DIAMOND-01

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

STUDY CODE: CLI24-001

STATISTICAL ANALYSIS PLAN (SAP)

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

Sponsor:	Menarini Ricerche S.p.A, Clinical Sciences Department, Via Sette Santi, 1; 50131 Florence, Italy
EudraCT-No.:	**2019-000941-10**
Investigational medicinal Product:	**SEL24/MEN1703**
Development Phase:	Phase I/II
Indication:	Acute Myeloid Leukemia (AML)
Date of First Patient In:	15MAR2017
Date of Last Patient Out:	13APR2023
SAP Version and date	3.0 10MAY2023
Protocol Version and date	12.0 20APR2021

SIGNATURE PAGE

I have read this report and confirm that to the best of my knowledge it accurately describes the planned statistical analyses of the study.

Global Biostatistics and Data Management Director	[redacted]	[redacted]	10MAY2023
		Signature	Date
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Table of contents

1. Version History

Version Date	Author	Description for Revision
1.0 18JAN2021	[redacted]	This is the first final version of this document
2.0 28MAR2022	[redacted]	Comments resolution
2.1 14APR2023	[redacted]	Added PK section and PK TLFs SAP alignment to the current SOP
3.0 10MAY2023	[redacted]	Comments resolution

2. List of abbreviations

ADaM	Analysis Data Model
ADR	Adverse Drug Reaction
AE	Adverse Event
$Ae_{(0-x)}$	Urinary recovery of unchanged drug over the collection interval
ALT	Alanine Aminotransferase
AML	Acute Myeloid Leukemia
API	Active Pharmaceutical Ingredient
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area Under the concentration-time Curve
AUC_{ext}	Area Under the concentration-time Curve obtained by extrapolation
$AUC_{(0-t)}$ or AUC_{last}	Area Under the concentration versus time Curve from time zero to t_{last}, calculated by the linear trapezoidal rule
$AUC_{(0-\infty)}$	Area Under the concentration-time Curve from time zero (predose) to the time of the last quantifiable concentration
$AUC_{(0-24)}$	Area Under the concentration-time Curve over the dosing interval
BLLOQ	Below the Lower Limit of Quantification
BP	Blood Pressure
BR	Breath Rate
BUN	Blood Urea Nitrogen
C_{last} or C_t	Last observed quantifiable concentration
CA	Competent Authority
CD25	Cluster of Differentiation 25; gene coding for the alpha chain of Interleukin 2 receptor protein
CDB	Clinical Database
CDISC	Clinical Data Interchange Standards Consortium
CL/F	Apparent Clearance
C_{max}	Maximum Plasma Concentration
CL_r	Renal Clearance
CR	Complete Response/Remission
CR_i	Complete Remission with Incomplete Blood Count Recovery
CR_h	Complete Remission with Incomplete Hematologic Recovery
CRF	Case Report Form

CRO	Contract Research Organization
CS	Clinically Significant
CSP	Clinical Study Protocol
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of Variation
DLT	Dose Limiting Toxicity
DM	Data Management
DMC	Data Monitoring Committee
DoR	Duration of Response
DSM	Drug Safety Manager
DSUR	Development Safety Update Report
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	Electronic Data Capture
EFS	Event-Free Survival
EU	European Union
FDA	(US) Food and Drug Administration
FLT3	Fms-like tyrosine kinase 3; a gene coding for FMS-like tyrosine kinase-3
FSH	Follicle-Stimulating Hormone
FSV	Final Study Visit
GCP	Good Clinical Practice
GGT	Gamma-Glutamyl Transpeptidase
HM	Haematologic Malignancies
HR	Heart Rate
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IMP	Investigational Medicinal Product
INR	International Normalized Ratio
λ_z	Apparent terminal phase rate-constant
LDH	Lactate Dehydrogenase
LLT	Lowest Level Term
MAD	Maximum Administered Dose

MedDRA	Medical Dictionary for Regulatory Activities
MLFS	Morphologic Leukemic-Free State
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
NSADR	Non-serious Adverse Drug Reaction
NSAE	Non-serious Adverse Event
ORR	Objective (or Overall) Response Rate
OS	Overall Survival
PD	Pharmacodynamic(s)
PD	Progressive Disease
PK	Pharmacokinetic(s)
PR	Partial Response/Remission
PS	Performance Status
PT	Preferred Term
QD	Once Daily
QA	Quality Assurance
RBC	Red Blood Cells
RD	Recommended Dose
RFS	Relapse-Free Survival
SADR	Serious Adverse Drug Reaction
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Statistical Analysis Report
SD	Stable Disease
SDv	Standard Deviation
SDTM	Study Data Tabulation Model
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)
SOC	System Organ Class
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
$t_{½}$	Half-life
t_{last}	Time of last observed quantifiable concentration

t_{max}	Time to Reach Maximum Concentration
TMF	Trial Master File
UA	Uric Acid
ULN	Upper Limit of Normal
V_z/F	Apparent volume of distribution, based on terminal phase
WBC	White Blood Cells
WHO	World Health Organization

3. Introduction

This statistical analysis plan reflects the amended final study protocol CLI24-001 Version 12.0, dated 20.04.2021 and it is based on internal SOP MR-CR-136/01. It follows the principles of the guidelines ICH Topic E3 and ICH Topic E9 regarding the structure and content of clinical study reports and regarding statistical principles for clinical trials. The study is sponsored by Menarini Ricerche S.p.A.

Section 4 provides an overall study overview and its objectives. In Section 5 the main information about study configuration and procedures is provided. The treatment schedule and dosing are presented in detail, specifying all the study assessments and endpoints. Section 6 collects some general specifications such as the tools used for data collection and analysis, coding systems, reporting formats and the followed standard procedures. All definitions and the general methodology for the study activities are reported in Section 7, whilst the specifications about the statistical methodology are reported in Sections 8 through 12. Finally, the complete index of tables, listings and figures for the Statistical Analysis Report is provided in Section 13.

3.1. Changes from study protocol

All analyses detailed in this document are as specified in the protocol and subsequent amendments, no major changes from the protocol-planned primary analysis have been performed.

4. Study overview

MEN1703 is a dual kinase inhibitor targeting PIM (PIM1, PIM2, PIM3) and FLT3 kinases which will be supplied as formulated drug product in a gelatin capsule.

This trial was designed as 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 was selected for further evaluation in Part 2. In Part 2 the safety and anti-leukemic activity of SEL24/MEN1703 was further assessed in the study population. The starting dose was 25 mg SEL24/MEN1703 taken orally QD for 14 consecutive days over a 21-day treatment cycle.

4.1. Study objectives

4.1.1 Primary objectives

In study Part 1 the primary objective is to estimate the MTD or MAD and determine the RD of SEL24/MEN1703 for Part 2. During Part 2 the aim is to further characterize the safety profile of single agent SEL24/MEN1703.

4.1.2 Secondary objectives

During Part 1 the following will be assessed/evaluated:

- Safety and tolerability of SEL24/MEN1703;
- Anti-leukemic activity of SEL24/MEN1703;

- PK profile of SEL24/MEN1703 and its metabolites as appropriate.

During Part 2:

- Anti-leukemic activity of single agent SEL24/MEN1703;
- PK profile of SEL24/MEN1703 and its metabolites as appropriate.

4.1.3 Exploratory objectives

The following will be assessed/determined, in Part 1 and 2:

- PD activity of SEL24/MEN1703;
- The genetic profile of AML cells.

5. Investigational plan

An overview of the Clinical Study Protocol will be provided in this Chapter.

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

5.1. Study configuration and structure

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 was selected for further evaluation in Part 2.
The starting dose was 25 mg SEL24/MEN1703 taken orally QD for 14 consecutive days over a 21-day treatment cycle.
In Part 2 the safety and anti-leukemic activity of SEL24/MEN1703 was assessed in the study population.
In both parts of the study, the criteria for retreatment described in the protocol had to be followed prior to proceeding to administer a further cycle of treatment.
The study consisted of 2 steps as shown below.

Part 1 was the dose escalation phase and was initially designed with an ATD for the first 4 cohorts. The occurrence of 2 events meeting the DLT definition at the 150 mg dose level led to an adjustment of the dose escalation plan for this study, whereby MEN1703 was more thoroughly evaluated following a 3 + 3 design from Cohort 2 (50 mg dose level) in order to assess for DLT, adverse events, and adequate PK profile data from at least 3 patients in each dose level (see Table 1). Patients were enrolled to cohorts in a sequential fashion following the dosing regimen and were observed for safety and tolerability during Cycle 1, prior to permitting dose escalation to the next dose level (cohort). From Cohort 4 onwards there had been a mandated recruitment interval of at least 7 days for each patient enrolled.

In case a patient experienced a toxicity qualifying as a DLT during Cycle 1 in any cohort, that cohort was 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) was 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 was named Cohort 4F.

No recruitment interval was applied in the cohort 4F where formulated SEL24/MEN1703 IMP was introduced, as this dose level had 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 progressed to the next Cohort 4b and onwards, according to the study design, using SEL24/MEN1703 formulated IMP only. In particular, it was 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 were still on treatment, continued receiving this formulation until treatment withdrawal per protocol.

Subsequently, a protocol amendment was implemented to treat up to 4 additional patients at 150 mg under Bayesian modified toxicity probability interval (mTPI) approach, with a target toxicity rate of ≤ 25%. The first patient treated under his protocol at 150 mg dose level experienced a DLT. As a consequence, the recruitment was stopped and the recommended dose (RD) for next development steps was determined at 125 mg.

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

Table 1: 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	0	2
5F	150 mg	0	1	1

*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 could have been treated at 150 mg formulated IMP according to a Bayesian modified toxicity probability interval (mTPI) with a target toxicity rate ≤ 25%. In case none of these 4 patients experienced a DLT, higher dose levels may have been considered.

The DMC consisting of the Principal Investigator at each site, plus the Medical Monitor and Sponsor representatives, reviewed all safety data available during Cycle 1 for each cohort and assessed for DLT during Part 1 of the study. Experts in the evaluation of the PK and PD data may have participated 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 2.

Table 2: 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.

DLT events for dose escalation decisions were 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 was conducted over 42 days. Ongoing safety events beyond Cycle 1 were reviewed across all cohorts during the study to help inform dose escalation decisions.

AEs are graded according to the NCI CTCAE V4.03. The AEs listed below were 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 diarrhoea 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 of the protocol) were considered for DLT assessment, according to the protocol definition.

MTD is defined as the highest dose level at which no more than 1 of 6 patients experiences a DLT during the DLT assessment window.

In addition to DLT evaluation, there was an ongoing assessment of all AE and SAEs, changes in laboratory values (clinical chemistry, haematology, urinalysis, lipid profiles) and ECGs as further measures of safety and tolerability. All safety parameters continued to be assessed beyond Cycle 1.

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

Three patients experienced DLTs at 150 mg dose level. Therefore, 125 mg dose level is considered the maximum tolerated dose (MTD) for the following expansion cohorts.

Part 2 enrolled patients at the RD identified in Part 1, based on recommendation by the DMC, in the expansion cohorts defined below:

- The *all-comers* cohort planned to enroll additional 20 unselected relapsed or refractory AML patients.
- The *IDH mutants* cohort planned to 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 enrol 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.
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).

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 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 are conducted, wherever possible, every 3 months after the Final Study Visit regardless of initiation of additional treatments for up to 1 year.

5.2. Schematic study design

A schematic representation of the drug administration schedule and the study design dose-escalation phase can be found below.

Figure 1: Study treatment outline

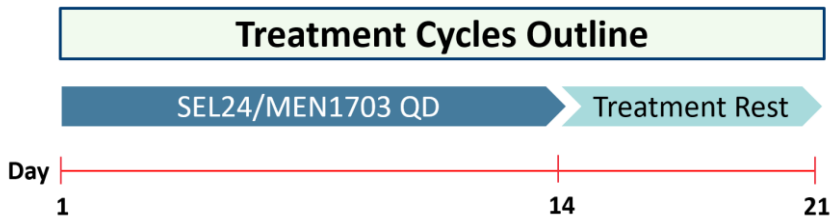
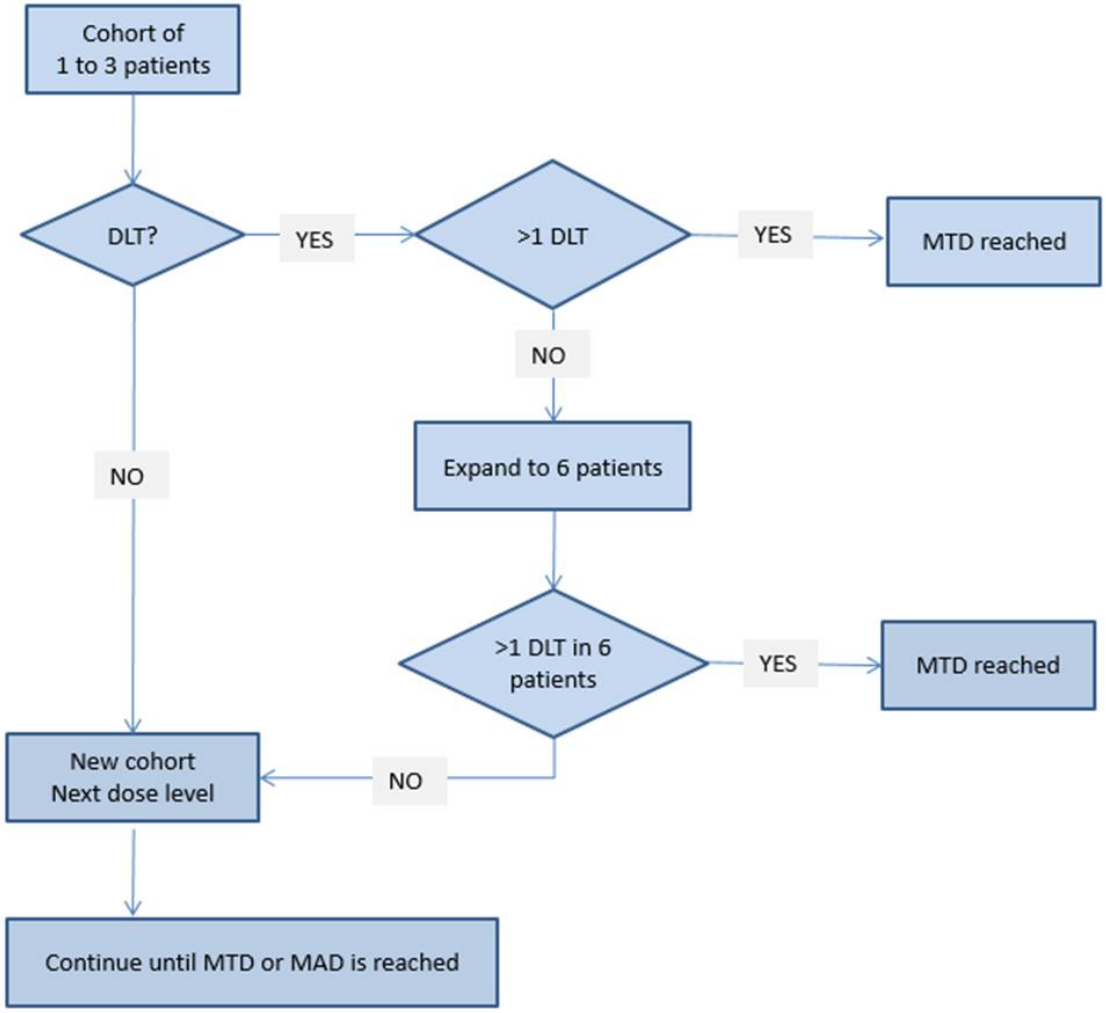


Figure 2: Cohort expansion and dose escalation plan


Cohort of
1 to 3 patients
DLT?
YES
>1 DLT
YES
MTD reached
NO
Expand to 6 patients
NO
>1 DLT in 6
patients
YES
MTD reached
New cohort
Next dose level
NO
Continue until MTD or MAD is reached

5.3. Study flow chart

Cycle	Screening	Cycle 1								Cycle 2			Cycle 3 onwards		Final Study Visit[17]	Follow Up[18]
Visit	≤28-days	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	
Tranfusion 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 of the protocol. 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 of the protocol).
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 to30 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 will be made approximately every 3 months from last dose of SEL24/MEN1703 for up to 1 year regardless of initiation of additional treatments to determine date of progression (where appropriate) and survival status.

5.4. Study Endpoints

5.4.1. Primary endpoints

Study **Part 1**:

- DLT evaluation at the end of one treatment cycle for each dose level.

Study **Part 2**:

- The number and frequency of AE, safety laboratory, vital signs and ECG assessments.

5.4.2. Secondary endpoints

Study **Part 1**:

- The number and frequency of AEs, safety laboratory, vital signs and ECG assessments

Study **Part 1** and **2**:

- 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. 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.

- Overall response rate (ORR), defined as the proportion of patients who have a complete remission (CR), complete remission with incomplete hematologic recovery (CRi), complete remission with partial hematologic recovery (CRh) or morphologic leukemia-free state (MLFS) response to therapy.

- Partial remission (PR) rate, defined as the proportion of patients who have a partial remission response to therapy.

- Duration of response (DoR), defined as the time from the date of first CR, CRi, CRh, CRMRD-, MLFS or PR until the date of documented relapse of any type, progressive disease or death due to disease progression for subjects who achieve CR, CRi, CRh, CRMRD-, MLFS or PR. Subjects who either do not relapse or die without report of relapse are considered nonevents and censored at their last relapse-free disease assessment date. Subjects who undergo an allogeneic HSCT will be considered non events and censored at the time of HSCT

- Relapse free survival (RFS), defined as the time from the date of first CR, CRi, CRh or CRMRD- until the date of documented relapse or death from any cause. Subjects who either do not relapse or do not die are censored at their last relapse-free disease assessment date.

- Event free survival (EFS), defined as the time from the date of first study drug intake until the date of documented relapse, treatment failure or death from any cause. For a subject who did not experience the event, EFS is censored at the date of last relapse-free disease assessment. Subject is not censored at HSCT.

- Overall survival (OS), defined as the number of days between the first study drug administration and death from any cause. Patients without the event are censored at the last date of follow-up.

- Evaluation of CYP2D6 phenotyping will be carried out. 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 and results will be reported separately.

Study **Part 2**:

- Transfusion conversion rate, 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, 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 HSCT rate, defined as the percentage of subjects undergoing allo-HSCT during the study period.

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

5.4.3. Exploratory endpoints

Study **Part 1** and **2**:

- Assessment of PD activity of SEL24/MEN1703 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;
- Analysis of relevant mutations in peripheral blasts and bone marrow 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.

5.4.4. Safety endpoints

Safety endpoints are included among primary and secondary endpoints (Sections 5.4.1 and 5.4.2).

5.4.5. PK endpoints

Study **Part 1** and **2**:

The PK profile of SEL24/MEN1703 and its metabolites, as appropriate, will be evaluated by analysis of concentration levels in plasma. 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 are recorded in the patient's records and in the eCRF. Left over sample aliquots could be analysed for metabolite identification purposes. The results of the metabolite identification analysis will be reported separately.

The following PK parameters will be derived, where appropriate, from the individual plasma concentration versus time profiles of SEL24/MEN1703 and its metabolites:

- C_{max}: the maximum observed concentration.
- t_{max}: the time at which C_{max} was apparent,
- C_t or C_{last}: the last quantifiable concentration,
- t_{last}: the time of the last quantifiable concentration,
- AUC_{0-t} or AUC_{last}: the area under the concentration versus time curve from time zero to t_{last}, calculated by the linear trapezoidal rule,
- AUC_{0-24}: the area under the concentration versus time curve from time zero to 24 hr, calculated by the linear trapezoidal rule.
- AUC_{extrap}: the extrapolated area under the concentration-time curve, calculated as C_t/λ_z,

- $AUC_{0-\infty}$: the area under the concentration-time curve estimated from time zero to infinity as the sum of AUC_{0-t} and AUC_{extrap},
- 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,
- t½: the apparent terminal half-life, calculated from $Ln(2)/\lambda_z$.
- CL/F: the apparent clearance calculated as $Dose/AUC_{0-\infty}$,
- CL_{ss}/F: the apparent clearance at steady state, calculated as $Dose/AUC_{0-t}$,
- V_z/F: the apparent volume of distribution based on the terminal phase, calculated as CL/λ_z.

Additional PK parameters may be calculated as appropriate.

Study **Part 1**

Urine samples will be collected from the first dose of SEL24/MEN1703 until 24 hours. The following PK parameters will be derived, where appropriate, from the individual urine samples of SEL24/MEN1703 and its metabolites:

- $Ae_{(0-x)}$: the urinary recovery of analyte over the collection interval, calculated as the sum of the amounts excreted over each collection interval. The amount excreted in urine for each collection interval is calculated as the product of the urine concentration and the urine volume.
- f_e: the fraction excreted, namely the fraction of the dose recovered unchanged in urine over the collection interval,
- CLr: the renal clearance, calculated from the fraction extracted multiplied by the total plasma clearance.

6. General specifications

6.1. Data validation

Medidata Classic Rave® 2021.1.4 is used as Electronic Data Capture system for data entry, by site personnel and for data cleaning and data locking by the Menarini Data Management team.
The eCRF data have been elaborated to create the SDTM (v1.7) and ADaM (v2.1) datasets based on CDISC standards.

6.2. Computer system and software used

The software used for all summary statistics and statistical analyses will be SAS® 9.04.01, SAS® Studio version 3.8 or higher (SAS Institute, Inc.). All tables and listings will be produced using PROC REPORT or procedure specific output displays using output delivery system (ODS). The summary tables and listings will use SAS monospace font of size 6. The default page type will be A4 and the default page orientation will be landscape.
Pharmacokinetic parameters (described in section 2.4.5 – PK endpoints) will be derived from individual measured concentrations using non-compartmental analysis (NCA) with a fully validated Phoenix™ WinNonlin (WNL) software, version 7 or higher (Pharsight®, Mountain View, California).

6.3. Coding systems

6.3.1. Clinical Terms

Concomitant diseases, medical procedures, and Adverse Events are coded with MedDRA version 23.1 or following versions.

6.3.2. Drugs

Drugs will be coded with WHO (ATC coding system) Drug version Sep-2020.

6.3.3. Classification criteria

Adverse Events are graded for severity using the classifications of Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03 (June 14, 2010). Further details about NCI CTCAE classification are specified in protocol version 12.0, section 7 and appendix C.

6.4. Report type, language, format

The statistical output will be in .pdf format and in English language.

- Dates will be presented with the DDMMMYYYY format.

- Counts and percentages:

  <group 1> xxx/(xxx.x%)

- Counts and percentages including also the count of the event of interest:

  <group 1> xxx/(xxx.x%)|xxx

- Descriptive statistics, laboratory parameters summary statistics:

N	xxx
Mean	xxx.xx
Median	xxx.xx
SD	xxx.xxx
Minimum	xxx.x
Maximum	xxx.x

Character values will be left aligned.

6.5. Standard Operating Procedures (SOPs) to be followed

[1]Code	Title
MR-GCS-DMST-210_SOP	Statistical Analysis Plan (SAP)
MR-GCS-DMST-211_SOP	Statistical Programs Writing
MR-GCS-DMST-211.3_WI	TLF programming
MR-GCS-CP&P-504	Use and management of Phoenix® WinNonlin® and pharmacokinetic data flow
MR-GCS-CP&P-505	Standard methods for non-compartmental analysis of pharmacokinetic data

6.6. Data Transfer Agreements

CD25 data

Data Transfer Agreement (DTA) between [redacted] and Menarini Ricerche S.p.A., version 2.0 of 29th January 2021.

CYP2D6 data

Data Transfer Agreement (DTA) between [redacted] and Menarini Ricerche S.p.A., version 3.0 of April 2021.

Data Management Plan

Data Management Plan V2.0 (2021).

Genetic Profile data

Data Transfer Agreement (DTA) between [redacted] and Menarini Ricerche S.p.A., version 2.0 of 28th April 2021.

Pharmacodynamics data

Data Transfer Agreement (DTA) between [redacted] and Menarini Ricerche S.p.A., version 2.0 of 29th January 2021.

Pharmacokinetics data

Data Transfer Agreement (DTA) between [redacted] and Menarini Ricerche S.p.A., version 1.0 of 14th April 2020.

Data Transfer Agreement (DTA) between [redacted] and Data Management & Clinical Sciences Unit of Menarini Ricerche S.p.A. – Statistics and Data Management Unit, version 4 of April 2023.

7. Definitions and general methodology

7.1. Data quality assurance

All tables, figures and data listings to be included in the report will be independently checked for consistency, integrity and in accordance with Menarini Ricerche standard procedures.

7.2. General considerations and key definitions

7.2.1. General considerations

Study day is defined as the number of days from the date of first dose of MEN1703 to the event/visit date.

7.2.2. Key definitions

Baseline values

The baseline value of an assessment is defined as the last available (non-missing) value before or on the date of first administration (Day 1) for Cycle 1.

Adverse Events (AEs)

An AE is any untoward medical occurrence in a patient (or a clinical investigation subject), receiving a medicinal product and which does not necessarily have a causal relationship with the treatment. Therefore an AE can be any unfavourable and unintended sign (including an abnormal clinically significant laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. All identified AEs are 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 are recorded on the Medical History eCRF page.

Adverse Drug Reactions (ADRs)

Untoward and unintended responses to an Investigational Medicinal Product (IMP) related to any dose administered. The definition covers also medication errors and uses outside what is foreseen in the protocol, including misuse and abuse of the product. The definition implies a 'reasonable possibility of a causal relationship between the event and the IMP. This means that there are facts (evidence) or arguments to suggest a causal relationship.

All AEs (including SAEs) have 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. For events not addressed in the NCI CTCAE v4.03, classifications will be performed according to the following grading:

- 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.

Serious Adverse Event (SAE) / Serious Adverse Drug Reaction (SADR)

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.

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.

Exceptions to SAE

For this study, the following events will be considered to be expected events in this population and during leukemia therapy (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, consider unrelated to study drug), 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, CO2, 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.

Causality Assessment of Adverse Events

All AEs (including SAEs) will be assessed for the relationship of the AE to the study drug using the following standard definitions:

1. **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.

2. **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.

3. **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.

4. **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.

5. **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.

Please also refer to supporting information provided in Appendix C of the study protocol. 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.

7.3. Analysis populations

The following analysis populations will be considered in the statistical analysis:

- **Safety population**: the safety set consists of all patients that have received at least one dose of SEL24/MEN1703.
- **DD population**: 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.
- **PK population**: all patients who received any dose of SEL24/MEN1703 and have sufficient data for PK analysis. Therefore, all subjects receiving study drug and having at least 1 measurable drug concentration will be included in the PK population. If there are subjects who do not have sufficient samples for the PK non-compartmental analysis (NCA), a modified NCA will be conducted in which some or all PK parameters may not be estimated for those subjects, but available PK concentrations will still be tabulated and graphed.

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 along with the safety population.

- **Efficacy population**: the efficacy set will consist of all patients in each cohort that have completed one cycle of treatment (considering both the treatment and the washout period - 21 days) and have taken at least 75% of the study drug during the first cycle.

Thus, anti-leukemic activity will be analyzed on both the safety and the efficacy population.

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

7.4. On study and pre-study closure activities

7.4.1. Data monitoring

The Data Monitoring Committee (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 ongoing 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 ongoing assessment of safety, antileukemic 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 of the study protocol).

7.4.2. Protocol Deviations and Data Review Meeting

Categories of protocol violations will be defined and will be integrated in the statistical analysis.

During the Data Review Meeting that will take place at the end of the study, the final list of Protocol Deviations will be defined. (Please refer to MedPace Protocol Deviation Plan V3.0 of 04 November 2021 for the full deviation categories list).

8. Determination of sample size

Due to the nature of the study, no formal sample size calculation is applicable. However, under Protocol Version 12.0, approximately 65 evaluable patients with AML were planned to be enrolled in this study, with 20 of them to be enrolled in the all-comers cohort and 20 in the IDH-mutants cohort (Part 2).

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 was 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 was 25 and 125 mg was considered the RP2D.

This cohort was then expanded to enroll 20 additional patients. Nevertheless, 3 patients were replaced and a total number of 23 patients were treated in this study phase. The replacement occurred when patients were not considered evaluable for safety and/or lacked one post-treatment bone marrow disease assessment.

9. Randomization Methodology

The study is non randomized.

10. Stopping Rules and Blinding

10.1. Stopping Rules

A data monitoring committee (DMC) external to both the Sponsor and clinical research organization (CRO) will be responsible for ongoing monitoring of the safety and efficacy according to the DMC Charter. The DMC will meet on a regular basis and will make recommendations as to whether the trial should continue, be amended, or be discontinued based on ongoing reviews of safety and efficacy data. DMC responsibilities and review schedules are outlined in an DMC charter.

10.2. Blinding

This is an open-label study; thus, study subjects and investigators will not be blinded to treatment assignment.

11. Statistical analysis and methods

11.1. Multiplicity adjustment

This section is Not Applicable

11.2. Descriptive statistics

All study variables will be presented by cohort, dose and overall, by using the appropriate descriptive statistics according to the variable nature, unless otherwise specified:

- **Continuous variables**: number of non-missing observations, arithmetic mean, median, standard deviation (SD), minimum, maximum;
- **Categorical variables**: number of non-missing observations and column percentages (N, %);
- **Time to event variables**: number of non-missing observations, number and percentage of censored observations, 1st quartile, median and its 95% Confidence Interval (CI), 3rd quartile, Kaplan-Meier survival curves.

The behaviour over time of study variables will be summarised by cohort and overall as follows:

- **Continuous variables**: descriptive statistics for each time point of interest;
- **Discrete variables**: descriptive statistics for each time point of interest.

11.3. Data imputation

The missing values will not be imputed because, for all the analyses, an observed-cases approach will be applied.
Regarding time-to-event variables analysis:

- OS, if a subject is censored with respect to the event of interest the censoring date is defined as the date of the last performed visit;
- RFS, EFS and DoR, if a subject is censored with respect to the event of interest the censoring date is defined as the date of the last relapse/progression/event-free disease assessment.

11.4. Patient disposition and Baseline tables

The following numbers will be presented, grouped by cohort and overall:

- Number of patients Screened;
- Number of patients Screening Failures;
- Number of patients in DD population;
- Number of patients in Safety population;
- Number of patients in Efficacy population;
- Number of patients who discontinued and reason for discontinuation.

The following baseline characteristics will be summarised by descriptive statistics computed on the Safety population:

- Demographics characteristics;
- Medical History and Concurrent Medical Conditions;
- Acute Myeloid Leukemia specific Medical History;
- Mutation status;
- Prior and Concomitant medications;
- Prior and Concomitant procedures.

11.5. Safety analysis

Safety and tolerability assessments will be evaluated on the safety population by means of descriptive statistics. Summary statistics (counts / (%) | number of events) will report the incidence of AEs using combinations of these variables for the descriptive statistics stratification: CTCAE toxicity grade, relationship with study drug, seriousness, System Organ Class or Body System, Preferred Term.
AEs summary tables will be created by Cohort (dose level) and Overall.
Counts and percentages will be produced for the results of the ECG, laboratory values (clinical chemistry, haematology, coagulation, bone marrow and urinalysis), vital signs, physical examination, classified as Normal/Abnormal NCS/Abnormal CS by Cohort (dose level) and Overall, stratified by Visit and timepoint – if applicable.
For ECG and hematology, clinical chemistry, coagulation and bone marrow laboratory data, the change from baseline will be summarized for each post baseline visit with descriptive statistics by cohort. For hematology and clinical chemistry laboratory parameters shift tables will be presented with the counts of individual shifts from each of the reference range categories from baseline to the worst post-baseline value by laboratory parameter by cohort and dose level.

11.5.1. Safety assessments

Safety and tolerability endpoints will be derived from the following measurements/evaluations:

- Incidence, severity (CTCAE grade), seriousness, and treatment related causality of AEs;
- Physical examination;
- Vital signs;
- Safety laboratory tests (Clinical Chemistry, Hematology, Coagulation, Lipid Profile and Urinalysis);
- 12-lead-ECG.

11.5.2. Adverse Events

All identified AEs are recorded and described on the appropriate AE page of the eCRF, except for those events occurring prior to the fist SEL24/MEN1703 intake, which are recorded on the Medical History eCRF page. All Adverse Events recorded in the eCRF will be listed. All AEs summaries will be based on the safety population.

The following information will be reported for all AEs listings: cohort and dose, patient ID, case ID, date of onset and resolution, duration in days, severity (grade) and seriousness of the event, assessment whether the event was serious or non-serious, relationship to IMP, and action taken regarding the IMP. In the listings, all AEs and their eventual follow-up will be reported. The Sponsor assessment for seriousness and causality will also be reported except for patients enrolled under Selvita sponsorship.

AE attributes that will be summarized into a new binary variable

- **Relationship to study drug**. If the AE is judged as *Definitely Related, Probably Related or Possibly Related* then the AE will be judged as Related to the study drug. If the relationship assessment is missing, the AE will be considered as related.
- **Seriousness of the AE**. If the AE is judged as 'Serious' or 'Exception to SAE reporting', then the AE will be judged as 'Serious'.

The number and percentage of patients experiencing one or more AEs will be summarized in the safety tables by cohort, dose level, relationship to study drug, and seriousness.

An overview of AEs will be provided with the number and percentage of patients reporting an event by cohort, dose level and overall. The summaries will be presented for the following categories:

- Any Serious AE
- Any Related AE
- Any Serious and Related AE
- Any AE by Relationship, Outcome, Severity (Grade) or Action Taken

If a patient experienced an AE and some follow-up AEs with the same preferred term, the AE and its follow-up(s) will count as one. The relationship with IMP, the seriousness and the action taken will be used to make filters in the summary safety tables; all events will be included in the listings.

Additionally the different groups of AEs - expressed as number and percentage of patients with each AE - will be presented by cohort and overall, by dose level and overall, by System Organ Class and Preferred Term or by Grade, System Organ Class and Preferred Term.

11.5.3. Vital Signs

A summary table of Vital Signs (systolic and diastolic BP (Blood Pressure - mmHg), temperature, heart rate) by Visit will be provided in the TLFs.

11.5.4. Physical Examination

A summary table of Physical Examination parameters by Body System and Visit will be provided in the TLFs.

11.5.5. 12-ECG

A summary table of 12-Lead ECG interpretation by Visit will be provided in the TLFs. Similarly, changes from baseline for each post baseline visit will be summarised.

11.5.6. Safety laboratory tests

An overall summary table of clinical chemistry, haematology, coagulation, lipid profile, bone marrow and urinalysis parameters by Visit, cohort, dose and time-point will be provided in the TLFs. The change from baseline will be summarized for each post baseline visit with descriptive statistics by cohort.

12. Efficacy evaluations

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.

12.1. Efficacy analysis

The Overall Survival (OS) is calculated as:

- In case of all-cause death:
  OS = date of death – date of first study drug administration + 1;
- In case of censored information not for drop-out:
  OS = date of end of observation period (i.e. study end / end of survival follow-up) – date of first study drug administration + 1;
- In case of censored information for drop-out:
  OS = last date known alive – date of first study drug administration + 1.

The Relapse Free Survival (RFS) is calculated as:

- In case of relapse or all-cause death:
  RFS = date of relapse or death (whichever comes first) – date of first CR, CRi, CRh or CR_{MRD-} + 1;
- In case of censored information:
  RFS = date of last relapse-free disease assessment – date of first CR, CRi, CRh or CR_{MRD-} + 1.

The Event Free Survival (EFS) is calculated as:

- In case of relapse, treatment failure or all-cause death:
  EFS = date of relapse, disease progression, treatment failure (failure to achieve CR/CRh/CRi/CR_{MRD-} after at least five cycles of treatment) or death (whichever comes first) – date of first study drug administration + 1;
- In case of censored information:
  EFS = date of last relapse-free/treatment-failure-free/progression-free disease assessment – date of first study drug administration + 1.

The Duration of Response (DoR) is calculated as:

- In case of relapse, progressive disease or death due to progressive disease:
  DoR = date of relapse of any type/progressive disease/death due to progressive disease – date of first CR, CRi, CRh, CR_{MRD-}, MLFS or PR + 1;
- In case of censored information:
  DoR = date of last relapse-free disease assessment – date of first CR, CRi, CRh, CR_{MRD-}, MLFS or PR + 1.

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 be summarized by cohort, by dose and overall.

Measures of anti-leukemic activity will be computed on both safety and efficacy populations and they will include:

- Changes (absolute and %) in pre- and post-treatment levels of leukemic blasts in the peripheral blood and/or bone marrow;
- Number and percentages of patients who reported as best overall response one of the following: CRMRD-, CR, CRh, CRi, MLFS, PR, SD, PD;
- Duration of response (DoR);
- Relapse-free survival (RFS);
- Event-free survival (EFS);
- Overall Survival (OS);
- Transfusion conversion rate;
- Transfusion maintenance rate;
- HSCT rate.

OS, RFS, EFS rates at specific timepoints (e.g. 6, 12 months) may also be performed with exploratory intent.

Transfusion conversion rate, transfusion maintenance rate and HSCT rate will be evaluated only in the IDH-mutants cohort.

Where possible disease assessment will be evaluated according to the response criteria in AML6 (Appendix D of Study Protocol). Efficacy analyses will be performed through descriptive statistics.

12.2. Subgroup analyses

Not applicable.

12.3. Pharmacokinetic analysis

The PK analysis will be run on the PK population.

Plasma concentration values Below the Lower Limit Of Quantification (BLLOQ) will be set to zero before the t_{max} and to "missing" after the t_{max}. Plasma concentrations reported as > BLLOQ at time zero, when the subject has not previously been dosed, will be set to their real value. Data-replacements will be implemented by the Global Clinical Pharmacology and Pharmacometrics department. A footnote should be added to the listing, tables, and figures, in order to indicate the LOQ value.

If actual sampling time is missing, the nominal time will be used.

If the 24-hours post dose sample is collected after the intake of the following dose, the corresponding concentration will be reported in the listing with a FLAG and excluded from the PK parameter calculation.

If urine volume is missing, concentrations will be reported in the listing and no PK parameters will be calculated.

If samples are collected during an unscheduled visit, individual concentrations and PK parameter will be reported in the listing with a FLAG, but they will be excluded from the summary statistics.

All PK plasma and urine concentrations and PK parameters will be summarized by cohort, cycle, day, IDH mutational status, and nominal time point, and by dose, cycle, day, IDH mutational status and nominal time point, by using the following descriptive statistics:

- Number of non-missing observations (N),
- Arithmetic mean (AM) and its 90% confidence interval (CI), standard deviation (SD), coefficient of variation (CV%) and standard error (SE),
- Geometric mean (GM) and its 90% CI and GM CV%,
- Median,
- Minimum (min) and maximum (max).

Individual plasma concentration data versus time will be presented in a data listing and visualized as individual concentration-time plots. Individual urine concentration data will be presented in a data listing.

Actual times will be used for calculation of PK parameters and replaced by nominal times when missing. Plot of individual and aggregated concentration versus time curves will be generated with nominal times.

13. Tables, listings and figures

13.1. Statistical Analysis Report

The TLF (Tables, Listings and Figures) will follow the list of tables, plots, and listings agreed with the Study Physician. The SAR will follow the list of tables, plots, and listings listed in the following section. The index is intended to provide the overall idea of the general output and ordering of the SAR, it will not necessarily be reproduced in the SAR.

13.2. Index of TLFs

13.2.1. Tables

Baseline Tables

Table 1.1: Patients Disposition
Table 1.2: Reason for discontinuation
Table 1.3: Demographics and Baseline Characteristics
Table 1.4: AML specific Medical History
Table 1.5: Mutation status
Table 1.6: Medical History by System Organ Class and Preferred Term
Table 1.7: Concomitant Medication by ATC Code
Table 1.8: Prior Medication for Cancer other than AML by ATC Code
Table 1.9: Prior Medication (Leukemia only) by ATC Code
Table 1.10: Number of Previous Treatments for Leukemia
Table 1.11: Drug Modification by Cycle
Table 1.12: Procedures by System Organ Class and Preferred Term

Safety Tables
Table 2.1 Adverse Events Summary
Table 2.1.1: Adverse Events by System Organ Class and Preferred Term
Table 2.1.2: Adverse Events by Grade, System Organ Class and Preferred Term
Table 2.1.2.1: Adverse Events by Grade, System Organ Class and Preferred Term (Grade < 3)
Table 2.1.2.2: Adverse Events by Grade, System Organ Class and Preferred Term (Grade >= 3)
Table 2.1.3: Adverse Events leading to Drug Withdrawn by System Organ Class and Preferred Term
Table 2.1.4: Adverse Events leading to Drug Interruption by System Organ Class and Preferred Term
Table 2.1.5: Adverse Events leading to Drug Reduction by System Organ Class and Preferred Term
Table 2.2.1: Related Adverse Events by System Organ Class and Preferred Term
Table 2.2.2: Related Adverse Events by Grade, System Organ Class and Preferred Term
Table 2.2.2.1: Related Adverse Events by Grade, System Organ Class and Preferred Term (Grade < 3)
Table 2.2.2.2: Related Adverse Events by Grade, System Organ Class and Preferred Term (Grade >= 3)
Table 2.2.3: Related Adverse Events leading to Drug Withdrawn by System Organ Class and Preferred Term
Table 2.2.4: Related Adverse Events leading to Drug Interruption by System Organ Class and Preferred Term
Table 2.2.5: Related Adverse Events leading to Drug Reduction by System Organ Class and Preferred Term

Table 2.3.1: Serious Adverse Events by System Organ Class and Preferred Term
Table 2.3.2: Serious Adverse Events by Grade, System Organ Class and Preferred Term
Table 2.3.2.1: Serious Adverse Events by Grade, System Organ Class and Preferred Term (Grade < 3)
Table 2.3.2.2: Serious Adverse Events by Grade, System Organ Class and Preferred Term (Grade >= 3)
Table 2.3.3: Serious Adverse Events leading to Drug Withdrawn by System Organ Class and Preferred Term
Table 2.3.4: Serious Adverse Events leading to Drug Interruption by System Organ Class and Preferred Term
Table 2.3.5: Serious Adverse Events leading to Drug Reduction by System Organ Class and Preferred Term
Table 2.4.1: Serious and Related Adverse Events by System Organ Class and Preferred Term
Table 2.4.2: Serious and Related Adverse Events by Grade, System Organ Class and Preferred Term
Table 2.4.3: Serious and Related Adverse Events leading to Drug Withdrawn by System Organ Class and Preferred Term
Table 2.4.4: Serious and Related Adverse Events leading to Drug Interruption by System Organ Class and Preferred Term
Table 2.4.5: Serious and RelatedAdverse Events leading to Drug Reduction by System Organ Class and Preferred Term
Table 2.5.1: Dose Limiting Toxicity by System Organ Class and Preferred Term
Table 2.5.2: Adverse Events leading to Death by System Organ Class and Preferred Term
Table 2.5.3 Related Adverse Events leading to Death by System Organ Class and Preferred Term
Table 2.6: Overall summary of Haematology Laboratory Parameters by Visit
Table 2.6.1: Change vs Baseline of Haematology Laboratory Parameters by Visit
Table 2.6.2: Shift Table for Haematology Laboratory Parameters
Table 2.7: Overall summary of Clinical Chemistry Laboratory Parameters by Visit
Table 2.7.1: Change vs Baseline of Clinical Chemistry Laboratory Parameters by Visit
Table 2.7.2: Shift Table for Clinical Chemistry Laboratory Parameters
Table 2.8: Overall summary of Coagulation Laboratory Parameters by Visit
Table 2.8.1: Change vs Baseline of Coagulation Laboratory Parameters by Visit
Table 2.9: Overall summary of Lipid Panel Parameters by Visit
Table 2.9.1: Change vs Baseline of Lipid Panel Parameters by Visit
Table 2.10: Overall summary of Bone Marrow Laboratory Parameters by Visit
Table 2.11.1: Change vs Baseline of Bone Marrow Laboratory Parameters by Visit
Table 2.12: Overall summary of Urinalysis Laboratory Parameters by Visit (Categorical Variables)
Table 2.12.1: Overall summary of Urinalysis Laboratory Parameters by Visit (Continuous Variables)
Table 2.13: Overall summary of Echocardiogram by Visit
Table 2.14: Overall summary of ECG by Visit
Table 2.14.1: Change vs Baseline of ECG by Visit
Table 2.15: Overall summary of ECOG Performance Status by Visit
Table 2.16: Overall summary of Physical Examination Parameters by Visit
Table 2.17: Overall summary of Vital Signs by Visit

Efficacy Tables (to be perfomed on both efficacy population as well as safety population)

Table 3.1: Summary of Tumor Response by Visit
Table 3.2: Summary of Tumor Response Endpoints
Table 3.3: Summary of Time to Event Endpoints

PK Tables

Table 4.1: Summary statistics of MEN1703 PK concentration in plasma by cohort, cycle, day, IDH mutational status and nominal time point, and by dose, cycle, day, IDH mutational status and nominal time point
Table 4.2: Summary statistics of MEN1703 PK parameters by cohort, cycle, day, IDH mutational status and nominal time point, and by dose, cycle, day, IDH mutational status and nominal time point.
Table 4.3: Summary statistics of MEN1703 PK concentration in urine by cohort, cycle, day, IDH mutational status and nominal time point, and by dose, cycle, day, IDH mutational status and nominal time point
Table 4.4: Summary statistics of MEN1703 urinary PK parameters by cohort, cycle, day, IDH mutational status and nominal time point, and by dose, cycle, day, IDH mutational status and nominal time point

Table 4.5: Summary statistics of MET3 PK concentration in plasma by cohort, cycle, day, IDH mutational status and nominal time point, and by dose, cycle, day, IDH mutational status and nominal time point
Table 4.6: Summary statistics of MET3 PK parameters by cohort, cycle, day, IDH mutational status and nominal time point, and by dose, cycle, day, IDH mutational status and nominal time point.

Table 4.7: Summary statistics of MET3 PK concentration in urine by cohort, cycle, day, IDH mutational status and nominal time point, and by dose, cycle, day, IDH mutational status and nominal time point
Table 4.8: Summary statistics of MET3 urinary PK parameters by cohort, cycle, day, IDH mutational status and nominal time point, and by dose, cycle, day, IDH mutational status and nominal time point

13.2.2. Listings

Listings
Listing 4.1: Demographic Characteristics
Listing 4.2: Reason for discontinuation
Listing 4.3: Tumor Hisory Characteristics
Listing 4.4: Tumor Hisory Previous Treatment
Listing 4.5: Medical History
Listing 4.6: Previous Treatment
Listing 4.7: Previous Procedure
Listing 4.8: Concomitant Medication
Listing 4.9 - 4.10: Adverse Event (Part 1 - Part 2)
Listing 4.11: Adverse Events
Listing 4.11.1: Adverse Events of Grade >= 3
Listing 4.11.2: Serious Treatment Emergent Adverse Events
Listing 4.11.3: Serious and Related Treatment Emergent Adverse Events
Listing 4.11.4: Dose Limiting Toxicities
Listing 4.11.5: Adverse Events leading to Drug Withdrawn
Listing 4.11.6: Adverse Events leading to Drug Interruption
Listing 4.11.7: Adverse Events leading to Drug Reduction
Listing 4.11.8: Adverse Events leading to death
Listing 4.12: Haematology
Listing 4.13: Clinical Chemistry
Listing 4.14: Coagulation
Listing 4.14.1: Lipid panel
Listing 4.15: Urinalysis
Listing 4.16: Bone Marrow
Listing 4.17: Electrocardiogram
Listing 4.18: ECOG Performance Status
Listing 4.19: Physical Examination
Listing 4.20: Vital Signs
Listing 4.21: Mutations
Listing 4.22: Treatment Intake – SEL24/MEN1703
Listing 4.23: Tumor Response by Timepoint
Listing 4.24: individual MEN1703 plasma PK concentrations
Listing 4.25: individual MEN1703 plasma PK parameters
Listing 4.26: Individual MEN1703 urinary PK concentrations over 24-hours
Listing 4.27: Individual MEN1703 urinary PK parameter
Listing 4.28: individual MET3 plasma PK concentrations
Listing 4.29: individual MET3 plasma PK parameters
Listing 4.30: Individual MET3 urinary PK concentrations over 24-hours
Listing 4.31: Individual MET3 urinary PK parameter

13.2.3. Figures

Figures
Figure 1: Overall Mean and Median timecourse – ALT (µkat/L)
Figure 2: Overall Mean and Median timecourse – AST (µkat/L)
Figure 3: Overall Mean and Median timecourse – Blasts (10^9/L)
Figure 4: Overall Mean and Median timecourse – Hemoglobin (g/L)
Figure 5: Overall Mean and Median timecourse – Lymphocytes (10^9/L)