:

- Baseline period is defined as the period from 28 days prior to the first dose to 28 days post first dose (C2D7). For subjects who are on treatment <28 days, baseline period is from 28 days prior to the first dose (in the event that this information is not available the ICF signature date will be exploited) until the end of treatment.
- Subjects are classified as baseline transfusion independent if there is no red blood cells (RBC) or platelet transfusions within the baseline period; otherwise, the subject is to be considered as baseline transfusion dependent.

Post-baseline transfusion status:

- Post-baseline period is defined as the period from 29 days post first dose (day after C2D7) until last dose.
- For subjects who are on treatment ≥84 days (C5D1 or more), subjects are classified post-baseline transfusion independent in the event of 56 consecutive days without any RBC or platelet transfusion within post-baseline period
- For subjects who are on treatment >28 days (C2D7) but <84 days (C4D21), post-baseline transfusion status is not evaluable
- Otherwise, the subject is considered post-baseline transfusion dependent.

Both transfusion conversion rate and maintenance rate apply to subjects who have evaluable post-baseline transfusion status.
Transfusion conversion rate is defined as the number of subjects who were transfusion dependent at baseline period but become transfusion independent at post-baseline period divided by the total number of subjects who were transfusion dependent at baseline period. Transfusion maintenance rate is defined as the number of subjects who were transfusion independent at baseline period and still maintain transfusion independent at post-baseline period divided by the total number of subjects who were transfusion independent at baseline period.

6. STUDY MEDICATION AND ADMINISTRATION

The Quality Control Standards and requirements for SEL24/MEN1703 study medication are described in separate release protocols/Certificate of Analysis.

SEL24/MEN1703 IMP will be supplied as gelatin capsules containing 25 and 100 mg SEL24/MEN1703 API (free base) (not-formulated API in capsule) and gelatin capsules containing 25 and 100 mg API (free base) as formulated drug product (formulated drug product in capsule), respectively. Details of the Investigational Product provided during Part 1 are reported in Table 3. Formulated drug only will be provided for Part 2.

The drug product used until the implementation of protocol amendment V8.0 is API directly filled by weight in capsules, which is a suitable procedure for small scale batches in early development stages. However, this formulation and manufacturing process are not suitable for later clinical phases and for industrial scale production for commercial purposes. Therefore, a formulation of drug product has been developed to guarantee a standardized manufacturing process.

Table 12: Composition of SEL24/MEN1703 for oral use

Active components	25 mg capsules: 25 mg SEL24/MEN1703 (free base) 100 mg capsules: 100 mg SEL24/MEN1703 (free base)
Excipients	[redacted]
Stability	Stability testing of SEL24/MEN1703 is on-going and the IMP shelf-life will be extended as appropriate during the course of the clinical study
Storage and handling	API in capsules: SEL24/MEN1703 IMP (API in capsules) must be stored at controlled room temperature [20-25 ºC (68-77 ºF)]. The bottles should be stored protected from light Formulated drug product in capsules: Do not store the SEL24/MEN1703 IMP (formulated drug product in capsules) above 25 °C (77 °F). Do not freeze. Store in the original package

Please refer to the current version of the IB for additional information on the physical, chemical and pharmaceutical properties of SEL24/MEN1703.

6.1. Labeling of SEL24/MEN1703

The IMP SEL24/MEN1703 will be labelled in compliance with the current valid international and corresponding national requirements. The label will report instructions on how to administer and store the SEL24/MEN1703 IMP in local language of the respective study country.

6.2. SEL24/MEN1703 Starting Dose and Duration of Treatment on Study

The starting dose of SEL24/MEN1703 will be 25 mg, taken orally once daily for 14 consecutive days over a 21-day treatment cycle. The cohort dose may be escalated by an increase in the daily dose level during the study based on the dose escalation rules.

Reasons for withdrawal from the study and SEL24/MEN1703 treatment are described in Section 3.4.

Continuation of the study treatment may be discussed between the Investigator and the Sponsor on a case-by-case basis. The DMC may also advise on the suitability of an individual patient to continue to receive study treatment.

Patients who experience a DLT will be permitted to receive further treatment with SEL24/MEN1703 according to the dose modification rules described in Section 4.4.

6.3. Storage of SEL24/MEN1703

SEL24/MEN1703 will be shipped to the site and must be stored at the site in a secure location under controlled room temperature conditions. Do not store SEL24/MEN1703 IMP (formulated drug product in capsules) above 25 °C (77 °F).

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

6.4. Blinding and Procedures for Un-blinding the Study

This is an open-label study, and there are no procedures for blinding and un-blinding.

6.5. Provision and Replacement of SEL24/MEN1703

Sufficient doses of SEL24/MEN1703 medication will be supplied. Where clinical supplies (or packaging) are apparently damaged on receipt or considered unfit for use by the study site, the Sponsor (or their delegate) must be notified immediately. Where required, clinical study supplies will be replaced. Further details on the handling of SEL24/MEN1703 at site will be described in the Pharmacy Manual.

6.6. Drug Accountability

The Investigator is obliged to keep sufficient documentation of the delivery, use and destruction or return of unused, used or partially used IMP. The documentation must include dates, quantities, patient numbers, batch numbers or other identification number. The Investigator may assign some or all of the Investigator's duties for drug accountability to an appropriate pharmacist. Roles and responsibilities of site staff will be recorded in the Investigator Site File.

The Investigator should maintain records that document adequately that the patients have been administered the doses specified in the protocol and reconcile all SEL24/MEN1703 received for the study. The local study monitor will be responsible for checking the drug accountability records maintained by the site during the monitoring visits.

The medication provided for this study is for use only as directed in the protocol. It is the Investigator and their institution's responsibility to establish a system for handling study drug so as to ensure that:

- deliveries of SEL24/MEN1703 are correctly received by a responsible person;

- such deliveries are recorded;
- study treatments are handled and stored safely and properly as stated on the label;
- study drug is only dispensed to study patients in accordance with the protocol; and
- any unused study drug is destroyed locally or returned for destruction in liaison with the study monitor.

Throughout the study, it must be possible to reconcile delivery records with records of usage and any destroyed/returned stock of SEL24/MEN1703. To help with compliance checks, records of usage should include the identification of the patient to whom the study treatment was dispensed and the quantity and date of dispensing, plus all unused supplies at the end of each treatment cycle. Patients will be asked to maintain a dosing diary and bring it with them to study visits to support reconciliation and compliance checks. This record is in addition to any drug accountability information recorded on the eCRF. Any discrepancies must be accounted for on the appropriate forms. Certificates of delivery and return must be signed by the responsible pharmacist, and copies retained in the Pharmacy File.

The return or destruction of unused drug will be conducted after written approval by the Sponsor, with appropriate documentation and drug accountability procedures completed following destruction.

6.7. Treatment Allocation

In order to ensure that the appropriate numbers of patients are enrolled to each cohort in Part 1 and in Part 2, and that enrolment to the study is appropriately controlled, on identifying a potential study patient, the Investigator is required to register a patient in the study. Patients will be registered in the study by using the Interactive Web Response System (IWRS) automated patient registration system (see the Study Operations Manual for specific instructions).
Prior to registration of Screening in IWRS and any study-specific evaluations being performed, all patients must have given written informed consent for the study. Patients must have completed the Screening evaluations and must meet all of the eligibility requirements listed in Section 3 prior to being registered in the system as enrolled. Study drug will be assigned through the IWRS.

There will be regular communication with the sites during the study, in addition to the Cohort Review Meetings to ensure that Investigators are aware of enrolment status on the study and of suitable times for patient enrolment.

6.8. Dosing Instructions

Patients will be instructed to take their assigned SEL24/MEN1703 dose at regular intervals in the morning on dosing days, swallowed with water or an alternative drink. Doses shall be taken on an empty stomach (at least 2 hours after and 1 hour before eating). Patients will be asked to record the exact time they take each dose, how many capsules they take, what they have eaten and drunk, and when, before and after each dose in their dosing diary (see Section 6.6). Patients enrolled once the DMC has approved the introduction of the formulated SEL24/MEN1703 will be instructed to take the assigned number of capsules, following the same dosing instructions.

Patients will be instructed not to make up missed doses or vomited doses. Full details of dosing instructions will be provided to patients in the PIS.

Patients must be informed that a SEL24/MEN1703 photosensitivity/phototoxicity effect cannot be excluded. For this reason, patients should minimize or avoid exposure to natural or artificial sunlight (tanning beds or UVA/B treatment) during the entire study period. If patients need to be outdoors when taking SEL24/MEN1703, they should wear loose-fitting clothes that protect skin from sun exposure and discuss other sun protection measures with the investigator. If a sunburn like reaction or skin eruption occurs, patients should contact the investigator.

6.9. Permitted and Restricted Concomitant Medications

Medications specifically prohibited in the exclusion criteria (Section 3.2) are not allowed during the ongoing study. If there is a clinical indication for any medication specifically prohibited during the study, discontinuation from study therapy may be required. The Investigator should discuss any questions regarding this with the assigned Medical Monitor for the study. The final decision on any supportive therapy or vaccination rests with the Investigator and/or the patient's primary physician. However, the decision to continue the patient on study treatment requires agreement from the Medical Monitor.

Note that use of erythropoiesis stimulating agents and growth factors during Cycle 1 is prohibited. Beyond Cycle 1, their use should be avoided; however, their use may be discussed with the Medical Monitor on a case-by-case basis.

6.9.1. Acceptable concomitant medications

All treatments that the Investigator considers necessary for their patient's welfare may be administered at their discretion in keeping with the standards of medical care. All concomitant medication will be recorded on the eCRF including all prescription, over-the-counter, herbal supplements, pre-medications, intravenous medications or transfusions. Note that the assessment of red cell transfusions will be part of the disease assessment criteria (see Section 5.3.11). If changes occur during the study period, documentation of drug dosage, frequency, route, and date may also be included on the eCRF. All concomitant medications the patient received within 30 days before the first dose of SEL24/MEN1703 and 30 days after the last dose of SEL24/MEN1703 should be recorded. Concomitant medications administered after 30 days from the last dose of SEL24/MEN1703 should be recorded for SAEs and any Events of Clinical Interest (ECIs) as defined in Section 7.10.

Sites should follow their institutional guidelines for treating hypophosphatemia, including administration of oral or I.V. phosphate supplements. Phosphate supplements should be started the same day any ≥Grade 3 hypophosphatemia is detected. Patients should be retested no less than every 24 hours, until phosphate levels are ≤Grade 2. SEL24/MEN1703 treatment may be reinstated per the retreatment guidelines provided in Section 4.4. Lower grade abnormalities should be monitored and corrected as soon as possible. Additional assessments should be carried out as clinically indicated.

6.9.2. Antibacterial and antifungal prophylaxis

Patients with grade 4 neutropenia should receive both antibacterial and antifungal prophylaxis according to institutional guidelines, as long as grade 4 neutropenia persists. Commonly used prophylactic agents (fluoroquinolones, azoles), with the exception of isavuconazole (not allowed, being a BCRP inhibitor) are not contraindicated, however careful clinical monitoring is recommended pending the clinical evaluation of potential for drug-drug interactions.

6.9.3. Potential for drug-drug interactions

Non-clinical drug interaction studies indicate that SEL24/MEN1703 may inhibit CYP2D6, and act as a substrate for CYP2D6 and BCRP. Between discontinuation of the following agents and the first administration of SEL24/MEN1703 (see Exclusion Criterion 16), a 7-day washout period, or a period corresponding to 4-5 half-lives of the agents, is therefore mandated:

- sensitive CYP2D6 substrates
- CYP2D6 substrates with a narrow therapeutic range
- strong or moderate CYP2D6 inhibitors
- BCRP inhibitors

In addition, any drug which is a CYP2D6 substrate, a strong or moderate inhibitor of CYP2D6, or a BCRP inhibitor should not be administered concomitantly with SEL24/MEN1703 during the study. If a patient requires a drug in these categories, the Investigator should explore the use of an alternative therapeutic treatment/agent. If this is not possible, SEL24/MEN1703 should be discontinued and a 7 day washout period allowed before administration of the required therapeutic agent commences. Following discontinuation of SEL24/MEN1703 for this reason, treatment with SEL24/MEN1703 cannot re-start once treatment with the CYP2D6 substrate, or inhibitor of CYP2D6 or BCRP has stopped. Examples of relevant drugs to consider are provided below.

CYP2D6 substrates:

- Sensitive CYP2D6 substrates: atomoxetine, desipramine, dextromethorphan, metoprolol, nebivolol, perphenazine, thioridazine, tolterodine, venlafaxine, nortriptyline
- CYP2D6 substrate with narrow therapeutic range: thioridazine

CYP2D6 inhibitors:

- Strong CYP2D6 inhibitors: quinidine, fluoxetine, paroxetine, bupropion, dacomitinibm, ecstasy, terbinafine
- Moderate CYP2D6 inhibitors: AMD070, cinacalcet, moclobemide, mirabegron, duloxetine, dronedarone, eliglustat, tipranavir/ritonavir, fluvoxamine, cimetidine

BCRP inhibitors:

- Representative BCRP inhibitors: cyclosporine, elacridar (GF120918), eltrombopag, gefitinib, curcumin, isavuconazole

Please refer to Appendix F for a (not-exhaustive) list of CYP2D6 substrates, CYP2D6 inhibitors and BCRP inhibitors.

7. ADVERSE EVENTS AND REPORTING REQUIREMENTS

7.1. Assessment of Safety

All patients who have received at least one dose of SEL24/MEN1703 will be considered evaluable for safety. All AEs and SAEs will be collected from the time the patient gives informed consent up to and including the 30 day follow up (Final Study Visit). There will be a baseline medical condition review taken at Screening. Events, other than the primary disease under evaluation, that worsen in severity or frequency from this baseline assessment during the study, should be recorded and reported as AEs.

7.2. Adverse Event Definition

An AE is defined as any new untoward medical occurrence or worsening of a pre-existing medical condition in a patient or clinical investigation patient administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including a clinically significant abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the IMP.

The definition covers also medication errors and uses outside what was foreseen in the protocol, including misuse and abuse of the product (see chapter 7.7.2).

Adverse events include:

- worsening (change in nature, severity, or frequency) of conditions present at the start of the study;
- intercurrent illness;
- drug interactions;
- experiences related or possibly related to concomitant medications;
- clinically significant abnormal laboratory values or shifts from baseline; and
- clinically significant abnormalities in physical examination, vital signs, weight, or ECG.

The Investigator must record all the available information concerning any non-serious AE (whether or not deemed related to the study treatment) in the corresponding section of the eCRF-AE pages, within 5 calendar days after the first knowledge of the occurrence of the event

Progression of the disease under study (i.e. AML) will not be captured as an AE.

Surgical procedures or other therapeutic interventions themselves are not AEs, but the condition for which the surgery/intervention is required is an AE and should be documented accordingly.

Planned surgical measures and the condition(s) leading to these measures are not AEs, if the condition(s) was (were) known before the period of observation and did not worsen during study. In the latter case, the condition should be reported as medical history.

7.3. Importance of Adverse Event Reporting

Timely and complete reporting of safety information is very important to assist in the identification of any untoward medical occurrence, thereby ensuring:

- the safety of study patients;
- a greater understanding of the overall safety profile of the investigational drug;
- recognition of any dose-related investigational drug toxicity;
- appropriate modification of study protocols;
- improvements in study design or procedures as required; and
- adherence to required ethical and regulatory requirements for clinical study conduct.

7.4. Evaluating Adverse Events

Following the patient's written consent to participate in the study, all AEs should be collected. All identified AEs must be recorded and described on the appropriate AE page of the eCRF, except for those events occurring prior to the first dose of study medication, which should be recorded on the Medical History eCRF page (unless related to the study procedures performed prior to dosing ; in this case they have to be reported as an AE). Where known, the diagnosis of illness or disorder should be recorded, rather than listing individual symptoms.

The following information should be captured for all AEs: date of onset and resolution, severity of the event (see definitions in Section 7.5), assessment whether the event was serious or non-serious, Investigator's opinion of the relationship to IMP (see definitions in Section 7.8) treatment required for the AE, action taken with IMP, and information regarding resolution/outcome.

7.5. Severity

All AEs (including SAEs) are to be accurately recorded on the AE page of the patient's eCRF. Each event will be graded for severity using the classifications of NCI CTCAE v4.03 (see Appendix C). For events not addressed in the NCI CTCAE v4.03, classifications the following grading will apply:

- **Mild (Grade 1)** - Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- **Moderate (Grade 2)** - Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activity of daily living.
- **Severe (Grade 3)** - Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activity of daily living.
- **Life-threatening (Grade 4)** - Life-threatening consequences; urgent intervention indicated.
- **Death (Grade 5)** - Related to adverse event.

7.6. Serious Adverse Events

An SAE is defined as any untoward medical occurrence that at any dose causes or qualifies as the following:

- Results in death.
- Is life-threatening:
  - "Life-threatening" means that the patient was at immediate risk of death at the time of the SAE; it does not refer to an SAE that hypothetically might have caused death if it were more severe.
- Requires hospitalization or prolongation of existing hospitalization:
  - This means that hospital inpatient admission or prolongations of hospital stay were required for the treatment of the SAE or that they occurred as a consequence of the event.
  - Visits to a hospital by ambulance or to the emergency room without admission will not be regarded as hospitalization unless the event fulfills any other of the serious criteria.
- Results in persistent or significant disability or incapacity:
  - "Persistent or significant disability or incapacity" means a permanent or significant and substantial disruption of a person's ability to carry out normal life functions.
- Is a congenital anomaly or birth defect.
- Is an important medical event:
  - Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in situations where none of the outcomes listed above occurred. Important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above should also usually be considered serious. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias, or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Note-1: These characteristics/consequences have to be considered at the time the event occurs. For example, regarding a life-threatening event, this refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
Any other AE/ADR which is not included in the above definitions will be considered as non serious.

Note-2: Hospitalization lasting less than 24 hours or pre-planned hospitalization for diagnostic procedures or medical intervention shall not qualify as SAE.

For the purposes of this study, specified events considered to be expected in this patient population and during leukemia therapy will not require to be reported as SAEs (see Section 7.6.1).

All patients with SAEs must be followed up for outcome until it is considered resolved, returns to baseline, is chronically ongoing, stabilized, or is otherwise explained by the Investigator.

If the Investigator detects a SAE in a study patient after the end of the period of observation and considers the event possibly related to prior study treatment or procedures, they should immediately (within 24 hours of awareness) contact the Sponsor to determine how this event should be documented and reported. For screening failure patients, SAEs detected after SF declaration will be recorded only if the event is considered as possibly related to study procedures.

7.6.1. Exceptions to SAE reporting

For this study, the following events will be considered to be expected events in this population and during leukemia therapy other than SEL24/MEN1703 (e.g. myelosuppression and events secondary to disease) and should not be reported to the Sponsor as serious events unless the Investigator considers any of these events to be clinically concerning and of unusual manifestation with regard to severity, duration, frequency, outcome or other characteristics of the event. It is important to note that these events (with the exception of progression of AML), still need to be captured as AEs on the AE eCRF and will be reviewed by the DMC in aggregate with all cumulative safety data.

Expected events during leukemia therapy are:

- Myelosuppression due to disease or leukemia therapy :
  - febrile or infection episodes.
  - epistaxis or bleeding except for catastrophic CNS or pulmonary hemorrhage.
  - anemia, neutropenia, lymphopenia, thrombocytopenia, leukopenia, leukocytosis.
- Events due to underlying disease:
  - symptoms associated with anemia:
    - ~ fatigue.
    - ~ weakness.
    - ~ shortness of breath.
  - electrolyte abnormalities (sodium, potassium, bicarbonate, CO_2, magnesium).
  - chemistry abnormalities (LDH, phosphorus, calcium, BUN, protein, albumin, uric acid, alkaline phosphatase, glucose).
  - coagulation abnormalities.
  - disease specific therapy (induction, maintenance, salvage, or stem cell therapy).
  - alopecia.
  - bone, joint, or muscle pain.
  - liver function test abnormalities associated with infection or disease progression.
  - disease progression.
- General therapy events:
  - events attributed to the use, placement and/or insertion of catheters.
  - renal failure associated with tumor lysis syndrome or antibiotic/antifungal therapy.

- rash due to antibiotic use.
- Hospitalization for the management of any of the above expected events.

Abnormal hematologic or clinical chemistry values, not considered to be clinically significant, will not be recorded on the adverse event eCRF, although all values will be recorded on the hematology and clinical chemistry laboratory eCRFs.

7.7. Other Important Events for Immediate Reporting

In addition to the above criteria, AEs meeting either of the below criteria, although not serious per ICH definition, are reportable to the Sponsor in the same timeframe as SAEs to meet certain local requirements and the study needs.

- a new cancer (that is not a condition of the study);
- a reported pregnancy or lactation after receipt of study treatment and for up to 30 days from last dose;
- an overdose (defined as any dose of SEL24/MEN1703 which is more than the assigned dose for that patient); or
- an AE which qualifies as a DLT during Cycle 1 for patients in Part 1 (see Section 7.7.3).

Such events must be reported within 24 hours to the Sponsor via the eCRF. Once the information is saved in the eCRF, a notification e-mail will be automatically generated and sent to the Sponsor's Study Drug Safety Unit (SDSU). Only in case of breakdown of the eCRF System, the specific paper report form, provided to the sites, will be used. In such case, the Investigator will be responsible for sending the corresponding paper form and inserting the data in eCRF as soon as the system works again. The reporting procedures can be found in the *SAE report form completion manual* distributed to the sites.

7.7.1. Exposure during pregnancy or lactation

Although pregnancy and lactation are not considered AEs, it is the responsibility of Investigators or their designees to report any pregnancy or lactation in a patient (spontaneously reported to them) or pregnancy in a patient's partner that occurs during the study.

Pregnancies and lactations that occur in patients after the ICF is signed but before starting study treatment must be reported by the Investigator if they cause the patient to be excluded from the study. Pregnancies and lactations that occur in a study patient or a pregnancy in a patient's partner from the time of first study treatment through to 30 days following cessation of SEL24/MEN1703 study treatment must be reported by the Investigator. All reported pregnancies must be followed to the completion or termination of the pregnancy. If the pregnancy continues to term, the outcome (health of infant) must also be reported.

Such events must be reported within 24 hours to the Sponsor.

Pregnancy and lactation will be reported to the Sponsor via EDC. ONLY if the eCRF system does not work, the specific paper report form (Pregnancy Exposure Report form) will be completed and sent to the Sponsor by email or fax (see Section 7.7). The "Pregnancy Exposure Report" form will be distributed to the sites to be used for this purpose. The outcome of the reported pregnancies will be always notified to the Sponsor using the Pregnancy Exposure Report form. If the pregnancy results in an abnormal outcome (miscarriage or new-born with congenital abnormality and/or stillbirth), this will be recorded in the eCRF as a SAE and managed as described in Section 7.10. The reporting procedures can be found in the *SAE report form completion manual* distributed to the sites.

7.7.2. Misuse and overdose

Both misuse and overdose issues should be reported to the Sponsor's SDSU within the same timelines as a SAE, even if they may not result in an adverse outcome (see Section 7.7). In the event of overdose, the patient should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

For the purpose of this protocol, an overdose is any dose of SEL24/MEN1703 which is more than the assigned dose level for that patient. The corresponding information should be entered on the overdose page in the eCRF no later than 24 hours of awareness by the site. Once the page is completed and saved by the staff involved in the study, an alert notification will be automatically sent to the Sponsor. ONLY if the eCRF system does not work or if the eCRF is not available, the paper CRF-AE report form shall be used and sent to the Sponsor by email.
The reporting procedures are described in detail in the *SAE report form completion manual* distributed to the sites.
In addition, if an AE (serious o non-serious) is associated with an overdose, it will be recorded on the AE page in the e-CRF, recording the overdose details.

If the pharmacy discovers that an overdose has or may have been administered, they should immediately contact the Investigator and Sponsor (or their delegate).

7.7.3. Dose limiting toxicity

DLT events for dose escalation decisions will be assessed at the end of Cycle 1 (and on Day 42 in the case of protracted neutropenia in the absence of active AML), for each patient in each cohort and should be reported within 24 hours of the Investigator or their study team first becoming aware of the event. The AEs listed below will be considered as DLT unless they are clearly and incontrovertibly attributable to the underlying disease or to an extraneous cause:

- Grade 5 toxicity
- Grade 4 neutropenia lasting ≥42 days from the start of the therapy cycle in absence of evidence of active AML (<5% blasts)
- Grade 3 or 4 non-hematologic toxicity, except:
  - Alopecia;
  - Grade 3 fatigue, asthenia, anorexia, fever, or constipation;

- Grade 3 nausea, vomiting, or diarrhea not requiring tube feeding, TPN, or hospitalization;
- Infection, bleeding, or other expected direct complications of cytopenias due to active leukemia;
- Grade 3 or 4 electrolyte imbalances that respond to correction i.e. return to ≤Grade 2, within 48 hours (h) from correction's onset;
- Grade 3 increase in aspartate aminotransferase (AST) and/or, alanine aminotransferase (ALT) and/or alkaline phosphatase (ALP) recovering ≤Grade 2 within 7 days.

Only **clinically significant** abnormalities in laboratory findings, physical examination, vital signs, weight or ECG (see Section 7.2) will be considered for DLT assessment, according to the protocol definition.

7.7.4. Investigational product complaints

Pharmaceutical technical complaints associated with the investigational product must be reported to the Sponsor immediately. The same reporting timelines as for SAEs apply.

7.8. Relationship

All AEs (including SAEs) will be assessed for the relationship of the AE to the study drug using the following standard definitions (for DLT events assessment for dose escalation decision please specifically refer to the above chapter 7.7.3):

- **Not Related:** The event or laboratory test abnormality (AE), with a time to drug intake with an unreasonable relationship and or non-plausibility and/or the existence of a clear alternative explanation.
- **Unlikely related** - The event or laboratory test abnormality (AE), with a time to drug intake that makes a relationship improbable (but not impossible). Disease or other drugs provide plausible explanations.
- **Possibly related** - The event or laboratory test abnormality (AE) has a reasonable time relationship to the drug intake, but it could also be explained by disease or other drugs. Information on drug withdrawal (dechallenge) may be lacking or unclear.
- **Probably related** - The event or laboratory test abnormality (AE) has a reasonable time relationship to the drug intake, it is unlikely to be attributed to a concurrent disease or other drugs and it follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge (AE reappearance after drug reintroduction) is not required to fulfil this definition.
- **Definitely related** - The event or laboratory test abnormality (AE) has a plausible time relationship to the drug intake and it cannot be explained by a concurrent disease or other drugs. The response to withdrawal of the drug (dechallenge) should be plausible (pharmacologically, pathologically). The event must be definitive pharmacologically or phenomenologically (i.e. an objective and specific medical disorder or a recognised pharmacological phenomenon), using a satisfactory rechallenge procedure if necessary.

Please also refer to supporting information provided in Appendix C. The relationship of the study treatment to an AE will be determined by the Investigator and subsequently reviewed by the Medical Monitor.

For reporting and data analysis purposes, AEs reported with a causality assessment of "Definitely", "Probably", and "Possibly" are to be considered as "having a reasonable causal relationship" to study drug. In case of disagreement between the Investigator and the Sponsor's Medical Monitor, the more conservative assessment will determine the reportability of the case.

7.9. Unexpected Adverse Events

The Sponsor will assess all SAEs whether they are expected or unexpected. An unexpected AE is any adverse drug event, the outcome, specificity, or severity of which is not consistent with that included in the Reference Safety Information chapter of the current IB.

7.10. Reporting Serious Adverse Events

Adverse events classified as serious require expeditious handling and reporting to the assigned Sponsor's Study Drug Safety Unit (SDSU) to comply with regulatory requirements, except for SAEs meeting the "exceptions to SAE reporting" definition (see Section 7.6.1).

For any SAE that occurs while a patient is on-study; within 30 days of the last study drug administration, regardless of any opinion as to the relationship of the SAE to the study drug; or if any SAE that the Investigator considers as related to the study drug occurs later than 30 days after the last study drug administration, the Sponsor's SDSU must be notified immediately (within 24 hours of becoming aware of the event).
The procedure for reporting is via eCRF. Once the event is entered and saved on the AE page in the eCRF, an automatic alert notification will be sent to the Sponsor's SDSU. ONLY in case of eCRF system unavailability, the paper CRF-AE report form can be completed and the PDF sent to the Sponsor's SDSU by email to meet the reporting timelines. As soon as the eCRF works again, the event should be recorded in the eCRF by the Investigator without further delay.
The Sponsor's SDSU and the SDSM contact details are listed below.

Table 13: Contact details for SAE reporting

SAE Facsimile Transmission:	sdsu@menarini.es
SDSM:	[redacted]
SDSM E-mail Contact:	[redacted]
SDSM Phone:	[redacted]
SDSM Mobile	[redacted]

7.11. Reporting of Serious Advert Events to Regulatory Authority

The Sponsor has appointed the centralized Study Drug Safety Unit (SDSU) team as responsible for the management of AEs from all the sites in compliance with the applicable regulatory

requirements (including SAEs and SUSARs management) and all safety communications to be submitted to the sites, RAs and ECs accordingly to the procedures described in the corresponding study Safety Management Plan (SMP).

In addition, the Sponsor shall ensure that all relevant information about any SUSAR, will be expeditiously reported to the CAs (including EudraVigilance Clinical Trial Module), and to ECs if applicable (as per country-specific requirements) with the following deadlines after the first knowledge, intended as the day when the Sponsor's receives the notification of the SUSAR or the monitor is aware of it:

- Fatal and life-threatening unexpected cases, no later than 7 days;
- Other unexpected serious cases, no later than 15 days.

The Sponsor shall ensure that all relevant new information and supporting documentation that subsequently become available will be also expeditly reported as follow-up information no later than 15 days after the first knowledge for all cases.
The following safety issues will be subject to expedited management for the identification of possible necessary actions:

- SAEs associated with the study procedures;
- Potential clinically significant findings emerging from non-clinical studies;
- An anticipated end or suspension for safety reasons of another study with the same study treatment.

When appropriate and applicable as per local regulatory requirements, the Sponsor will arrange the adequate information also to the Investigators. The Sponsor (through the SDSU) will distribute the validated CIOMS I form to the investigators (via e-mail) with a safety letter.

For the US, the Investigator must ensure the study team is aware and comply with any additional local reporting requirements. For all SAEs that are related and unexpected, the Sponsor will assign a case number to be used in all future correspondence regarding the event and can provide an IND Safety Reports in MedWatch form or CIOMS form describing the event, for the Investigators to report to their Institutional Review Board (IRB)/ Ethics Committee (EC) or other committee (as per local requirements). Other SAEs (i.e. expected or unrelated SAEs) should be reported per the relevant institution's procedures (if required).

Where required, submission of Safety Updates by the Investigator to Competent Authorities should be handled according to local regulations. Otherwise, periodic safety reports to the regulatory agencies will be handled by the Sponsor (or their delegate). These safety updates will also include SAEs that do not require expedited reporting to the authorities.

In addition, a periodic line-listing of SUSARs occurred with SEL24/MEN1703 is to be reported to European Investigators (as per country requirements) every 6 months by the Sponsor SDSU. Periodically (at least annually), the IB will be updated to include new and relevant safety information. Until such time that an AE becomes identified in the IB, it should be considered unexpected for expedited reporting purposes

7.12. Follow Up Information on a SAE

After the End of Study Visit, the Investigator is not requested to actively follow-up the patient unless ongoing SAEs are present. However, if after the end of the study, the Investigator becomes aware of any SAEs with a suspected causal relationship to the study treatment, this SAE should be duly reported to the Sponsor and recorded in the eCRF if still available. If the eCRF is not available anymore, the paper CRF SAE form will be used as a backup.

Collection of complete information concerning SAEs is extremely important. Thus, follow-up information that becomes available as the SAE evolves, as well as supporting documentation (e.g. hospital discharge summaries and/or autopsy reports), should be collected subsequently, if not available at the time of the initial report, and immediately sent using the same procedure as the initial SAE report. The original SAE form must be kept on file at the study site. The Sponsor will also review SAE reports for missing information and open queries to the site for resolution as appropriate.

Appropriate diagnostic tests should be performed and therapeutic measures, if indicated, should be instituted. Appropriate consultation and follow-up evaluations should be carried out by the Investigator (or designee). A SAE is followed until it is considered resolved, returns to baseline, is chronically ongoing, stabilized, or is otherwise explained by the Investigator.

8. DATA EVALUATION

8.1. Data Monitoring Committee

The DMC consists of the Principal Investigators (or their representatives), the Medical Monitor, and Sponsor representatives. It may also include invited experts (such as a PK or PD data expert). During Part 1 the DMC will meet by telephone (or in person if possible) to review safety data from the first treatment cycle of the current cohort under evaluation. The DMC will also convene periodically during Part 2, after every 2 months or a further 6 patients have been enrolled (whichever comes first), to consider ongoing safety and tolerability at the RD. They will also consider PK and PD data as available and on-going safety data from prior cohorts. Appropriate representatives of the Sponsor and the coordinating personnel will also attend and minute the meeting. Decisions of the DMC will be documented, filed in the eTMF, and will be distributed to all study sites.

Further details on the composition of the DMC, as well as the process for data review and decision making, are described in the DMC charter for this study.

The DMC will:

- review the safety data from the first cycle of treatment for each cohort during Part 1 and make dose-escalation decisions;
- consider other AEs, or possible trends in AEs, during Part 1 which may inform dose escalation decisions or selection of the RD for Part 2;
- confirm the MTD or MAD and select the RD for further evaluation in Part 2;
- review the safety data package for Part 1; perform on-going assessment of safety, anti-leukemic activity, PK and PD data in Part 2;
- support the implementation of supportive care guidelines during the study, by ongoing review of AEs and need for treatment delays; consider these data both for DLT evaluation, possible need for dose modification for individual patients, or recommendation for withdrawal (see Section 3.4).

8.2. Populations

Two populations for analysis are considered:

The dose determining set will consist of all patients in each cohort that have completed one cycle of treatment and patients that discontinued earlier due to a DLT occurring in this period. This population will be used for the dose escalation Part 1.

For all other objectives, the safety set consisting of all patients that have received at least one dose of SEL24/MEN1703 will be used. Patients will be also be categorized by cohort and by dose level received.

For some objectives (e.g. anti-leukemic or PD activity), a subgroup of patients of the safety set with respective baseline and post-baseline measurements will be used.

Patients who were screened but did not receive any treatment will be listed and will not be part of any summary table.

8.3. Completion of the Study

The study will be completed when all patients have completed their Final Study Visit assessment. On completion of the study, data will be reconciled and the database will be locked for analysis.

Study start is defined by First Patient In (FPI) i.e. when the first patient receives the first dose of study drug. Study Completion is defined by Last Patient Out (LPO) of the study i.e. when the last patient enrolled in the study has completed the last dose of study drug or discontinued for any reason and been followed up to the Final Study Visit.
End of Study is defined as the Final Study Visit of the last subject who discontinues the study treatment.

An addendum (or addenda) to the Clinical Study Report will be generated as required to report any data obtained during the Follow-up Assessments.

8.4. Statistical Considerations

Detailed statistical analysis information will be provided separately in the Statistical Analysis Plan (SAP). The SAP will detail all data handling rules, including the management of missing values and the handling of data for withdrawn patients. The SAP will also outline protocol deviation criteria. Any deviations to the planned analyses specified or populations defined within the SAP will be justified in writing and presented within the final clinical study report.

The clinical database lock will occur after all data are reconciled (i.e. “cleaned”) for all patients who participate in both Part 1 and Part 2. A single clinical study report will be generated for this study. The SAP will be finalized and signed before the database is locked.

In all tables, listings and figures the dose-escalating cohorts will be reported from the lowest to the highest dose. Part 1 will be reported together with Part 2. Where appropriate, those patients who received the same dose in Part 1 or Part 2 in both cohorts may be combined and summarized, as well as being summarized separately. The same is valid for the two cohorts, “all-comers” and “IDH-mutants” patients.

8.4.1. Missing data/discontinuation

Due the dose escalation design of the study no missing imputation of missing values will be done for the primary objective. Reasons for discontinuation of the study and the study treatment will be listed and summarized.

8.5. Demographic, Medical History, Prior Medication and Other Baseline Characteristics

Demographic characteristics, medical history, prior medication and other baseline data will be listed and summarized using descriptive statistics for continuation data and contingency tables for categorical data. Prior medication will be summarized by ATC terms.

8.6. Study Treatment

The number of doses of SEL24/MEN1703 by cycle and over entire study period will be listed and summarized using descriptive statistics. The time of study drug administration until last treatment received will be listed and presented by descriptive statistics.

8.7. Concomitant Medication

Concomitant medication and significant non-drug therapies after the start of study treatment will be listed and summarized by ATC term in contingency tables.

8.8. Methods for Assessment of Safety Parameters

All safety and tolerability assessments will be based on the safety analysis set, which is defined as all patients who have received at least one dose of study medication.

No formal statistical analysis will be performed on safety data.

Vital signs, resting 12-lead ECGs, clinical chemistry, hematology, coagulation, lipid profile, and urinalysis data will be listed by cohort, dose and time-point.

The number and percentage of patients experiencing one or more AEs will be summarized by cohort, dose, relationship to study drug, and severity. AEs will be coded using MedDRA terminology. AEs that have missing onset dates will be considered to be treatment-emergent, unless the stop date is known to be prior to the first administration of the study medication.

SAEs and DLTs will also be presented separately.

8.9. Methods for Assessment of Anti-Leukemic Activity

No formal statistical analysis will be performed on anti-leukemic parameters.

Anti-leukemic activity data will be collected throughout Part 1 and Part 2 and will summarized by cohort, by dose and overall. In Part 2 response may be summarized and an exact 95% confidence interval (CI) calculated.

Measures of anti-leukemic activity will include:

- Changes in pre- and post-treatment levels of leukemic blasts in the peripheral blood and/or bone marrow;
- Duration of response (DoR);
- Relapse-free survival (RFS);
- Event-free survival (EFS);
- Overall Survival (OS)
- Transfusion conversion rate;
- Transfusion maintenance rate;
- HSCT rate.

Where possible disease assessment will be evaluated according to the response criteria in AML[6]. (see Appendix D).

8.10. Methods for Assessment of PK Data

The analysis plan for PK assessment for SEL24/MEN1703 in the study will be described in the SAP. Pharmacokinetic parameters will be estimated for each patient using a fully validated version of WinNonlin 8.0 (Phoenix™, Pharsight®) or equivalent. The following parameters will be derived, where appropriate, from the individual plasma concentration versus time profiles of SEL24/MEN1703 and its metabolites. PK analysis in urine will be described separately.

Table 14: Pharmacokinetic Parameters

Parameter	Definition
C_{max}	The maximum observed concentration.
t_{max}	The time at which C_{max} was apparent.
AUC_{0-t}	The area under the concentration versus time curve from time zero to the sampling time at the last quantifiable concentration (C_t) at t_{last} (the time of the last quantifiable concentration) calculated by the linear trapezoidal rule.
λ_z	The apparent terminal rate constant, estimated using the negative slope of the least square regression analysis of the log concentration versus time data for the terminal linear portion of the curve.
$t_{1/2}$	The apparent terminal half-life, calculated from $\mathrm{Ln}\,2 / \lambda_z$.
$AUC_{0-\infty}$	The area under the concentration-time curve estimated from time zero to infinity as the sum of the 2 areas: AUC_{0-t} and AUC_{extrap}, where AUC_{extrap} is calculated as C_t/λ_z.
CL	The systemic clearance calculated as: $Dose/AUC_{0-\infty}$.
V_{ss}	The apparent volume of distribution at steady state calculated as: $Dose/AUC \times (AUMC/UC_{0-\infty} - t_{1/2})$.

Additional PK parameters may be calculated as appropriate.

8.11. Methods for Assessment of PD Data

The Sponsor will exploit flow cytometry for the analysis of relevant biomarkers (e.g. pS6). Since such investigation is of exploratory nature, the Sponsor may choose to prepare separate analysis plan and report for the PD analysis.

8.12. Methods for assessment of the genetic profile of AML cells

The Sponsor will exploit Next Generation Sequencing and/or qRT-PCR to analyze the genetic profile of AML cells. Since such investigation is of exploratory nature, the Sponsor may choose to prepare separate analysis plan and report for this analysis.

8.13. Estimated Sample Size

After completion of Part 1 (dose escalation) and definition of RD, approximately 40 evaluable patients are to be enrolled in the Part 2, namely 20 patients in the 'all comers' and 20 patients in the IDH mutated patients cohort . .

The study Part 1 was initially designed with an accelerated titration design for the first 4 cohorts, then a 3+3 design had to be followed from the former fifth cohort (150 mg dose level) onwards. However, following the occurrence of 2 DLTs at the 150 mg dose level, one of which resulted in a fatal treatment-related outcome, the study design has then been revised to follow a 3+3 design from Cohort 2 onwards in order to assess for DLT, adverse events, and adequate PK profile data from at least 3 patients in each dose level from 50 mg onwards. The final number of patients treated in Part 1 will therefore be dependent upon the number of cohorts (dose levels) investigated, as well as the number of cohort expansions.

In Part 1 a conventional algorithm will be used to identify the MTD or MAD, escalating on 0/3 or 1/6 DLTs, and de-escalating if 2 or more patients with DLTs are encountered. The MTD will be the highest dose level at which 0 or 1 of 6 patients experience a DLT, with the next higher dose having at least 2 of 3 or 2 of 6 patients experiencing a DLT. At the 150 mg dose cohort, up to 4 additional patients will be treated with formulated IMP according to a Bayesian modified toxicity probability interval (mTPI) with a target toxicity rate $\leq 25\%$.

Part 2 of the study further evaluates safety and tolerability of SEL24/MEN1703 in AML population where there is rationale to treat. The expansion cohort in 'all comers' has already enrolled 23 unselected AML patients. An additional expansion cohort ("IDH mutants") will enroll approximately 20 relapsed or refractory AML patients harboring an IDH mutation (either IDH1 or IDH2).

Considering that IDH inhibitors are approved/available only in some of the participating countries, it is anticipated that the study will enroll both IDH inhibitor pre-treated and IDH inhibitor naïve patients. For this reason, the recruitment will aim to have a balanced distribution across the two sub-populations to explore the differences in SEL24/MEN1703 activity between pre-treated and IDH inhibitor naïve patients, if any.

9. QUALITY ASSURANCE

9.1. Data recording / Monitoring of the Study and Regulatory Compliance

The project manager, or their designee, will make an initiation site visit to each institution to review the protocol and its requirements with the Investigator(s), inspect the drug storage area, and fully inform the Investigator of his/her responsibilities and the procedures for assuring adequate and

correct documentation. During the initiation site visit the electronic case report forms (eCRFs) and other pertinent study materials will be reviewed with the Investigator's site staff. During the course of the study, the monitor will make regular site visits in order to review protocol compliance, examine eCRFs and individual patient's medical records and assure that the study is being conducted according to pertinent regulatory requirements. All eCRF entries will be verified with source documentation. The review of medical records will be done in a manner to assure that patient confidentiality is maintained.

All eCRF data will be collected using an eCRF within a fully validated and CFR 21 Part 11–compliant Electronic data capture system. The Investigator's site staff will be responsible for entering study data into the eCRF in accordance to the eCRF Completion Guidelines provided by Sponsor. All data shall be entered into the eCRF by the Investigator's site staff as closely as possible to the time when they become available and not later than 10 business days. These data will then be source-data verified and reviewed by the Clinical Research Associates (CRAs) before data cleaning by Data Management is performed. All queries will be raised and resolved within the electronic data capture system. During entry, programmatic checking of the data will be performed and, once saved into the database, more complex programmatic checks will also be performed. During the conduct of the study, all system users will have real-time access to the data. The level of access to the data and study privileges will be determined by their user role.

After all queries have been resolved, the SAP approved and signed, and any summary/analysis populations approved, the database will be locked and the data released for summary and analysis. All summary and analysis of the data will be performed using appropriate version of SAS® and WinNonLin 8.0, or equivalent.

9.2. Study Monitoring

Study Monitors will be responsible for the monitoring of the study.

The Study Monitor will review the progress of the study on a regular basis to ensure adequate and accurate data collections. Monitoring site visits to review eCRF, patient case notes, administrative documentation, including the Investigator Site File, and frequent telephone/e-mail communications with site will be performed throughout the study.

At each study monitoring visit, the Investigator will make available all records pertaining to the study. To allow sufficient time to assemble documentation for the Study Monitor, monitoring visits will be confirmed in advance of planned visits.

9.3. Clinical Study Audit

The Sponsor, Sponsor representative or external regulatory agency may at any time during or after completion of the study conduct a GCP audit. Prior notice will be given to each site selected for audit in advance of a planned audit.

9.4. Clinical Study Report

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

9.5. Data Retention and Availability

The Investigator is required to maintain copies of all essential study documentation, including the Investigator Site File, a disc containing all eCRF data (including the full audit trail and all data queries), signed informed consent forms, and records for the receipt and disposition of study medications, must be retained for at least 25 years after the end of the clinical study, unless other EU laws require archiving for a longer period. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the Sponsor. It is the responsibility of the Sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

During the study, the Investigator must make study data accessible to the Study Monitors, the Sponsor (or a third-party auditor assigned by the Sponsor), and relevant IEC/IRBs and Regulatory Agencies. A file for each patient must be maintained that includes the signed informed consent form and all source documentation related to that patient. The Investigator must ensure the availability of source documents from which the information in the eCRF was derived.

9.6. Curricula Vitae and Financial Disclosure of Investigators

All Principal Investigators will be required to provide a current signed and dated curriculum vitae, a completed FDA Form 1572 (required in the USA; in the EU, if applicable) and a financial disclosure statement (required in the USA; in the EU, if applicable). All Sub-investigators will be required to provide a current curriculum vitae and a financial disclosure statement.

9.7. Protocol Modifications

No modification of the protocol should be implemented without the prior written approval of the Sponsor. Any such changes which may affect a patient's treatment or informed consent, especially those increasing potential risks, must receive prior approval by the IRB/IEC. The exception to this is where modifications are necessary to eliminate an immediate hazard to study patients, or when the change involves only logistical or administrative aspects of the study (e.g. change in monitor, change in telephone number). Other administrative revisions which may impact the clinical portion of a study will be duly reported to the IRB/IEC by the Principal Investigator.

10. ETHICS REVIEW/INFORMED CONSENT/ETHICAL CONSIDERATIONS

The Investigator will obtain written informed consent from each patient, or their authorized representative, participating in the study. The form must be signed, witnessed and dated. The informed consent form will contain all the Essential Elements of Informed Consent set forth in 21 CFR, Part 50, the ICH Guideline for Good Clinical Practice, and the terms of the Declaration of Helsinki, the US Health Insurance Portability and Accountability Act regulations (HIPAA), the US Common Rule (45 CFR 46.116) , the EU Regulations 536/2014 and 679/2016 as applicable. Copies of the signed document should be given to the patient and filed in the Investigator's study file, as well as the patient's medical record if in conformance with the institution's Standard Operating Procedures (SOPs) and the applicable Laws and Regulations.

The final study protocol and patient informed consent form will be approved by the appropriate IEC/IRB for each investigational site. Approval will be received in writing before initiation of the study.

Changes to the protocol during the study will be documented as amendments. Depending on the contents of the amendment and local legal requirements, the amendment will be submitted for approval to the relevant IEC/IRBs and to the relevant competent authorities prior to implementation. Exceptions are cases of changes made to protect patient safety, which will be implemented immediately.

If an amendment substantially alters the study design, increases the potential risk to the patients, affects the treatment of the patient, or might otherwise influence the willingness of the patient to participate in the study, then the information sheet must be revised and submitted to the relevant IEC/IRB and, where necessary, to the relevant competent authorities, for review and approval. When a patient is currently undergoing study procedures and is affected by the amendment, then the patient must be asked to consent again using the new information sheet.

10.1. Ethical Conduct of the Study

The study will be conducted in accordance with ICH GCP, the Declaration of Helsinki, the European Union Clinical Trials Directive 2001/20/EC, the EU Clinical Trials Regulation 536/2014 when it will come into force, the GCP Directive 2005/28/EC, the requirements of local IEC/IRB, and the US Code of Federal Regulations, Title 21 CFR Part 50. Relevant updates to these regulations will be implemented as they come into force.

10.2. Informed Consent

The principles of informed consent in the Declaration of Helsinki and GCP guidelines will be implemented before any protocol-specific procedures or interventions are carried out.

All patients will be informed that their participation is voluntary and that they can cease participation at any time without necessarily giving a reason and without any penalty or loss of benefits to which they are entitled.

With the help of the information sheet the patient will be informed about the IMP(s) and anticipated effects and the reason, design, and implication of the study. The patient must give consent to participate prior to enrolment in the study. This consent must be given in writing. The Investigator who conducts the informed consent discussion must also sign. The Investigator may delegate this responsibility to a suitably qualified member of the study team (e.g. Sub-Investigator) if permitted by local regulations. This delegation of responsibility must be recorded in the Study File. By giving signed consent, the patient will confirm that his or her participation is voluntary and that he or she will follow the instructions of the Investigator and answer the questions asked. Signatures must be personally dated.

The signed and dated consent form will be securely kept by the Investigator. Prior to participation in the study, the patient should receive a copy of the signed and dated written informed consent form.

The consent form and information sheet must include all elements required by law, local regulations, GCP and ICH guidelines including consent to allow the Sponsor, Sponsor representative, or external regulatory auditor to review the patient's medical records. This gives permission to examine, analyze, verify, and reproduce any records and reports that are important to the evaluation of the study.

Any party with direct access must take all adequate reasonable precautions within the constraints of the applicable regulatory requirement(s) to maintain the confidentiality of the patients' identities and Sponsor's proprietary information. It is the CRA's responsibility to verify that each patient has consented, in writing, to direct access and that the documents are safely archived.

10.3. Patient Participation Card

A study participation card will be offered to sites for use by each patient on the study. The card will indicate that he or she is participating in a clinical study and give the name and contact details of the Sponsor and the Investigator/study site. If used, the patient will be asked to retain this card while participating in the study and show it to any other medical practitioners consulted during this time. Patients will be advised to contact the Investigator/study site if there are any questions. A sample patient participation card is shown below. Use of Patient Participation cards is optional. Relevant contact information will always be provided in the patient information sheet.

Figure 2: Sample patient participation card

Dear Patient, ***Please inform any physician you are going to visit during the course of the study that you are participating in a clinical trial by presenting this contact card.*** ***Please carry this card with you at all times until the end of the study.*** **Patient Name:** ..... is participating in an open-label trial and is receiving an investigational product, SEL24/MEN1703, a novel PIM and FLT3 kinase inhibitor.		**Study Contact Card: Clinical Trial CLI24-001** A Phase I/II Study of SEL24 in Patients with Acute Myeloid Leukemia **In the case that additional medications must be prescribed, you need more information about the clinical trial, or there is a worsening condition of the patient, please contact the treating study physician:** Name: ..... Phone:

10.4. Insurance

Appropriate insurance for this study will be arranged by the Sponsor of the clinical study, in accordance with the regulatory requirements of the countries involved.
Details on the insurance company will be provided as a separate document upon patient's request, in accordance with national requirements.
A copy of the country-specific insurance certificate will be held in the TMF and in the Investigator Site File.

10.5. Institutional Review Board/Independent Ethics Committee

The study will not be initiated without approval of the IRB/IEC and compliance with all administrative requirements of the governing body of the institution. This protocol, consent procedures, and any amendments must be approved by the IRB/IEC in compliance with current regulations of the FDA and the EU as applicable and in accordance with ICH GCPs. A letter of approval will be sent to the Sponsor prior to initiation of the study and when any subsequent modifications are made. The IRB/IEC will be kept informed about the progress of the study as well as of any serious and unexpected adverse events by the Investigator, CRO, or the Sponsor, as required by national regulations.

10.6. Patient Privacy

In order to maintain patient confidentiality, all case report forms, study reports and communications relating to the study will identify patients by an assigned patient number; patients should not be identified by name and/or date of birth. In accordance with local, national or federal regulations, the Investigator will allow the Sponsor or their designee personnel access to all pertinent medical records in order to verify the data gathered on the case report forms and to audit the data collection process. Regulatory agencies may also request access to all study records, including source documentation for inspection. Clinical information will not be released without the written permission of the patient as outlined in the patient consent form.

11. DATA CONFIDENTIALITY AND PUBLICATION POLICY

The original eCRFs and all data generated during the clinical study are the property of the Sponsor. It is intended that the study design and main results will be published on www.clinicaltrials.gov and on other applicable country specific websites (e.g., https://www.clinicaltrialsregister.eu).
In addition, all information regarding SEL24/MEN1703 and the Sponsor's operations (e.g. patent applications, formulas, manufacturing processes, basic scientific data, or formulation information) supplied by the Sponsor to the Investigator and not previously published is considered confidential. This confidential information remains the sole property of the Sponsor and shall not be disclosed to others without the written consent of the Sponsor. The Investigator agrees to use this information only to perform this study and will not use it for other purposes, including publications and presentations, without the Sponsor's written consent.

Any proposed publication or presentation (including a manuscript, abstract, or poster) for submission to a journal or scientific meeting should be sent to the Sponsor for review prior to submission. Publication of the results will not include confidential information without the permission of the Sponsor. The full terms of confidentiality, intellectual property and publication policy are described in the current Clinical Trial Agreement between the Sponsor and the Site.

The Sponsor may announce quality assured summary data in order to comply with Financial Regulatory Authorities, while ensuring, so far as possible, that such announcements will not compromise the Investigators ability to publish the data in appropriate scientific forums.

12. DATA PROTECTION

12.1. General Principles on Personal Data Compliance

All clinical trial information shall be recorded, processed, handled, and stored in such a way that it can be accurately reported, interpreted and verified; at the same time, the confidentiality of records and of the personal data of the patients shall remain protected in accordance with the Laws and Regulation on personal data protection from time to time applicable such as the EU General Data Protection Regulation 679/2016 and the EU Regulation on clinical trials on medicinal products for human use 536/2014 or the US Health Insurance Portability and Accountability Act regulations (HIPAA), the US Common Rule (45 CFR 46.116).

This section defines the appropriate technical and organisational measures that shall be implemented to protect information and personal data processed against unauthorised or unlawful access, disclosure, dissemination, alteration, or destruction or accidental loss as well as to assure the fulfillment of patients' privacy rights.

12.2. Acknowledgment

The Site, the Investigator, the Central Lab and the CRO as well as their appointed staff and service providers acknowledge that:

(i) the performance of the study will imply processing of sensitive personal data;

(ii) personal data processing is regulated by the applicable U.S. Federal, European (i.e. the EU General Data Protection Regulation 679/2016 and the EU Regulation on clinical trials on medicinal products for human use 536/2014) and local laws (i.e. the laws of the country where the study is conducted) as well as by the Sponsor's national legislation.;

(iii) strict compliance with the applicable data protection laws and this section of the protocol is deemed by the Sponsor as an essential condition of collaboration with the Site, the Investigator, the Central Lab and the CRO.

12.3. Data Controllers and Data Processors

The Sponsor, the Site, the Investigator and the CRO acknowledge that according to the applicable privacy laws, Sponsor and Site will act as independent data controllers while CRO and the Investigator will act as data processors respectively of the Sponsor and of the Site. Before the beginning of the study, the Site will instruct in writing Investigator as its data processor as required by the applicable laws and regulations. However, if specific local laws or regulations mandate a different definition of the privacy roles, the Sponsor, the Site, the Investigator and the CRO will implement the relevant legal instruments.

12.4. Duties of the Parties involved in the performance of the study

Collection and use of patients' personal data (i.e. subjects' data), including their biological samples, will be carried out in full respect of the provisions of the information notices submitted to patients in the ICF, as well as the privacy rights, the fundamental freedoms and the dignity of data subjects. All the parties involved in this study undertake to adopt adequate measures to warrant that data will always be processed securely and in compliance with privacy laws.

The Site, the Investigator, the Sponsor, the CRO and the Central Lab as well as their appointed staff and service providers, each in its respective remit and within the limits of their specific role in the study, shall implement the following safety measures (physical, logical, organizational, technical, electronic, I.T. etc) to ensure adequate protection of the personal data of the patients involved in the study. In particular:

(i) [redacted]

[redacted]

All actions related to the implementation of the afore mentioned measures shall be provided by the Sponsor, the Site and/or the CRO to the competent authorities (including data protection authorities) and IRB/IEC if and when requested. If such authorities or the Sponsor consider the implementation of the afore mentioned measures insufficient to guarantee an adequate level of protection of the patients' personal data, the Site, the Investigator, the CRO and the Central Lab undertake to adopt all the necessary activities to overcome such remarks to assure the full compliance with the data protection laws.

12.5. Archiving of the clinical trial master file and patients' personal data

Unless other EU laws require archiving for a longer period, the Sponsor, the Site and the Investigator shall archive the content of the clinical trial master file, including the relevant patients' personal data, for at least 25 years after the end of the clinical study. However, medical records shall be archived in accordance with the national laws of the country where the study is performed. The patient code pairing list (i.e. the list that where the patient number is linked to the patients' identification data such as name and surname), shall be archived care of the Investigator.

U.S. Federal laws require that an Investigator maintain all study records for the indication under investigation for two years following the date a Product Licensing Application is approved or, if no application is to be filed or if the application is not approved for such indication, until two years after the investigation is discontinued and the FDA is notified.

The content of the clinical trial master file shall be archived in a way that ensures that it is readily available and accessible, upon request, to the competent authorities. Should the Investigator wish to move the study record to another location, he/she must notify the Sponsor in writing. No study documents should be destroyed without prior written agreement between the Sponsor and Investigator.

Any transfer of ownership of the content of the clinical trial master file shall be documented. The new owner shall undertake the responsibilities set out in this protocol.

The Sponsor appoints the Study Manager as responsible person/s for archives. Access to archives shall be restricted to those individuals.

The media used to archive the content of the clinical trial master file shall be such that the content remains complete and legible throughout the period referred to in the first paragraph. Any alteration to the content of the clinical trial master file shall be traceable.

12.6. Data Breach

Data Breach is data breach of security leading to the accidental or unlawful destruction, loss, alteration, unauthorised disclosure of, or access to, personal data transmitted, stored or otherwise processed. In particular: destruction of personal data is where the data no longer exists, or no longer exists in a form that is of any use to the Sponsor, Site, CRO and Investigator etc.; data loss is when the data may still exist, but the Sponsor, Site, CRO and Investigator etc. has lost control or access to it, or no longer has it in its possession; damage is where personal data has been altered, corrupted, or is no longer complete; data unavailability is where, following a data incident (such as a network outage, a natural or man- made disaster, etc.), personal data become temporarily inaccessible to the Sponsor, Site, CRO and Investigator etc.

Whoever becomes aware in any way of a Data Breach (see definitions above) affecting the patients' personal data and/or personal data collected in the context of the study, shall, as appropriate, immediately (and in any case no later than 24 hours from the knowledge of a Data Breach) inform the study manager, the Sponsor's Data Protection Officer, who may be contacted at dpo@menarini.com, the Site and the CRO at privacy@medpace.com and shall provide the following information if known:

(i) Data Breach Type (e.g. data loss, unauthorized access, loss of company device, etc.);
(ii) Person or source that first reported the Data Breach;
(iii) Date and Time when the person who first reported the Data Breach became aware of it;
(iv) Data Breach Date and Time (actual or presumed);
(v) Place (specify if actual or alleged) where the Data Breach occurred ;
(vi) Data Breach Description;
(vii) Indicate the source of the Data Breach (e.g. I.P. source) - (if relevant);
(viii) Indicate the affected infrastructure/system/application/cloud/software/hardware/ database and their location;
(ix) List or describe the processing/storage systems affected by the Data Breach (if relevant);
(x) Number of data patients involved (if known);
(xi) Amount of allegedly breached data;
(xii) Other relevant information.

Once all the above information have been provided, the Sponsor and/or the Site should have a reasonable degree of certainty that a security incident has occurred that has led to personal data being compromised.

Then, as appropriate, Sponsor and Site, each one in its respective remit, shall manage the Data Breach in accordance with the applicable data protection regulations.

For Data Breach affecting personal data of patients enrolled within the European Union, Sponsor and the Site autonomously or jointly -depending on the circumstances and their privacy responsibilities as defined by the Regulation 679/2016- shall:

1. collect the necessary evidence and information;
2. categorise the breach;
3. determine the risk probability and level to the rights and freedom of the concerned patients;

4. identify and put in place appropriate remedies to minimise the impact of the Data Breach;
5. determine the notification and communication duties vis à vis the competent supervisory authority and/or the concerned patients.

12.7. Information notice on personal data protection and pseudonymisation

Prior to patients' enrolment in the study, the Investigator and/or the Site (including their personnel) shall provide each patient with adequate, law-compliant "information notices and consent forms to process personal data" as included in the ICF (or, as the case may be, through a separate, specific form) provided by the Sponsor or delegated CRO and shall collect his/her written consent to the processing of personal data according to the actual performance conditions in which the study is carried out. The Investigator is responsible to archive the signed ICF in accordance with the security measures described above.

Among other things, the ICF (or the separate form) shall inform patients about:

(i) the applicable data protection legislation;
(ii) what kind of data shall be collected during the study listing them in detail or by category;
(iii) the purpose of data processing (for the performance of the study and/or for pharmacovigilance purposes and/or to register new medicines) and the legal basis;
(iv) whether granting the consent(s) to process personal data is a necessary or an optional condition to take part in the study;
(v) the use of data for future scientific researches/secondary use of data (if any). Please refer to Section 12.11;
(vi) the pseudonymisation procedure and scope;
(vii) who can access patients' data and under what circumstances (Investigator and Site for the study conduction, Sponsor for analysis of data, regulatory authorities for registration of new medicine and/or for inspections, and the central lab. The complete list will be available upon request);
(viii) the period of data retention/storage as defined in Section 12.5 above, including the storage of the biological sample;
(ix) to which entities/countries outside the EU patients' data will be transmitted (including US). The complete list will be available upon request;
(x) patients' data protection rights as defined by the EU General Data Protection Regulation 679/2016;
(xi) Data Controllers/Data Processors and the relevant contact details;
(xii) Sponsor's Data Protection Officer contacts (dpo@menarini.com);
(xiii) in case of genetic data processing the possible findings, also with regard to unexpected findings that might be disclosed on account of the processing of the genetic data.

12.8. Genetic Data

- The collection of genetic data for performing genetic tests and screening shall be limited to the personal and family information that is absolutely indispensable for performing the study.
- If genetic data are processed in the context of the study for pregnancy follow-up purposes (pharmacovigilance) only (i) the collection of genetic data for performing genetic tests and

screening shall be limited to the personal and family information that is absolutely indispensable for pregnancy follow-up; (ii) the source, nature and mechanism for samples taking and storage will be under the pregnant health care provider and its local procedures; genetic data shall be processed pursuant to the applicable pharmacovigilance laws and regulations; genetic data shall be communicated/transmitted using high security standard. The provisions below shall be implemented as applicable from time to time.

- The source, nature and mechanisms for samples taking and storage will be under the site and its local procedures.
- Without prejudice to applicable laws and regulations, the protocol shall be subject to confidentiality obligations that will assure the secrecy of the data for at least one year after the conclusion of the [study - use the same protocol terminology/definitions].
- The measures to keep patients' identification data separated from biological materials and genetic information are reported in Section 12.4 and Section 12.5.
- Access to the premises where genetic data are stored shall be controlled by security staff and/or electronic devices also based on biometrics. Any person admitted after closing time, on whatever grounds, shall have to be identified and their data recorded
- Preservation, use, and transportation of biological samples shall be carried out in such a manner as to also ensure their quality, integrity, availability and traceability.
- Genetic data shall be transmitted electronically by certified electronic mail after encrypting and digitally signing the information to be transmitted. Web application-based communication channels may be used if they rely on secure communication protocols and they can guarantee the digital identity of the server providing the service as well as of the client station from which the data are accessed by means of digital certificates issued by a certification authority in pursuance of the law.
- Electronically processed genetic data may be accessed provided that authentication systems are based on tokens/devices.
- Genetic data and biological samples contained in lists, registers and/or databases shall be processed with encryption techniques and/or by means of identification codes and/or any other techniques that can make them temporarily unintelligible also to the persons authorised to access them.
- In order to minimise the risks of accidental disclosure and/or unlawful/unauthorised access, patients' identities will be disclosed only when strictly necessary (e.g. to prevent a physical prejudice).
- Genetic and medical data will be processed separately from any other personal data that can identify the patients directly.
- The ICF will detail the possible findings regarding genetic data, also with regard to unexpected findings that might be disclosed as result of the test / elaboration of genetic data;
- The ICF will detail whether the data subject is allowed to limit the scope of communication of his/her genetic data and the transfer of biological samples, including their possible use for additional purposes;
- The ICF will detail the retention period of genetic data and biological samples (if different from the general retention period of other data processed in the context of the study).

12.9. Transfer of patients' data outside the European Union

The study performance entails transferring patients' personal data (coded pseudonymized data)

outside the EU. To this extent, the Sponsor, the Site, the Investigator, the Central Lab and the CRO, undertake to export such data in compliance with adequate safeguards/legal basis as required by the Regulation 679/2016 including the Commission Decisions, the Standard Contract Clauses, the Privacy Shield, patients' specific consent. The updated list of foreign countries is available upon request.

12.10. Exercise of patients' data privacy rights

Each study patient has the right to contact the Sponsor, the Site, the Investigator, the Central Lab and the CRO to exercise the rights afforded to the patient by the law, including the afforded ones under articles 15 to 22 of Regulation (EU) 2016/679, as from to time to time applicable and compatible with the study. Namely: knowing whether or not any data referring to his/her is being processed in the context of the study; access his/her data; verify the data's content, origin, exactness, location (including, where applicable, the non EU countries where the data might be); obtain a copy of the data including their transmission to another entity indicated by the patient; ask that the data are supplemented, updated, amended; in the circumstances set forth by the law, ask that the processing of data is restricted, that data are anonymised or frozen; oppose to the processing of his/her data for legitimate reasons. Each patient has the right to lodge a complaint with his/her local supervisory authority and/or to notify to the Data Protection Officer any use of his/her personal data the patient regards as inappropriate.

Each study patient is free to withdraw at any time from the study. In such case, each study patient may ask the Sponsor, the Site, the Investigator, the Central Lab and the CRO to destroy/delete his/her personal data including his/her biological samples, unless they have been permanently anonymised, thus preventing any further processing or analysis of his/her data. However, data and results of tests that may have been used to determine the results of the study shall not be deleted, to avoid altering or impairing altogether the results of the study. Please refer to Section 12.8.

If the Site, the Investigator, the Central Lab and the CRO receives a request for data privacy rights exercise, the concerned recipient shall immediately inform the Sponsor DPO by email at dpo@menarini.com

The request shall be fulfilled within the term set forth by the applicable privacy laws (normally 30 days). The Sponsor, the Site, and the Investigator, the Central Lab and the CRO shall implement adequate organisational measures to reply to patients within the above mentioned deadline.

12.11. Future research

Upon IRB/IECs and regulatory agencies approvals received, with patients' optional and additional consent, the Sponsor and/or the Site may use the data collected during the course of the study for further medical and scientific research purposes. These may include, for example: retrospective clinical studies; clinical studies pertaining to the patients' pathology/medical condition(s) or similar conditions; studies which compare the data of this Study with those from other sources to identify the factors involved in a disease; registration of new medicines.

In the context of these additional research activities, patients' data will be processed, pseudonymised and transferred abroad and may be shared with future research partners.

13. END OF CLINICAL TRIAL AND ARCHIVING

The study will end with the collection and analysis of study data and the issue of the clinical study report. All essential documents will be archived by the Sponsor according to the relevant SOP.

13.1. Archiving Of Electronic Documentation/Data

As described in Section 12.5, duplicate electronic media such as CDs/DVDs (1 for routine access and 1 for back-up) containing the patient data in PDF format (i.e., eCRFs) for each site will be prepared by the Sponsor or a delegate for archiving purposes. The electronic media, of not re-printable type, will be appropriately labelled recording the files/data included. The files should contain at least the eData copy clearly reporting the system name, study code and the eCRF version used; for eCRF data also the electronic signature and the associated audit trails have to be included. The Investigator should verify whether the provided electronic media represent a complete copy of eCRFs generated during the study. The Investigator has to confirm the receipt and correctness of the material by signing a dedicate form provided by the Sponsor, the signed form has to be collected and archived in the TMF. Investigators will be also responsible for electronic media refreshment approximately every 7 years to ensure long term archiving of files/data. Two copies of the same electronic media prepared for the sites or cumulative electronic media with the same content will be archived by the Sponsor and refreshed approximately every 7 years to ensure long term archiving of files/data. In addition the Sponsor is responsible to create 2 electronic media (1 for routine access and 1 for back-up) containing an integrated SAS database with all study data (e.g., eCRF, central laboratory), with appropriate refreshment procedures.

APPENDIX A: EASTERN COOPERATIVE ONCOLOGY GROUP PERFORMANCE SCORE

Grade	ECOG Performance Score[8]
0	Fully active. Able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (e.g. light house work, office work).
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

APPENDIX B: CREATININE CLEARANCE ALGORITHM

Creatinine clearance should be calculated using the Cockcroft-Gault Formula[9], which is given below:

$$\text{CrCl} = \frac{(140 - \text{Age}) \times \text{Mass (in kilograms)} \times (0.85 \text{ if Female})}{72 \times \text{serum Creatinine (in mg/dL)}}$$

APPENDIX C: SUPPORTING INFORMATION FOR ASSESSMENT OF ADVERSE EVENTS

National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v4.03 can be found at the website of the National Cancer Institute.
http://evs.nci.nih.gov/ftp1/CTCAE

The following table provides supporting information to assess the relationship of AEs with study (test) drug.

1	**Not related**	This category applies to those adverse events which, after careful consideration, are clearly and incontrovertibly due to extraneous causes (disease, environment, etc.).
2	**Unlikely (must have two)**	In general, this category can be considered applicable to those adverse events which, after careful medical consideration at the time they are evaluated, are judged to be unrelated to the test drug. An adverse event may be considered unlikely if or when: 1. It does not follow a reasonable temporal sequence from administration of the test drug. 2. It could readily have been produced by the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient. 3. It does not follow a known pattern of response to the test drug. 4. It does not reappear or worsen when the drug is readministered.
3	**Possibly (must have two)**	This category applies to those adverse events for which, after careful medical consideration at the time they are evaluated, a connection with the test drug administration appears unlikely but cannot be ruled out with certainty. An adverse event may be considered possibly related if or when: 1. It follows a reasonable temporal sequence from administration of the test drug. 2. It could not readily have been produced by the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient. 3. It follows a known pattern of response to the test drug.
4	**Probably (must have three)**	This category applies to those adverse events for which, after careful medical consideration at the time they are evaluated, are felt with a high degree of certainty to be related to the test drug. An adverse event may be considered probably related if or when: 1. It follows a reasonable temporal sequence from administration of the test drug. 2. It could not be reasonably explained by the known characteristics of the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient. 3. It disappears or decreases on cessation or reduction in dose. There are important exceptions when an adverse event does not disappear upon discontinuation of the drug, yet drug-relatedness clearly exists (e.g., bone marrow depression, fixed drug eruptions, tardive dyskinesia). 4. It follows a known pattern of response to the test drug.
5	**Definitely (must have all)**	This category applies to those adverse events which, the Investigator feels are incontrovertibly related to test drug. An adverse event may be assigned an attribution of definitely related if or when: 1. It follows a reasonable temporal sequence from administration of the test drug. 2. It could not be reasonably explained by the known characteristics of the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient. 3. It disappears or decreases on cessation or reduction in dose with re-exposure to drug. (Note: this is not to be construed as requiring re-exposure of the patient, however, a category of definitely related can only be used when a recurrence is observed.) 4. It follows a known pattern of response to the test drug.

APPENDIX D: AML RESPONSE CRITERIA

Category	Definition	Comment
Response[#]		
CR without minimal residual disease (CR_{MRD-})	If studied pretreatment, CR with negativity for a genetic marker by RT-qPCR, or CR with negativity by MFC	Sensitivities vary by marker tested, and by method used; therefore, test used and sensitivity of the assay should be reported; analyses should be done in experienced laboratories (centralized diagnostics)
Complete remission (CR)	Bone marrow blasts <5%; absence of circulating blasts and blasts with Auer rods; absence of extramedullary disease; ANC ≥1.0 x 10^9/L (1000/µL); platelet count ≥100 x 10^9/L (100 000/µL)	MRD^+ or unknown
CR with incomplete hematologic recovery (CRi)	Bone marrow blasts <5%; absence of circulating blasts and blasts with Auer rods; absence of extramedullary disease with incomplete recovery of peripheral blood counts (ANC < 1.0 × 10^9/L [1000/µL] or platelet count < 100 × 10^9/L [100 000/µL])	
CR with partial hematologic recovery (CRh)[10, 11]	Bone marrow blasts <5%; absence of circulating blasts and blasts with Auer rods; absence of extramedullary disease with partial recovery of peripheral blood counts (ANC > 0.5 × 10^9/L [500/µL] and platelet count > 50 × 10^9/L [50 000/µL])	
Morphologic leukemia-free state (MLFS)	Bone marrow blasts <5%; absence of blasts with Auer rods; absence of extramedullary disease; no hematologic recovery required	Marrow should not merely be "aplastic"; at least 200 cells should be enumerated or cellularity should be at least 10%
Partial remission (PR)	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%	Especially important in the context of phase 1-2 clinical trials
Treatment failure		

Primary refractory disease	No CR or CRi after 2 courses of intensive induction treatment; excluding patients with death in aplasia or death due to indeterminate cause	Regimens containing higher doses of cytarabine are generally considered as the best option for patients not responding to a first cycle of 7+3; the likelihood of responding to such regimens is lower after failure of a first
Death in aplasia	Deaths occurring ≥7 d following completion of initial treatment while cytopenic; with an aplastic or hypoplastic bone marrow obtained within 7 d of death, without evidence of persistent leukemia	
Death from indeterminate cause	Deaths occurring before completion of therapy, or <7 d following its completion; or deaths occurring ≥7 d following completion of initial therapy with no blasts in the blood, but no bone marrow examination available	
Response criteria for clinical trials only		
Stable disease	Absence of CR_{MRD-}, CR, CR_i, PR, MLFS; and criteria for PD not met	Period of stable disease should last at least 3 mo
Progressive disease (PD)*,†	Evidence for an increase in bone marrow blast percentage and/or increase of absolute blast counts in the blood: • >50% increase in marrow blasts over baseline (a minimum 15% point increase is required in cases with <30% blasts at baseline; or persistent marrow blast percentage of >70% over at least 3 mo; without at least a 100% improvement in ANC to an absolute level (>0.5 x 10^9/L [500/µL], and/or platelet count to >50 x 10^9/L [50 000/µL] nontransfused); or • >50% increase in peripheral blasts (WBC x % blasts) to >25 x 10^9/L (>25 000/µL) (in the absence of differentiation syndrome)†; or	Category mainly applies for older patient given low intensity or single-agent "targeted therapies" in clinical trials. In general, at least 2 cycles of a novel agent should be administered. Some protocols may require blast increase in 2 consecutive marrow assessments at least 4 wk apart; the date of progression should then be defined as of the first observation date. Some protocols may allow transient addition of hydroxyurea to lower blast counts. "Progressive disease" is usually accompanied by a decline in ANC and platelets and increased transfusion requirement and decline in performance status or increase in symptoms.

	• New extramedullary disease	
Relapse		
Hematologic relapse (after CR_{MRD-}, CR, CR_i, CRh)	Bone marrow blasts ≥5%; or reappearance of blasts in the blood; or development of extramedullary disease	
Molecular relapse (after CR_{MRD-})	If studied pretreatment, reoccurrence of MRD as assessed by RT-qPCR or by MFC	Test applied, sensitivity of the assay, and cutoff values used must be reported; analyses should be done in experienced laboratories (centralized diagnostics)

Table adapted from Döhner H, *et al 2017*[6]

Footnotes

ANC, absolute neutrophil count; IDH, isocitrate dehydrogenase; MLFS, morphologic leukemia-free state; WBC, white blood cell.

*The authors acknowledge that this new provisional category is arbitrarily defined; the category aims at harmonizing the various definitions used in different clinical trials.

†Certain targeted therapies, for example, those inhibiting mutant IDH proteins, may cause a differentiation syndrome, that is, a transient increase in the percentage of bone marrow blasts and an absolute increase in blood blasts; in the setting of therapy with such compounds, an increase in blasts may not necessarily indicate PD.[#] In case bone marrow aspirate/biopsy is consistent with CRi or better but still a minimal percentage of peripheral blasts is detected, the response assessment can be postponed up to 2 weeks and will be based on repeated peripheral blood results and last bone marrow aspiration results.

APPENDIX E: LOCAL LABORATORY PARAMETERS

Clinical Chemistry	Hematology, including Coagulation*
Calcium	Red cell count
Total protein	Mean corpuscular volume
Albumin	Hemoglobin, free hemoglobin
Total bilirubin and direct bilirubin	Hematocrit
Alanine transaminase (ALT, SGPT)	Absolute reticulocyte count
Aspartate transaminase (AST, SGOT)	Platelet count
Lactate dehydrogenase (LDH)	White blood cells
Alkaline phosphatase	Leukocyte differential count (% or absolute)
Glucose (random)	International normalized ratio or prothrombin time
Sodium	Activated partial thromboplastin time
Potassium	Fibrinogen
Bicarbonate	D-dimer
Chloride	**Urinalysis**
Magnesium	Glucose
Urea = Blood urea nitrogen	Protein
Creatinine	Bilirubin
Phosphate	Ketones
Uric acid	Blood
C-reactive protein	pH
Lipid profile	Specific gravity (microscopic exam when indicated)
Triglycerides	HCG (female pre-menopausal patients; at Screening)
Cholesterol	FSH (female menopausal patients; at Screening)
Low-density lipoprotein (LDL)	
High-density lipoprotein (HDL)	

**Additional coagulation parameters will be performed in patients who develop coagulation abnormalities during the study treatment; in these patients, additional parameters and time-points for coagulation assessment may be performed as clinically indicated to ensure a comprehensive evaluation of coagulation abnormalities.*

This is the full testing panel to be carried out by sites; any exceptions due to local testing restrictions must be notified to Sponsor to ensure safety assessment is not jeopardized. The lipid panel describes the minimum assessments to be tested. Local sites may also report (calculate) other parameters as standard, such as very low-density lipoprotein (VLDL) or the cholesterol/HDL ratio.

APPENDIX F: List of Relevant CYP2D6 Substrates, CYP2D6 Inhibitors, and BCRP Inhibitors

INN/General	Brand name (not exclusive)	Indication
CYP2D6: SENSITIVE SUBSTRATES* OR SUBSTRATES WITH NARROW THERAPEUTIC RANGE**		
atomoxetine	Strattera	ADHD
desipramine	Norpramin	Depression
dextromethorphan	Robitussin	Cough
metoprolol	Lopressor, Toprol	Beta blocker
nebivolol	Bystolic	Beta blocker
perphenazine	*same*	Antipsychotic/schizophrenia
thioridazine	*same*	Antipsychotic/schizophrenia
tolterodine	Detrol	Incontinence
venlafaxine	Effexor	Depression/anxiety
nortriptyline	Aventyl	Depression
CYP2D6: STRONG INHIBITORS		
bupropion	Wellbutrin, Zyban	Smoking cessation/depression
dacomitinib	*same*	EGFR inhibitor
ecstasy	*same*	--
fluoxetine	Prozac	SSRI
paroxetine	Paxil	SSRI
quinidine	--	Antiarrhythmic
terbinafine	Lamisil	Antifungal (skin)
CYP2D6: MODERATE INHIBITORS		
AMD070	--	--
cinacalcet	Sensipar	Calcium reduction
dronedarone	Multaq	Antiarrhythmic
duloxetine	Cymbalta	Nerve pain/depression
eliglustat	Cerdelga	Gaucher disease
mirabegron	Myrbetriq	Overactive bladder
moclobemide	Amira	Depression/anxiety
tipranavir/ritonavir	--	HIV
fluvoxamine	Luvox	Obsessive-compulsive disorder
cimetidine	Tagamet	Histamine H2 receptor antagonist
BCRP: INHIBITORS		
cyclosporine	Sandimmune	Immunosuppressant
elacridar (GF120918)	--	--
eltrombopag	Promacta, Revolade	Thrombocytopenia
gefitinib	Iressa	EGFR inhibitor
Curcumin	-	-
isavuconazole	Cresembra	Antifungal (systemic)

* *Sensitive CYP substrates* refers to drugs whose plasma AUC values have been shown to increase 5-fold or higher when co-administered with a known CYP inhibitor.

** *CYP substrates with narrow therapeutic range* refers to drugs whose exposure-response relationship indicates that small increases in their exposure levels by the concomitant use of CYP inhibitors may lead to serious safety concerns (e.g., Torsades de Pointes).

CYP2D6 substrates and inhibitors obtained from the University of Washington, School of Pharmacy Drug Interaction Database Program (updated July 2016);
BCRP inhibitors obtained from the FDA website;

Isavuconazole added by the Sponsor, being its potential use relevant to the study population for antifungal prohylaxis and its potential DDI with IMP.

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