First in man study with MEN1112, a CD157 targeted monoclonal antibody, in relapsed or refractory Acute Myeloid Leukemia

NCT: 02353143

Date: 04 November 2019

MENARINI RICERCHE

CLINICAL STUDY PROTOCOL

[redacted]

First in man study with MEN1112, a CD157 targeted monoclonal antibody, in relapsed or refractory Acute Myeloid Leukemia

ARMY
Anti CD157 Receptor Monoclonal AntibodY

Study code	**ARMY-1**
Study Nick Name	**ARMY**
EudraCT-Number	**2014-002433-59**
Investigational Medicinal Product	**MEN1112 (5.0mg/mL) concentrate for solution for infusion**
Development phase of study	**I**

[redacted]

1. SIGNATURES

The signatories have read the clinical trial protocol titled "First in man study with MEN1112, a CD157 targeted monoclonal antibody, in relapsed or refractory Acute Myeloid Leukemia" - ***Final Version 7.0, 04 November 2019*** - carefully and agree to adhere to its provisions. Changes to the protocol have to be stated by the Sponsor in amendments to the clinical trial protocol which, if they are substantial, have to be authorised by the Competent Authorities and Ethics Committees before translating them into action.

Sponsor's Representative	**Signature**	**Date**
[redacted]		

Co-ordinating Investigator	**Signature**	**Date**
[redacted]		

PRINCIPAL INVESTIGATOR'S STATEMENT

My signature below documents my agreement with the contents of this clinical trial protocol titled "First in man study with MEN1112, a CD157 targeted monoclonal antibody, in relapsed or refractory Acute Myeloid Leukemia***" - Final Version 7.0, 04 November 2019 -*** with regard to the execution of the study and the required documentation/data collection. I agree to comply with this clinical trial protocol in its entirety and with the International Conference of Harmonisation (ICH) guidelines for Good Clinical Practice (GCP).

Principal Investigator	**Signature**	**Date**
..... (printed name)	.....	.....

2. PROTOCOL SYNOPSIS

Study Title **Sponsor Code** **Nick name/Acronym**	First in man study with MEN1112, a CD157 targeted monoclonal antibody, in relapsed or refractory Acute Myeloid Leukemia. ARMY-1 **ARMY - Anti CD157 Receptor Monoclonal AntibodY**
Phase	Phase I
Indication	Acute Myeloid Leukemia (AML).
No. of sites & countries	Approximately 20 EU sites.
Investigational Medicinal Product	MEN1112 (5.0 mg/mL) concentrate for solution for infusion.
Design (see also § 2.1)	Open label, 3+3 dose escalation and cohort expansion, multicentre, phase I study.
Treatment (see also § 2.1)	**Step 1 (dose escalation phase)**: In protocol versions from 1.0 to 4.1 n=3 Dose Limiting Toxicity (DLT) evaluable patients per cohort (expanded to n=6 DLT evaluable patients in case of DLT occurrence, with the exception of cohort 0.3 mg/kg which was expanded to n=6 DLT evaluable patients regardless of DLT occurrence) were treated with MEN1112 at escalating doses of 0.1, 0.3, 0.6, 1.0, 1.7, and 2.5 mg/kg using *"one-shot"* infusions. Starting from protocol version 6.1/6.2, n=3 Dose Limiting Toxicity (DLT) evaluable patients per cohort (expanded to n=6 DLT evaluable patients in case of DLT occurrence) will be treated with MEN1112 at escalating doses of 1.7, 2.0, 3.0, 5.0 mg/kg per each dose cohort using a modified schedule of administration that will include a *"ramp-up"* approach at Cycle 1. Additional intermediate dose levels may be explored, under a 3+3 design, upon recommendation of the independent Data Safety Monitoring Board (iDSMB) that will be appointed to guide dose escalation decisions in place of the Cohort Review Committee (CRC) that was appointed for this role up to Protocol Version 4.1. [redacted]

[redacted]

Step 2 (cohort expansion phase): Under Protocol Version 4.1, two patients experienced DLTs at the dose level of 2.5 mg/kg using the *"one-shot"* schedule of administration in Cycle 1. Therefore, the 1.7 mg/kg dose level was defined as the maximum tolerated dose (MTD) for the schedule of administration encompassing the *"one-shot"* infusion since Cycle 1; as a consequence, the expansion phase was opened to enrol up to 25 patients with MEN1112 given as *"one-shot"* infusions since Cycle 1.

Starting from protocol version 6.1/6.2, up to 30 patients will be treated with MEN1112 given at the MTD identified in Step 1 using the *"ramp-up"* approach during Cycle 1. The iDMSB, already implemented for Step 1, will also be appointed to assess the data collected during the Step 2 of the study.

Up to Protocol Version 4.1, MEN1112 was administered by intravenous *"one-shot"* weekly infusions for two 21-day cycles, followed by *"one-shot"* monthly infusions in patients demonstrating clinical benefit (as per Investigator's judgement) as long as such benefit was maintained. Starting from protocol version 6.1/6.2, MEN1112 will be administered for two 21-day cycles; the first two infusions of Cycle 1 will be given using a ***"3-day ramp-up"* schedule of administration,** i.e. the complete MEN1112 dose will be split in three days. Starting from the third infusion of Cycle 1 onwards, MEN1112 will be administered as *"one-shot"* infusions. The treatment plan by dose level will be therefore as following:

DOSE LEVEL	CYCLE 1	CYCLE 2
1.7 mg/kg	Visit 1/Day 1: 0.1 mg/kg Visit 2/Day 2: 0.6 mg/kg Visit 3/Day 3: 1.0 mg/kg Visit 8/Day 8: 0.1 mg/kg Visit 9/Day 9: 0.6 mg/kg Visit 10/Day 10: 1.0 mg/kg Visit 12/Day 15: 1.7 mg/kg	Visit 16/Day 22: 1.7 mg/kg Visit 20/Day 29: 1.7 mg/kg Visit 24/Day 36: 1.7 mg/kg

2.0 mg/kg	Visit 1/Day 1: 0.1 mg/kg Visit 2/Day 2: 0.7 mg/kg Visit 3/Day 3: 1.2 mg/kg Visit 8/Day 8: 0.1 mg/kg Visit 9/Day 9: 0.7 mg/kg Visit 10/Day 10: 1.2 mg/kg Visit 12/Day 15: 2.0 mg/kg	Visit 16/Day 22: 2.0 mg/kg Visit 20/Day 29: 2.0 mg/kg Visit 24/Day 36: 2.0 mg/kg
[redacted]		
3.0 mg/kg	Visit 1/Day 1: 0.2 mg/kg Visit 2/Day 2: 1.0 mg/kg Visit 3/Day 3: 1.8 mg/kg Visit 8/Day 8: 0.2 mg/kg Visit 9/Day 9: 1.0 mg/kg Visit 10/Day 10: 1.8 mg/kg Visit 12/Day 15: 3.0 mg/kg	Visit 16/Day 22: 3.0 mg/kg Visit 20/Day 29: 3.0 mg/kg Visit 24/Day 36: 3.0 mg/kg
5.0 mg/kg	Visit 1/Day 1: 0.3 mg/kg Visit 2/Day 2: 1.7 mg/kg Visit 3/Day 3: 3.0 mg/kg Visit 8/Day 8: 0.3 mg/kg Visit 9/Day 9: 1.7 mg/kg Visit 10/Day 10:3.0 mg/kg Visit 12/Day 15: 5.0 mg/kg	Visit 16/Day 22: 5.0 mg/kg Visit 20/Day 29: 5.0 mg/kg Visit 24/Day 36: 5.0 mg/kg

[redacted]

Starting from protocol version 6.1/6.2, Cycle 1 and Cycle 2 will constitute the Treatment period, followed by a 4-week End of Treatment period and a Follow-up period. During the Follow-up period, only safety and/or efficacy assessments are scheduled; however, to serve the best interest of the patients, for those achieving at least a partial response according to protocol-defined criteria, the Sponsor commits to consider providing MEN1112 to allow the prosecution of the infusions at the frequency recommended by the iDSMB on an individual basis and after discussion with the treating

	Investigator and the Medical Monitor.
Primary objectives	To identify the DLT and MTD of MEN1112 when given intravenously during Cycle 1 in patients with relapsed or refractory AML.
Secondary objectives	The following will be assessed/determined: ▪ Safety and tolerability of MEN1112 ▪ Pharmacokinetic profile after single and repeat doses of MEN1112 following intravenous (IV) administration ▪ Potential of MEN1112 immunogenicity ▪ Clinical activity of MEN1112 ▪ Correlation of baseline patient's and disease characteristics with clinical activity of MEN1112
[redacted]	[redacted]
Study duration	Individual study period: 6 months from the first drug administration (except for female patients of childbearing potential, who will be required to undergo a monthly pregnancy test until 6 months from the last study drug administration). Overall observational period: 6 months from last patient in.
Inclusion criteria	**Patients meeting ALL the following criteria will be eligible for entry into the study:** 1. Male or female patients aged ≥ 18 years. 2. Documented definitive diagnosis of AML (according to WHO criteria, 2008) that is relapsed/refractory to standard treatment, for which no standard therapy is available or the patient refuses standard therapy. For the purpose of this study, refractory AML is defined as following: *Failure to achieve Complete Remission/Complete Remission with incomplete blood count recovery (CR/CRi) (International*

	Working Group (IWG criteria, 2003) following at least 1 cycle of cytotoxic chemotherapy (or hypomethylating agents if unsuitable for cytotoxic chemotherapy) and unlikely, as per Investigator's judgement, to achieve CR/CRi with further cytotoxic chemotherapy (or hypomethylating agents if unsuitable for cytotoxic chemotherapy). 3. White Blood Cells (WBC) count ≤ 10 x 10^9/L at Visit 1/ Day 1; hydroxyurea is allowed to lower WBC count. 4. Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2 at Visit 1/Day 1. 5. Life expectancy of at least 2 months. 6. Adequate renal and hepatic laboratory assessments: - Aspartate aminotransferase (AST), alanine aminotransferase (ALT) and alkaline phosphatase (ALP) ≤3.0 × Upper Limit of Normal (ULN), unless considered due to leukemic organ involvement. - Total Bilirubin ≤2.0 × ULN. - Serum creatinine ≤2.0 × ULN. 7. A female of childbearing potential may be enrolled providing she: – has a negative pregnancy test during screening period and – is routinely using an effective method of birth control 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, associated with inhibition of ovulation, intrauterine device, total sexual abstinence or bilateral tubal occlusion) until 6 months from the last study drug administration – undergoes a monthly pregnancy test until 6 months from the last study drug administration. 8. Able to give written informed consent before any study related procedure. **NOTE:** Inclusion criteria will be evaluated during the Screening

	Period, with the exception of inclusion criteria 3 and 4, which will be evaluated at Visit 1/Day 1; inclusion criteria 5 and 6 will be re-evaluated prior to the first study drug administration (Visit 1/Day 1).
Exclusion criteria	**Patients will not be eligible to participate in the study if they meet ANY of the following exclusion criteria:** 1. Acute promyelocytic leukaemia (French-American-British [FAB] M3 classification). 2. Active central nervous system involvement. 3. Haematopoietic stem cell transplantation (HSCT) performed within 3 months prior to Screening Period. Patients with prior allogeneic HSCT performed more than 3 months prior to Screening Period are eligible with Medical Monitor approval. 4. Active infection requiring intravenous antibiotics. 5. Life-threatening illnesses other than AML, uncontrolled medical conditions or organ system dysfunction which, in the investigator's opinion, could compromise the patient's safety or interfere with the patient's ability to comply with the study activities. 6. Anti-tumour therapy within 14 days of study Visit 1/Day 1, excluding hydroxyurea. 7. Prior participation in an investigational study (procedure or device) within 21 days of study Visit 1/Day 1. 8. Major surgery within 28 days of study Visit 1/Day 1. 9. Radiotherapy within 28 days prior to study Visit 1/Day 1 or scheduled along the study conduct. 10. Known history of human immunodeficiency virus (HIV) or active infection with hepatitis C virus (HCV) or hepatitis B virus (HBV). 11. Known hypersensitivity to MEN1112 excipients. 12. Other active malignancies. History of malignancy in the last 12 months (except basal cell or squamous cell skin cancer or carcinoma in situ of the cervix or breast or non-melanoma skin cancer). 13. Pregnant or breast-feeding women.

	NOTE: Exclusion criteria will be evaluated during the Screening Period, with the exception of exclusion criteria 6, 7, 8 and 9, which will be evaluated at Visit 1/Day 1; exclusion criteria 4 and 5 will be re-evaluated prior to the first study drug administration (Visit 1/Day 1).
Study procedures and assessments (see also § 2.2)	PRIOR to any study procedures, written Informed Consent shall be obtained by the patient. **Screening Period (Day -7 to 0)** ▪ Check of Inclusion/Exclusion Criteria ▪ Demographic data collection ▪ Medical and medication general history ▪ AML history, i.e. date of onset of AML, relapsed or refractory status following the last AML treatment, de novo or secondary AML status, number and category of previous AML treatments (including autologous and allogeneic HSCT), and duration of last CR (for relapsed patients), and disease features when available (i.e. AML karyotype, NPM1 and/or FLT3-ITD mutational status, FAB subtype) ▪ Physical examination, including vital signs (i.e. blood pressure [BP], heart rate [HR], breathing rate [BR], body temperature [T]) ▪ Weight measurement ▪ Performance Status (PS) evaluation ▪ 12-lead Electrocardiogram (ECG) ▪ Blood sampling and urine collection for safety lab tests, including pregnancy test (if applicable) ▪ Blood sampling for anti-HIV antibodies, anti- Hepatitis B core Antigen (anti-HBcAg) antibodies, Hepatitis B Virus-Deoxyribonucleic acid (HBV-DNA), Hepatitis C Virus-Ribonucleic acid (HCV-RNA) ▪ [redacted] ▪ [redacted]

- Blood sampling for immunogenicity assessment [redacted]
- Recording of Adverse Events (AEs) and change in concomitant medications

NOTE: Results of laboratory tests for anti-HIV antibodies, anti-HBcAg antibodies, HBV-DNA, HCV-RNA which have been performed within 3 months prior to Screening Period in the context of the standard patient's management (either in the local lab or in a different lab, provided that they comply with local standard procedures) can be reported in the electronic-Case Report Form (e-CRF) under Screening Period procedures and added in the patient file as source document. In such case, there is no need to repeat the above mentioned tests.

TREATMENT PHASE

CYCLE 1

Visit 1/Day 1, first 3-day *"ramp-up"* dose

Prior to study drug administration

- Re-check inclusion/exclusion criteria and confirmation of patient's eligibility prior to start treatment
- Physical examination, including vital signs
- Weight measurement
- PS evaluation
- 12-lead ECG
- Blood sampling and urine collection for safety lab test
  NOTE: Check that WBC count is $\leq$ 10 x 10^9/L; hydroxyurea is allowed to lower WBC count.
- Blood sampling for Pharmacokinetics (PK) [redacted]
- Recording of AEs and change in concomitant medications

	▪ Tumour lysis syndrome (TLS) risk assessment (see *Appendix I: TLS Manual for Investigator*) ▪ TLS prophylaxis (see *Appendix I: TLS Manual for Investigator*) ▪ Premedication (see §8.4.2) *Study drug administration* ▪ Study drug administration, given as a 6h infusion with constant infusion rate ▪ Blood sampling for safety lab test at following time points after start of infusion: 2h, 4h, 8h, 12h ▪ Vital signs every 15 minutes during the first hour of study drug administration and then at the same time points of blood sampling for safety lab test ▪ 12-lead ECG at the end of infusion ▪ Blood sampling for PK [redacted] (at the end of infusion and 6h after the end of infusion) ▪ Recording of AEs and change in concomitant medications **Visit 2/Day 2 (one day after the completion of Visit 1) and Visit 3/Day 3 (one day after the completion of Visit 2)** *Prior to study drug administration* ▪ Physical examination, including vital signs ▪ PS evaluation ▪ 12-lead ECG ▪ Blood sampling for safety lab test ▪ Blood sampling for PK [redacted] (pre-infusion) ▪ Recording of AEs and change in concomitant medications ▪ TLS prophylaxis (see *Appendix I: TLS Manual for Investigator*) ▪ Premedication (see §8.4.2) *Study drug administration* ▪ Study drug administration, given as 6h infusion with constant infusion rate

	▪ Blood sampling for safety lab test at the following time points after start of infusion: 2h, 4h, 8h, 12h ▪ Vital signs every 15 minutes during the first hour of study drug administration and then at the same time points of blood sampling for safety lab test ▪ 12-lead ECG at the end of infusion ▪ Urine collection at the end of infusion (ONLY at Visit 3/Day 3) ▪ Blood sampling for PK [redacted] at the end of infusion, 6h after the end of infusion (ONLY at Visit 2/Day 2), 14h after the end of infusion (ONLY at Visit 3/Day 3) ▪ Recording of AEs and change in concomitant medications **Visit 4/Day 4 one day after the completion of the entire first *"ramp-up"*** ▪ Physical examination, including vital signs ▪ PS evaluation ▪ Blood sampling for safety lab test ▪ [redacted] ▪ Blood sampling for PK [redacted] 24h after the end of last *"ramp-up"* dosing infusion ▪ Bone marrow aspirate for morphologic assessment, [redacted] ▪ Recording of AEs and change in concomitant medications **Visit 5-6/Day 5-6, at one and two days after Visit 4, respectively** ▪ Blood sampling for PK [redacted] (44h and 68h after the end of last *"ramp-up"* dosing infusion) ▪ Recording of AEs and change in concomitant medications **Visit 8/Day 8 (five days after the completion of Visit 3), Visit 9/Day 9 (one day after the completion of Visit 8) and Visit 10/Day**

	10 (one day after the completion of Visit 9), second 3-day *"ramp-up"* administration *Prior to study drug administration* ▪ Physical examination, including vital signs ▪ Weight measurement (ONLY at Visit 8/Day 8) ▪ PS evaluation ▪ Blood sampling for safety lab test NOTE: Check that WBC count is ≤ 10 x 10^9/L (ONLY at Visit 8/Day 8); hydroxyurea is allowed to lower WBC count. ▪ Blood sampling for PK [redacted] (pre-infusion) ▪ Recording of AEs and change in concomitant medications ▪ TLS prophylaxis (see *Appendix I: TLS Manual for Investigator*) ▪ Premedication (see §8.4.2) *Study drug administration* ▪ Study drug administration, given as 6h infusion with constant infusion rate ▪ Blood sampling for safety lab test at the following time points after start of infusion: 2h, 4h, 8h, 12h ▪ Vital signs every 15 minutes during the first hour of study drug administration, after then at the same time points of blood sampling for safety lab test ▪ Blood sampling for PK [redacted] (at the end of infusion) ▪ Recording of AEs and change in concomitant medications **Visit 11/Day 11, one day after the completion of the entire second *"ramp-up"*** ▪ Physical examination, including vital signs ▪ PS evaluation Blood sampling for safety lab test including pregnancy test, if applicable ▪ Recording of AEs and change in concomitant medications

Visit 12/Day 15 (five days after Visit 10), first *"one-shot"* infusion

Prior to study drug administration

- Physical examination, including vital signs
- Weight measurement
- PS evaluation
- Blood sampling for safety lab test
  NOTE: Check that WBC count is ≤ 10 x 10^9/L; hydroxyurea is allowed to lower WBC count.
- Blood sampling for PK [redacted] (pre-infusion)
- Recording of AEs and change in concomitant medications
- TLS prophylaxis (see *Appendix I: TLS Manual for Investigator*)
- Premedication (see §8.4.2)

Study drug administration

- Study drug administration, given as a 6h infusion with constant infusion rate
- Blood sampling for safety lab test at the following time points after start of infusion: 2h, 4h, 8h, 12h
- Vital signs every 15 minutes during the first hour of study drug administration, after then at the same time points of blood sampling for safety lab test
- Blood sampling for PK [redacted] (at the end of infusion)
- Recording of AEs and change in concomitant medications

Visit 13-15/Day 16-18, one, two and three days after Visit 12

- Physical examination including vital signs
- PS evaluation
- Blood sampling for safety lab test (at 24h, 48h and 72 h after start of infusion)
- Recording of AEs and change in concomitant medications

CYCLE 2

	Visit 16/Day 22, seven days after Visit 12 *Prior to study drug administration* ▪ Physical examination including vital signs ▪ Weight measurement ▪ PS evaluation ▪ Blood sampling for safety lab test ▪ [redacted] ▪ Blood sampling for PK [redacted] (pre-infusion) ▪ Bone marrow aspirate for morphologic assessment, [redacted] ▪ Recording of AEs and change in concomitant medications ▪ Premedication (see §8.4.2) *Study drug administration* ▪ Study drug administration, given as a 6h infusion with constant infusion rate ▪ Vital signs every 15 minutes during the first hour of study drug administration and at 15 minutes after end of infusion ▪ Blood sampling for PK [redacted] (at the end of infusion) ▪ Recording of AEs and change in concomitant medications **Visit 17-19/Day 23-25, one, two and three days after the completion of Visit 16, respectively** ▪ Physical examination including vital signs ▪ PS evaluation ▪ Blood sampling for safety lab test ▪ Recording of AEs and change in concomitant medications **Visit 20/Day 29, seven days after the completion of Visit 16** *Prior to study drug administration* ▪ Physical examination including vital signs ▪ Weight measurement

	▪ PS evaluation ▪ Blood sampling for safety lab test ▪ Blood sampling for PK [redacted] (pre-infusion) ▪ Recording of AEs and change in concomitant medications ▪ Premedication (see §8.4.2) *Study drug administration* ▪ Study drug administration, given as a 6h infusion with constant infusion rate ▪ Vital signs every 15 minutes during the first hour of study drug administration and at 15 minutes after end of infusion ▪ Blood sampling for PK [redacted] at the end of infusion ▪ Recording of AEs and change in concomitant medications **Visit 21-23/Day 30-32, one, two and three days after the completion of Visit 20, respectively)** ▪ Physical examination including vital signs ▪ PS evaluation ▪ Blood sampling for safety lab test ▪ Recording of AEs and change in concomitant medications **Visit 24/Day 36, seven days after the completion of Visit 20** *Prior to study drug administration* ▪ Physical examination including vital signs ▪ Weight measurement ▪ PS evaluation ▪ Blood sampling for safety lab test ▪ Blood sampling for PK [redacted] (pre-infusion) ▪ Recording of AEs and change in concomitant medications ▪ Premedication (see §8.4.2) *Study drug administration* ▪ Study drug administration, given as a 6h infusion with constant infusion rate

	▪ Vital signs every 15 minutes during the first hour of study drug administration and at 15 minutes after end of infusion ▪ Blood sampling for PK [redacted] (at the end of infusion and at 1h and 6h after the end of infusion) ▪ Recording of AEs and change in concomitant medications **Visit 25-27/Day 37-39, one, two and three days after the completion of Visit 24, respectively** ▪ Physical examination including vital signs ▪ PS evaluation ▪ Blood sampling for safety lab test including pregnancy test (only at Visit 27, if applicable) ▪ Blood sampling for PK [redacted] (24h, 48h and 72h after the end of infusion) ▪ Recording of AEs and change in concomitant medications **Visit 28-29/Day 40-41, one and two days after Visit 27, respectively** ▪ Blood sampling for PK [redacted] (96h and 120h after the end of infusion) ▪ Recording of AEs and change in concomitant medications **Visit 30/Day 42, the day after Visit 29** ▪ Physical examination including vital signs ▪ PS evaluation ▪ Blood sampling for safety lab test ▪ [redacted] ▪ Blood sampling for PK [redacted] (144h after the end of infusion) ▪ Bone marrow aspirate for morphologic assessment, [redacted] ▪ Recording of AEs and change in concomitant medications

NOTES:

- During Cycle 1, under the *"ramp-up"* dosing scheme, an administration visit will encompass the three *"ramp-up"* infusions (to be split in up to four days, in case of specific infusion-related toxicities, see §8.4.7) to complete the administration of MEN1112.
- Prior to start MEN1112 infusion, results of the safety lab tests (including hepatic function tests) should be duly checked by the Investigator to confirm that eligibility criteria are met (Visit 1/Day 1, prior of infusion) or no treatment withdrawal/dose interruption criteria are met (any subsequent infusion).
- One of the following adjustments is allowed:
  - +1 day for any *"ramp-up"* administration visit in case of WBC count >$10x10^9$/L on the first day of such visit, in order to lower the WBC count using hydroxyurea. This is applicable also to the *"one-shot"* infusion visit of Cycle 1 (Visit 12/Day 15).
  - + 1 day for each study drug administration visit (i.e. first *"ramp-up"* and *"one-shot"* administration visit).
- In case of study visit re-schedule due to infusion related toxicities (see §8.4.7), WBC count recovery, or any other reasons, the interval of 5 days (Cycle 1) or 7 days (Cycle 2) between the end of any study drug administration visit and the start of the following one should be guaranteed.
- Moreover, at each infusion during the study conduct, in case of interruption due to drug-related toxicities:
  - The infusion duration will be prolonged [redacted] using a constant infusion rate; this infusion duration will then be applied to every subsequent infusions.
  - In case the interruption lasts >24 hours, the safety assessments will be repeated when the infusion is resumed according to the time-points scheduled for

	the original visit. o If any interruption occurs during Cycle 1 and the 3rd infusion of Cycle 2, blood sampling for PK [redacted] will also be taken at the time of each infusion interruption and just before each infusion resumption. • During Cycle 1, under the *"ramp-up"* dosing scheme, prior to start each administration visit WBC count should be ≤ 10 x 10^9/L. In case the *"ramp-up"* administration visit is split due to infusion-related toxicities, WBC count should be ≤ 10 x 10^9/L also prior to start the second part of the *"ramp-up"* administration visit. • During Cycle 1, patients must be treated and monitored as in-patients up to at least 24 hours after each study drug administration visit. [redacted] • As the consumption of fibrinogen is a marker of disseminated intravascular coagulation, the investigator shall carefully monitor the fibrinogen decrease rate and consider prompt treatment with fresh frozen plasma even in the presence of fibrinogen values within normal range. **END of TREATMENT** **Visit 31-34/Day 43/50/57/64, one week, two weeks, three weeks and four weeks after Visit 24, respectively** ▪ Blood sampling for PK [redacted] ▪ Blood sampling for immunogenicity assessment (ONLY at Visit 34) ▪ Recording of AEs and change in concomitant medications **NOTE:** During the End of Treatment, a time-frame of + 1 day is allowed at any visit, however the scheduled time of the following

visits should be maintained.

FOLLOW-UP PERIOD

Visit 35-38/Day 65/85/121/149, one, twenty-nine, fifty-seven and eighty-five days after Visit 34, respectively

- Physical examination, including vital signs
- PS evaluation
- Blood sampling for safety lab test including pregnancy test (if applicable)
- Bone marrow aspirate for morphologic assessment on Visit 35 and Visit 37 only in patients showing peripheral blood labs consistent with CR/CRi/ Partial Remission (PR)
- Recording of AEs and change in concomitant medications

  NOTES:
  - To serve the best interest of the patients, for those achieving at least a partial remission, the Sponsor commits to consider providing MEN1112 to allow the prosecution of the infusions at the frequency recommended by the iDSMB on an individual basis and after discussion with the treating Investigator and the Medical Monitor. In this case, premedication and safety assessments will resemble those already described for study drug administration visits, unless differently advised by the iDSMB.
  - During Follow-up Period, a time-frame of + 2 days each is allowed at any visit, however the scheduled time of the following visits should be maintained.

END OF STUDY

End of Study Visit (180 days after Visit 1/Day 1)

- Physical examination and vital signs
- PS evaluation
- Blood sampling for safety lab test including pregnancy

	test (if applicable) ▪ [redacted] ▪ Bone marrow aspirate for morphologic assessment, [redacted] ▪ Recording of AEs and change in concomitant medications **NOTES:** • At the End of Study Visit, a time-frame of + 5 days is allowed. • All patients shall undergo the End of Study Visit at the scheduled date or at the time of study withdrawal. Unscheduled assessments showing disease progression and leading to patient's withdrawal can replace the End of Study Visit provided that all assessment/procedures scheduled for this visit are completed. • In case the patient is discontinued from the study within the treatment period, the End of Study Visit bone marrow aspirate is highly recommended to be performed. **Blood safety lab tests** will be performed at the local laboratory and will include: albumin, alkaline phosphatase, Alanine Aminotransferase (ALT), AST, Blood Urea Nitrogen (BUN)/Urea, serum creatinine, uric acid, sodium, chloride, potassium, phosphorus, calcium, total bilirubin, direct bilirubin, Gamma-Glutamyl Transpeptidase (GGT), glucose, Lactate Dehydrogenase (LDH), total proteins, prothrombin time and/or prothrombin activity, International Normalized Ratio (INR), partial thromboplastin time, fibrinogen, D-dimer, amylase, platelets, Red Blood Cells (RBC), Mean Corpuscular Volume (MCV), haemoglobin, haematocrit, WBC with differential (absolute and %) and Beta Human Chorionic Gonadotropine (ß-HCG) (if applicable). **Urinalysis** will be performed at the local laboratory and will include: pH, density, proteins, glucose, ketones, nitrite, RBC, WBC, epithelial cells, casts, bacteria, yeast and crystals.

	PK [redacted] will be performed centrally (see § 10.1.2 for details) and will include pharmacokinetic analysis [redacted] **GENERAL NOTES:** • For each safety lab test, blood sampling for PK [redacted] (except for those to be collected at the end of infusion) and for vital signs, a window of +/- 5% of the required time interval is allowed. • The total dose calculated for the first study drug administration can be applied also for the following ones providing that actual patient's weight is within ±10% of the weight measured prior to the first study drug administration; otherwise, the total dose to be given shall be calculated based on the weight measured at the corresponding visit. • Any effort aimed at preserving patient's safety and/or further clarifying an adverse event is recommended, including unscheduled assessments (e.g. additional safety lab sampling, additional safety lab parameters). The anonymized documentation of the above unscheduled assessment shall be then provided to the Sponsor. • It is strongly recommended not to start the treatment on the day prior to -or on- weekends/holidays, unless the treatment is deemed not deferrable by the Investigator in view of the specific patient's clinical situation. In such case, the site shall anyway guarantee the actual availability of site personnel as well as the actual feasibility of ALL study procedures as required by the protocol.
Study Endpoints	**Primary Endpoints** • Identification of **DLT** defined as an adverse event occurring during the first treatment cycle, judged to be related to MEN1112 and meeting any of the following criteria: • Grade 3 non-haematological toxicity lasting more

than 7 days

- Grade ≥ 4 non-haematological toxicity.

Note: Common complications of AML (in particular infections, bleedings, fatigue) will not contribute to DLT assessment.

- Identification of MTD defined as one dose level below the Maximum Administered Dose (i.e. one dose level below the one at which ≥ 2 DLTs out of 6 treated patients occur).

Secondary Endpoints

- Complete remission (CR) rate at any time point, where CR is defined as: bone marrow blasts <5%, absence of extramedullary disease, absolute neutrophil count >1 x 10^9/L and platelet count > 100 x 10^9/L.
- Composite complete remission (CRc) rate at any time point, defined as the proportion of patients having either CR or CRi (where CRi is defined as: all criteria for CR except residual thrombocytopenia [platelets <100 x 10^9/L] and/or neutropenia [absolute neutrophil count <1 x 10^9/L]).
- Best response rate, defined as the best observed response at any time point between CR, CRi and partial remission ([PR]: all haematological criteria for CR with bone marrow blasts 5-25% and decrease of pre-treatment bone marrow blast percentage by at least 50%).
- Duration of CRc: number of days between the date of CR/CRi achievement and the date of the last assessment confirming CR/CRi.
- Overall Survival (OS), defined as the number of days between the first study drug administration and death from any cause.
- Correlation of baseline characteristics with clinical activity of MEN1112.

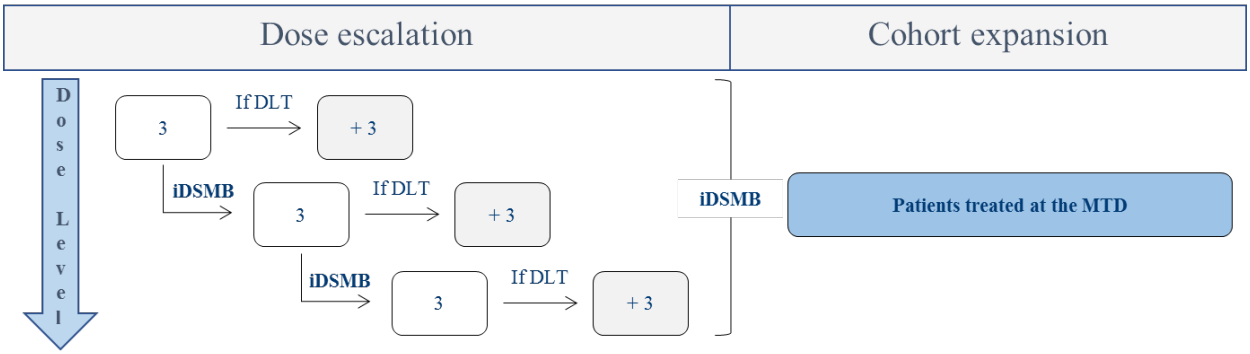
[redacted]

	[redacted]
Immunogenicity Endpoint	Incidence of anti-MEN1112 auto-antibodies.
Pharmacokinetic endpoints	PK parameters will be calculated, as data permit, following each of the three doses of the first *"ramp-up"* administration visit during Cycle 1 and following the third *"one-shot"* administration visit during Cycle 2. The following PK variables will be assessed following the 1st and 2nd dose of the first *"ramp-up"* administration visit during Cycle 1: C_{max}, t_{max}, C_{trough}, C_{avg}, $AUC_{(0-t)}$ The following PK variables will be assessed following the 3rd dose of the first *"ramp-up"* administration visit during Cycle 1: C_{max}, t_{max}, C_{trough}, C_{avg}, C_{last}, t_{last}, $AUC_{(0-t)}$, $AUC_{(0-\infty)}$, $\%AUC_{ex}$, k_e, $t_{1/2}$, CL, V_{ss}, Vd, $AUMC_{(0-\infty)}$, MRT. Total AUC following the first *"ramp-up"* administration visit during Cycle 1 will be calculated as the sum of $AUC_{(0-t)}$ related to each dose. The following pharmacokinetic variables will be assessed following the 3rd *"one-shot"* administration visit during Cycle 2: C_{max}, t_{max}, C_{trough}, C_{avg}, C_{last}, t_{last}, $AUC_{(0-t)}$, $AUC_{(0-\infty)}$, $\%AUC_{ex}$, k_e, $t_{1/2}$, CL, V_{ss}, Vd, $AUMC_{(0-\infty)}$, MRT, accumulation ratio (Ro).
Safety endpoints	▪ Incidence, severity, seriousness and treatment related causality of Treatment Emergent Signs and Symptoms (TESSs). ▪ Frequency of clinically significant abnormalities in physical examination, safety laboratory tests, vital signs and 12-Lead ECG.
Sample size	Due to the nature of the study, no formal sample size calculation is applicable. [redacted] Starting from protocol version 6.1/6.2, up to approximately 6 DLT evaluable patients per dose level will be treated with MEN1112 during the dose escalation phase, while up to approximately 30 patients will be treated in the cohort expansion phase. Considering

	that the patients no-DLT evaluable during the dose escalation phase will be replaced, and assuming a drop-out rate of 30%, up to approximately 60 patients will be treated with MEN1112. This number might be higher in case additional intermediate dose levels will be investigated.
Analysis Populations	▪ **Safety population:** all patients receiving study drug. ▪ **DLT population:** [redacted] Starting from protocol version 6.1/6.2 and following amendments: - All patients receiving at least 80% of the scheduled study drug administration during the first treatment cycle and with a safety follow-up of at least 6 days after the last administered dose or having experienced a DLT. ▪ **Efficacy population:** all patients completing the first treatment cycle and having a post-cycle peripheral blood lab test and bone marrow aspirate. ▪ **PP population:** all patients of the efficacy population excluding patients who experience major protocol violation(s). ▪ **PK population:** all patients receiving the study treatment and with reliable drug assay data relevant for the PK parameter of interest.

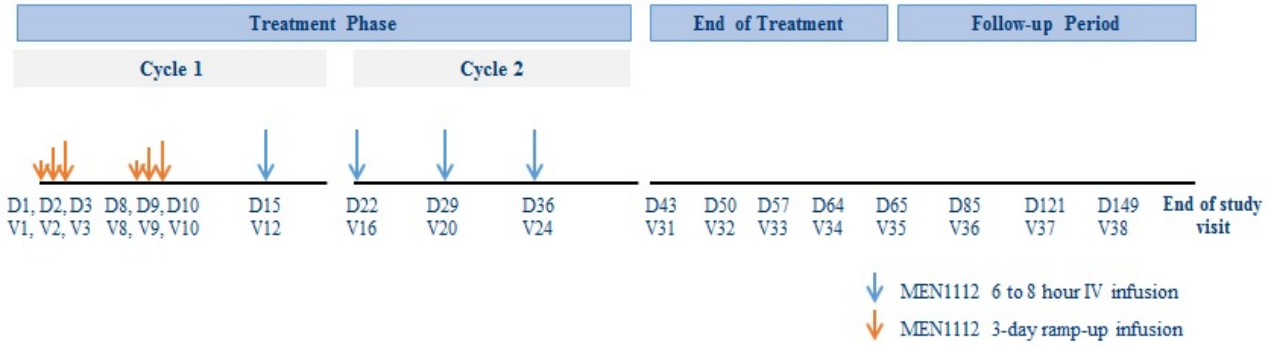
Statistical analysis	All study variables (with the exception of PK variables) will be presented by dose-cohort and overall, by using the appropriate descriptive statistics according to the variable nature, unless otherwise specified: ▪ Continuous variables: number of non-missing observations, arithmetic mean, standard deviation (SD), minimum, median, 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 and event rate every 28 days. The behaviour over time of study variables will be summarised by treatment cohort and overall as follows: ▪ Continuous variables: descriptive statistics for each time point and for the absolute/percentage differences to baseline. ▪ Discrete variables: descriptive statistics for each time point and shift tables to baseline. *Pharmacokinetic Analysis* The PK analysis will be run on the PK population. All PK variables (i.e. serum concentrations and parameters) will be summarized by cohort using the following descriptive statistics: • Number of non-missing observations (N) • Arithmetic mean and its 90% CI, SD, coefficient of variation (CV%) and standard error (SE) • Geometric mean (GM) and its 90% CI and GM CV% • Minimum, median, maximum The concentration of MEN1112 will be summarized for each scheduled sampling time point using descriptive statistics. Individual serum concentration data versus time will be presented in a data listing and visualized as individual concentration-time plots.

2.1 SCHEMATIC STUDY DESIGN



Study treatment outline

Starting from protocol version 6.1/6.2, MEN1112 will be administered for two 21-day cycles; the first two infusions of Cycle 1 will be given using a "3-day ramp-up" schedule of administration, i.e. the complete MEN1112 dose will be split in three days. Starting from the third infusion of Cycle 1 onwards, MEN1112 will be administered as "one-shot" infusion:



DX= Day of treatment administration or follow-up
VY= Visit on Day X (example V8 on Day 8 of treatment administration)

2.2 STUDY FLOW-CHART

Prior to any study procedures, written informed consent shall be obtained by the patient.

PROCEDURE	STUDY VISITS/DAYS																		
	Screening Period Day -7 to Day 0	TREATMENT PHASE - CYCLE 1*								TREATMENT PHASE - CYCLE 2*								END OF TREATMENT **	FOLLOW-UP PERIOD***	End of Study****
		Visit 1 Day 1	Visit 2-3 Day 2-3	Visit 4 Day 4	Visit5-6 Day 5-6	Visit 8-10 Day 8-10	Visit 11 Day 11	Visit 12 Day 15	Visit 13-15 Day 16-18	Visit 16 Day 22	Visit 17-19 Day 23-25	Visit 20 Day 29	Visit 21-23 Day 30-32	Visit 24 Day 36	Visit 25-27 Day 37-39	Visit 28-29 Day 40-41	Visit 30 Day 42	Visit 31-34 Day 43/50/57/64	Visit 35-38 Day 65/85/121/149	EoS Visit
Incl./Excl. criteria	xa	xa																		
Demographics	X																			
Medical history and AML history	X																			
Physical examination	X	X	X	X		X	X	X	X	X	X	X	X	X	X		X		X	X
PS evaluation b	X	X	X	X		X	X	X	X	X	X	X	X	X	X		X		X	X
Vital signs	X	xc	xc	X		xc	X	xc	X	xd	X	xd	X	xd	X		X		X	X
Weight measurement	X	X				xe		X		X		X		X						
12-Lead ECG	X	x f	x f																	
Safety Lab Tests g	X	xh	xi	X		xh· i	X	xh	X	X	X	X	X	X	X		X		X	X
Blood sampling	x j· k· l· n· m			xn						xn							xn	xk		xn
Bone marrow aspirate	xo			xo						xo							xo		xp	xo
Pregnancy Test q	X						X								X				X	X
Urinalysis	X	xr	xr																	

PROCEDURE	STUDY VISITS/DAYS																		
	Screening Period Day -7 to Day 0	TREATMENT PHASE - CYCLE 1*								TREATMENT PHASE - CYCLE 2*								END OF TREATMENT **	FOLLOW-UP PERIOD***	End of Study****
		Visit 1 Day 1	Visit 2-3 Day 2-3	Visit 4 Day 4	Visit5-6 Day 5-6	Visit 8-10 Day 8-10	Visit 11 Day 11	Visit 12 Day 15	Visit 13-15 Day 16-18	Visit 16 Day 22	Visit 17-19 Day 23-25	Visit 20 Day 29	Visit 21-23 Day 30-32	Visit 24 Day 36	Visit 25-27 Day 37-39	Visit 28-29 Day 40-41	Visit 30 Day 42	Visit 31-34 Day 43/50/57/64	Visit 35-38 Day 65/85/121/149	EoS Visit
Blood sampling for P [redacted] testsS		X	X	X	X	X		X		X		X		X	X	X	X	X		
TLS Risk Assessment		X																		
TLS Prophylaxis		X	X			X		X												
Premedication		X	X			X		X		X		X		X						
Study drug administration		X	X			X		X		X		X		X						
Adverse eventst	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

a = Inclusion criteria will be evaluated during the Screening Period, with the exception of inclusion criteria 3 and 4, which will be evaluated at Visit 1/Day1; inclusion criteria 5 and 6 will be re-evaluated prior to the first study drug administration (Visit 1/Day1).
Exclusion criteria will be evaluated during the Screening Period, with the exception of exclusion criteria 6, 7, 8 and 9, which will be evaluated at Visit 1/Day 1; exclusion criteria 4 and 5 will be re-evaluated prior to the first study drug administration (Visit 1/Day 1).

b = Performance status evaluation according to ECOG scale.

c = Vital signs to be collected prior to study drug administration and every 15 minutes during the first hour of study drug administration and then at the same time points of blood sampling for safety lab tests.

d = Vital signs to be collected prior to study drug administration and every 15 minutes during the first hour of study drug administration and 15 minutes after the end of infusion.

e = Weight measurement ONLY prior to the first *"ramp-up"* dose.

f = 12-Lead-ECG should be performed prior to study drug administration and at the end of infusion.

g = Safety lab tests will be performed locally, to guarantee the management of the patient (the specific time points are listed in *Appendix III: Timings of safety blood sampling*).

h = Check of WBC count ≤10 X 10^9 L prior to the first *"ramp-up"* study drug administration (Visit 1/Day 1, Visit 8/Day 8) and at Visit 12/Day 15; hydroxyurea is allowed to lower WBC count.

i = In case the *"ramp-up"* administration visit is split due to infusion-related toxicities, WBC count should be ≤ 10 x 10^9/L also prior to start the second part of the *"ramp-up"* administration visit.

j [redacted].

k = Blood sampling for immunogenicity assessment to be collected during the Screening Period (Day -7 to Day 0) and at Visit 34.

l = [redacted]

m = Blood sampling for anti-HIV antibodies, anti-HBcAg antibodies, HBV-DNA, HCV-RNA to be tested according to local standard procedures ONLY in case results of laboratory tests for have not been performed within 3 months prior to Screening Period.

n = Blood sampling for CD157 receptor occupancy assessment.

o = Bone marrow aspirate for morphologic assessment, [redacted]. In case the patient is discontinued from the study within the treatment period, the End of Study Visit bone marrow aspirate is highly recommended to be performed.

p = Bone marrow aspirate for morphologic assessment to be performed ONLY at Visit 35, and Visit 37 in case peripheral blood labs are consistent with CR/CRi/PR.

q = Pregnancy test (if applicable) will be performed locally during the Screening Period, Visit 11, Visit 27, Visit 35, Visit 36, Visit 37, Visit 38 and End of Study Visit; female patients of childbearing potential are required to undergo a monthly pregnancy test until 6 months from last study drug administration.

r = Urinalysis will be performed at Visit 1/Day 1 pre-infusion and at the end of Visit 3/Day 3 infusion.

s = Timings of each blood sampling for PK & exploratory tests are listed in *Appendix II: Timings of Blood sampling for PK & exploratory tests*. If any interruption occurs during Cycle 1 and the 3rd infusion of Cycle 2, blood sampling for PK & exploratory tests will also be taken at the time of each infusion interruption and just before each infusion resumption.

t = Recording and active follow-up of AEs will be performed from Informed Consent signature to the End of Study Visit or 70 days after last study drug administration whichever occurs last.

* = One of the following adjustments is allowed:

- +1 day for any *"ramp-up"* administration visit in case of WBC count >10x10^9/L on the first day of such visit, in order to lower the WBC count using hydroxyurea. This is applicable also to the *"one-shot"* infusion visit of Cycle 1 (Visit 12/Day 15).
- + 1 day for each study drug administration visit (i.e. first *"ramp-up"* and *"one-shot"* administration visit).

In case of study visit re-schedule due to infusion related toxicities, WBC count recovery, or any other reasons, the interval of 5 days (Cycle 1) or 7 days (Cycle 2) between the end of any study drug administration visit and the start of the following one should be guaranteed.

** = During the End of Treatment, a time-frame of + 1 day is allowed at any visit, however the scheduled time of the following visits should be maintained.

*** = During Follow-up Period, a time-frame of + 2 days each is allowed at any visit, however the scheduled time of the following visits should be maintained.

- To serve the best interest of the patients, for those achieving at least a partial remission, the Sponsor commits to consider providing MEN1112 to allow the prosecution of the infusions at the frequency recommended by the iDSMB on an individual basis and after discussion with the treating Investigator and the Medical Monitor. In this case, premedication and safety assessments will resemble those already described for study drug administration visits, unless differently advised by the iDSMB.

**** = At the End of Study Visit, a time-frame of + 5 days is allowed.

3. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

[redacted]

Laboratories involved in the study are provided in section 8.5.1.1. Further details will be addressed in the specific Laboratory Manual.

4. TABLE OF CONTENTS

4.1 GLOSSARY

ADA	Anti-Drug Antibodies
ADCC	Antibody-Dependent Cell-mediated Cytotoxicity
ADL	Activities of Daily Living
ADP	Adenosine DiPhosphate
ADR	Adverse Drug Reaction
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AML	Acute Myeloid Leukaemia
AST	Aspartate Aminotransferase
ATL	Adult T leukaemia/lymphoma
AUC	Area Under Curve
%AUCex	Percentage of $AUC_{(0-\infty)}$ obtained by extrapolation
$AUC_{(0-t)}$	AUC from time 0 until the last quantifiable concentration
$AUC_{(0-\infty)}$	AUC from time 0 until infinity
$AUC_{(0-7days)}$	AUC from time 0 until 7th day
$AUMC_{(0-\infty)}$	Area under the first moment curve from zero to infinity
BLLOQ	Below the Lower Limit of Quantification
BP	Blood Pressure
BR	Breathing Rate
BUN	Blood Urea Nitrogen
CA	Competent Authority
CDC	Complement Dependent Cytotoxicity
CHO	Chinese Hamster Ovary
CI	Confidence Interval
CL	Systemic Clearance
C_{last}	Last quantifiable serum concentration values
CLL	Chronic Lymphocytic Leukaemia
C_{max}	Maximum serum Concentration
CR	Complete Remission
CRc	Composite Complete Remission
CRC	Cohort Review Committee
CRi	Complete Remission with incomplete blood count recovery
CRF	Case Report Form
CRO	Contract Research Organization
CRS	Cytokine Release Syndrome
C_{trough}	Pre-dose serum concentration
CV	Coefficient of variation
DA	Daunorubicin plus cytosine Arabinoside
DLT	Dose Limiting Toxicity
DNA	Deoxyribonucleic acid
DRM	Data Review Meeting
DSM	Drug Safety Manager
DSUR	Development Safety Update Report
EC	Ethics Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
e-CRF	electronic Case Report Form
EDC	Electronic Data Capture
ELN	European Leukemia Net prognostic system
EU	European Union

FAB	French American British
[redacted]	[redacted]
FLT3	Fms-Like Tyrosine kinase 3
GCP	Good Clinical Practice
GGT	Gamma-Glutamyl Transpeptidase
GM	Geometric Mean
GMP	Good Manufacturing Practice
GPI	GlycosylPhosphatIdylinositol
h	hour
HBcAg	Hepatitis B core antigen
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HED	Human Equivalent Dose
HEENT	Head, Eyes, Ears, Nose and Throat
HIV	Human Immunodeficiency Virus
HR	Heart Rate
HSCT	Haematopoietic Stem Cell Transplantation
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ID	Identity
iDSMB	Independent Data Safety Monitoring Board
IEC	Independent Ethics Committee
IFN	InterFeroN
IL	Interleukin
IMP	Investigational Medicinal Product
INR	International Normalized Ratio
IRB	Institutional Review Board
ITD	Internal Tandem Duplication
IV	Intravenous
IWG	International Working Group
k_e	Apparent terminal elimination rate constant
LDH	Lactate Dehydrogenase
LLOQ	Lower Limit of Quantification
MAD	Maximum Administered Dose
MBH	Menarini Biotech
MCV	Mean Corpuscular Volume
MLL	Mixed Lineage Leukemia
MoAB	Monoclonal Antibody
MRT	Mean Residence Time
MTD	Maximum Tolerating Dose
NHL	Non Hodgkin Lymphoma
NHP	Non-Human Primate
NK	Natural Killer
NOAEL	No Observed Adverse Effect Level
NPM1	Nucleophosmin
OS	Overall Survival
PD	Pharmacodynamics
pH	Potential of Hydrogen
PD	Pharmacodynamics
PK	Pharmacokinetics
PR	Partial Remission
PS	Performance Status

QA	Quality Assurance
RBC	Red Blood Cells
RNA	Ribonucleic Acid
Ro	Accumulation Ratio
RR	Respiratory Rate
SADR	Serious Adverse Drug Reaction
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SDST	Study Drug Safety Team
SE	Standard Error
SIV	Site Initiation Visit
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
ß-HCG	Human Chorionic Gonadotropine
SST	Serum-Separating Tube
SUSAR	Suspected Unexpected Serious Adverse Reaction
T	Body Temperature
$t_{1/2}$	Terminal serum half-life
t_{last}	Time to C_{last}
TESS	Treatment Emergent Sign and Symptoms
TK	ToxicoKinetic
TLS	Tumor Lysis Syndrome
TMF	Trial Master File
t_{max}	Time to C_{max}
TNF	Tumour Necrosis Factor
ULN	Upper Limit of Normal
Vd	Volume of distribution
Vss	Volume of distribution at steady state
WBC	White Blood Cells
WHO	World Health Organization

5. ETHICAL AND LEGAL ASPECTS

5.1 GENERAL ASPECTS

This study will be carried out in compliance with the study protocol, the recommendations on biomedical research on human subjects of the Declaration of Helsinki, ICH-GCP Guidelines, EU regulations in force (EU Directive 2001/20 of April 4, 2001, as amended), and national requirements of the participating countries. Furthermore, the study will be conducted in agreement with Sponsor or CRO's Standard Operating Procedures (SOP) requirements as agreed. The agreed SOPs are listed in the project management plan and monitoring plan of the study. All clinical work conducted under this protocol is subject to GCP rules. This includes audit/inspections by the Sponsor and/or its delegate (e.g. CRO), and/or by national/international Health Authority representatives at any time. All Investigators must agree to the audit/inspection of the study site, facilities, and of study-related records by the Health Authority representatives and/or by the Sponsor, and/or its delegates, which must be performed in accordance with national laws concerning personal data protection.

5.2 INDEPENDENT ETHICS COMMITTEE AND LEGAL REQUIREMENTS

Before starting the study in a study site, study protocol and relevant documentation must be submitted to and approved by the Institutional Review Board/Ethics Committees (IRB/ECs) and the Competent Authorities (CAs) of the participating countries.

In addition, all local national legal requirements for the conduct of a clinical study have to be followed prior to the start of the study.

The CAs and IRB/ECs of the participating countries will be informed about any changes in the study protocol, the end of the study, or the premature study termination as appropriate and within the requested time period.

5.3 PATIENT INFORMATION AND DECLARATION OF CONSENT

Before any study-related procedures may be performed, informed consent must be obtained from the patient by means of a signed declaration.

The Informed Consent Form (ICF) must be approved in the corresponding local language and in accordance with local laws and regulations by the IRB/ECs prior to be submitted to the patient.

In the patient information leaflet, patients will be given information and fully comprehensive explanation in easily understandable terms of the study procedures, regarding the benefits, restrictions, discomforts, and risks in taking part in the study, the properties of the Investigational Medicinal Product (IMP), the method of assignment to treatments, and any medically accepted and readily available treatment other than the IMP.

Patients will also be informed about the measures taken to ensure their confidentiality according to the pertinent legislation.

After being duly informed and interviewed by the Investigator, the patient freely has to date and sign an ICF before being enrolled into the study and before undergoing any study procedure. The Investigator must store the original of the signed ICF in the Investigator's File, and the patient will be provided with a copy of it.

The process of obtaining informed consent shall be documented in the patient source documents.

If a protocol amendment would affect the terms of the ICF, it will be revised to reflect the protocol change and submitted to IRB/EC for approval. The Investigator will ensure that this new consent form is signed by all patients subsequently entered in the study and those currently in the study, before the changes take effect on their participation in the trial.

5.4 PATIENT INSURANCE

For patients participating in the study, Menarini Ricerche S.p.A. has stipulated an insurance policy in accordance with local regulatory requirements.

Details on the insurance in accordance with national requirements will be made available to patients in the ICF and/or provided as a separate document.

A copy of the insurance certificate will be provided to each Investigator and will be filed in the Investigator's File at the sites and in the study's Trial Master File (TMF).

5.5 DOCUMENTATION OF STUDY-RELATED DATA AND RECORD RETENTION

It is the responsibility of the Investigator to document all study related data for each patient in a case report form (CRF). For this study, an e-CRF will be used. The Investigator has to guarantee the accuracy of the documented data and has to comment any missing or spurious data.

In addition to the e-CRF the Investigator will maintain adequate records that fully document the participation of the patient in the clinical study including the study assessments (patient source data documentation). Details on the source data documentation are provided in section 10.3.

As required by EU Regulation 536/2014, the Investigator will keep essential documents at least 25 years after the end of the clinical trial. Patients' data (e.g.: e-CRFs, lab data) have to be archived for the same period of time. These documents should be retained for a longer period however, if required by the applicable regulatory requirements or by an agreement with the Sponsor. No study documents should be destroyed without prior written agreement between Sponsor and Investigator. Patients' records have to be archived according to national law requirements. Should the Investigator wish moving the study record to another location, he/she must notify the Sponsor in writing.

5.6 CONFIDENTIALITY

By signing the study protocol, the Investigator affirms that any information provided by the Sponsor will be maintained in confidence, and that such information will be divulged to IRB/ECs or CAs only under an appropriate understanding of confidentiality with such a committee or institution.

In order to maintain the patient's confidentiality, all data collected by the Investigator will be recorded pseudonymously in the e-CRF. Patient's data will be identified by a unique patient number.

The Investigator agrees that within national regulatory restrictions and ethical considerations, representatives of the Sponsor, any regulatory agency, and IRB/ECs may consult study source documents in order to verify data in the e-CRF. Patient medical records pertinent to the study will be reviewed by the study monitor to assure adequate source documentation, accuracy, and completeness of e-CRFs. The review will be conducted in accordance with relevant SOPs and with strict adherence to professional standards of confidentiality, GCP, and the relevant data protection legislation.

5.7 PROTOCOL MODIFICATIONS

The protocol must be read thoroughly by everybody whom the information therein concerns and the instructions must be exactly followed.

Changes in the study protocol will require a protocol amendment. Such amendments will be agreed upon and approved in writing by all signatories of the protocol. If amendments are substantial, i.e. are likely to have an impact on the safety of the patients, or to change the interpretation of the scientific documents in support of the conduct of the study, or if they are otherwise significant, the IRB/ECs and the CAs in the participating countries have to approve these amendments before implementation.

Changes which have no significant impact on medical or scientific validity of the study will be agreed upon and approved in writing by all signatories of the protocol and the IRB/ECs will be notified of this protocol amendment.

Any substantial amendments of the protocol will be integrated in an updated study protocol. The Principal Investigator must ensure full compliance with the updated study protocol.

5.8 STUDY COMMENCEMENT

The study can commence in an individual study site only after all prerequisites are fulfilled according to GCP/ICH guidelines, any local regulatory requirements, and the Sponsor's/CRO's SOPs.

5.9 PATIENT'S SAFETY

If any event(s) related to the conduct of the study or the development of the IMP affects the safety of the study participants, the Sponsor and the Investigator will take appropriate urgent safety measures to protect the patients against any immediate hazard. The CAs and IRB/ECs will be informed forthwith about these new events and the measures taken.

5.10 DATA PROPERTY/PUBLICATION POLICY

All data generated in the study (e.g. e-CRFs, the structured data files in the clinical database system, the results of the statistical evaluation, and medical interpretation as well as the final clinical study report) are the property of Menarini Ricerche S.p.A.

It is intended that study design and main results will be published on www.clinicaltrials.gov. In addition, the results of the study may be published as scientific literature. Results may also be used in submissions to CAs and IRB/ECs. The conditions mentioned below are intended only to protect confidential commercial information (patents, etc.), and not to restrict publication.

All information concerning MEN1112 (such as patent applications, formulae, manufacturing processes, basic scientific data, or formulation information supplied to the Investigator by Menarini Ricerche S.p.A. and not previously published) are considered confidential by Menarini Ricerche S.p.A. and will remain the sole property of Menarini Ricerche S.p.A. The Investigator agrees not to use it for other purposes without written consent from Menarini Ricerche S.p.A.

Menarini Ricerche S.p.A. will use the information obtained in this clinical study in connection with the development of MEN1112 and therefore may disclose it to other Investigators or concerned CAs and IRB/ECs in the European Union or abroad. In order to allow for the use of information derived from this clinical study, the Investigator has an obligation to provide Menarini Ricerche S.p.A. with complete test results and all data recorded during this study.

Prior to submitting the results of this study for publication or presentation, the Investigator will allow Menarini Ricerche S.p.A. at least 30-day time to review and comment upon the publication manuscript. Menarini Ricerche S.p.A. will provide any manuscript of the results of this study at least 30 days before publishing to the authors for a complete review. In accordance with generally recognised principles of scientific collaboration, co-authorship with any Menarini Ricerche S.p.A. personnel will be discussed and mutually agreed upon before submission of a manuscript to a publisher.

It is agreed, that the results of the study will not be submitted for presentation, abstract, poster exhibition, or publication by the Investigator until Menarini Ricerche S.p.A. has reviewed/commented and agreed to any publication.

5.11 DATA PROTECTION

5.11.1 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 applicable law on

personal data protection 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.
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 fulfilment of patients' privacy rights.

5.11.2 Acknowledgment

The Site, the Principal investigator, the Centralised Laboratories, the CRO as well as their appointed staff and service providers acknowledge that:

(a) the performance of the study will imply processing of sensitive personal data;
(b) personal data processing is regulated by the applicable 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. In particular, it is hereby acknowledged that being the Sponsor a company incorporated under Italian law, it has to mandatorily comply with Italian legal provisions on data protection: therefore the Site, the Principal investigator, the Centralised Laboratories, the CRO shall cooperate with the Sponsor to allow the fulfilment of such obligations;
(c) 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 Principal investigator, the Centralised Laboratories, the CRO.

5.11.3 Data Controllers and Data Processors

The Sponsor, the Site, the Principal 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 Principal investigator will act as data processors respectively of the Sponsor and of Site. Before the beginning of the study, the Site will instruct in writing Principal Investigator as its data processor. However, if specific local laws or regulations mandate a different definition of the privacy roles, the Sponsor, the Site, the Principal investigator and the CRO will implement the relevant legal instruments (e.g. if pursuant to the local laws the Site is a data processor of the Sponsor, a Data Processing Agreement will be finalised; if pursuant to the local laws Sponsor and Site are join controllers, a Joint Controllership Agreement will be finalised).

5.11.4 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, 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 Principal investigator, the Sponsor, the CRO and the Centralised Laboratories 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) DATA SAFETY. The Site and/or the Principal Investigator shall adopt all the necessary measures to prevent or minimise the risks of theft, fire, flooding, partial or total loss, accidental disclosure or illegal/unauthorised access to patient's data or Sponsor's proprietary confidential information. To this extent, before the beginning of the study, the Site and/or the Principal Investigator shall ensure that the actual measures they have implemented are fit-for-purpose and law-compliant, and in particular:

- In order to minimise the risk of unauthorized access and theft, the hardware on which patients' personal data are stored shall be placed in a restricted-access area, accessible only to those individuals who need to retrieve the patients' personal data included in the database for professional purposes; the same safeguards shall be put in place for non-electronic databases;
- Any electronic database containing the patients' personal data shall be password-protected by means of a strong password. Systems shall be set so that passwords must be updated at least every three months and feature at least 8 characters, with upper-case and lower-case recognition, containing at least three "special" characters, such as upper case letters [A-Z], lower case letters [a-z], numbers [0-9], symbols [!, #, $, etc.] or other special characters [Á, ë, ö, etc.]. Passwords shall not include elements which may easily be associated with the assignee or information regarding him/her, such as name and year of birth (e.g. "johnbrown80") or easily predictable strings of characters (e.g. "qwerty", "12345", "admin", "user", etc.);
- Adequate cryptographic protection measures shall be put in place for data "at rest" and "in transit" (these include, for example, file system or database cryptography, or any other equivalent IT measure which renders data unintelligible to those who are not authorised to access them);
- High level security measures shall be implemented also on the files or databases which contain the "key" to match the patients' personal data (i.e. name, surname, etc.) with their respective "Patient IDs" (as defined at point (iv) below);

- Backup processes and other measures that ensure rapid restoration of business critical systems shall be implemented;
- Updated Antivirus and firewall programs shall be installed on the IT devices.

The Site shall regularly test and update the measures listed above.

The Site shall, upon request from the Sponsor and/or the CRO, provide detailed written information about the measures listed above.

The CRO shall ensure that the selected sites for the study have implemented the above listed measures.

(ii) TRANSMISSION OF DATA. All the parties that transfer data through internet and/or to the centralised database(s) used to process study's data or to generate statistical analyses shall implement secure protocols based on cryptographic standards which make data unintelligible to unauthorized individuals.

(iii) SECURITY OF THE CENTRALISED DATA BASE. The centralised database held by the Sponsor shall have the following safeguards in place:

- Appropriate authentication methods, which differentiate between different users according to their respective roles so as to ensure that access to a specific set of subjects' data is permitted exclusively to those for whom access to such data is essential in the context of their work for the study;
- Appropriate measures to ensure that the authentication credentials are periodically updated (i.e. password change);

(iv) PSEUDONYMIZATION. All personal data that may allow identification of the patients involved in the study shall be adequately dissociated from the other data pertaining to the study ("pseudo-anonymization" process). The Principal Investigator shall adequately dissociate the identification data of patients from the data pertaining to the study by linking results to an alphanumerical code ["Patient ID"], whose format shall not make it possible to identify the patient directly or indirectly, so as to ensure that only anonymous data are transmitted to the Sponsor, the Centralised Laboratories and /or the CRO. Site/Principal Investigator shall securely store a separate list (e.g.: identification log) with the identification code, together with all signed informed consents, in accordance with the security measures as defined above.

As outlined below, samples shall only be stored for as long as strictly necessary for the study's performance for a maximum of 10 years from the date of the Last Subject Last Visit before destruction. Biological samples and any other examination (e.g. X-ray, ECG) shall bear Patient ID, and in no case will they bear other information that may lead to the direct or indirect identification of the patient, especially when, in accordance with this protocol, samples shall be forwarded and shared outside the clinical Site (e.g. in case of centralized reading or local laboratory analysis).

(v) TRAINING. The parties shall ensure that any personnel involved in the study have received proper training on data protection issues.

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 Ethics Committees 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 Principal Investigator, the CRO and the Centralised Laboratories undertake to adopt all the necessary activities to overcome such remarks to assure the full compliance with the data protection laws.

5.11.5 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 Principal 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 trial. However, medical records and the identification code list (i.e. the list that where the Patient ID is linked to the patients' identification data such as name and surname), including the relevant patients' personal data, shall be archived in accordance with the national laws of the country where the study is performed.

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.

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 (see § 3) as responsible person 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.

5.11.6 Data Breach

Data Breach is an incident regarding personal data security and 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 Site, Sponsor, CRO, Principal Investigator, etc.; data loss is when the data may still exist, but the Site, Sponsor, CRO, Principal Investigator etc. has lost control or access to it, or no longer has it in their 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 Site, Sponsor, CRO, Principal Investigator, etc.

Anomalous Event is an event that is not part of the standard operational scope of an infrastructure, network or service and which affects, or is likely to affect, personal data; this may include theft or loss of IT devices and other physical events (e.g. an unauthorised access to a locked storage room containing paper files with personal data), and/or electronic/IT anomalies (e.g. cyber-attacks, default or hacking of cloud services), which may, in any way, entail loss, unavailability, alteration, theft, copy or dissemination of personal data.

Whoever becomes aware in any way of an Anomalous Event and/or of a Data Breach 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 an Anomalous Event and/or of a Data Breach) inform the Study Manager (see § 3), the sponsor's Data Protection Officer, who may be contacted [redacted] the Site and the CRO (details of this latest are included in the separate Operational Contact List) and shall provide the following information:

(i) Anomalous Event / Data Breach Type (e.g. data loss, unauthorized access, loss of company device, etc.);

(ii) Person or source that first reported the Anomalous Event/ Data Breach;

(iii) Date and Time when the person who first reported the Anomalous Event / Data Breach became aware of it;

(iv) Anomalous Event / Data Breach Date and Time (actual or presumed);

(v) Place (specify if actual or alleged) where the Anomalous Event / Data Breach occurred;

(vi) Anomalous Event / Data Breach Description;

(vii) Indicate the source of the Anomalous Event / 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 Anomalous Event/Data Breach (if relevant);

(x) Number of data subjects 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 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.

5.11.7 Information Notice in Personal Data Protection and Pseudonymisation

Prior to patients' enrolment in the study, the Principal 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 Principal Investigator is responsible for archiving 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 (e.g. to perform the study and /or for pharmacovigilance purposes and/or to register new medicines, any future research), 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 § 5.11.11;
(vi) The pseudonymisation procedure and scope;
(vii) Who can access patients' data and under what circumstances. In the context of this study, only coded data will be forwarded to the Sponsor, to other companies belonging to the Sponsor's group, Sponsor's licensors-licensees or to third parties acting on behalf of the Sponsor, including the CRO. However, European Medical Regulatory Authorities, the European Medicines Agency, the Insurance Company and the Sponsor (and its delegates), may inspect the study files to ensure that the results of the study have been properly recorded, as well as for scientific research, pharmacovigilance, safety and insurance purposes: this may

require matching personal code with patient's data and identity. Moreover, patients' data can be disclosed in an aggregate or pseudonymised form in scientific publications;

(viii) The period of data retention/storage as defined in § 5.11.4 above, including the storage of the biological sample;

(ix) To which entities/countries outside the EU patients' data will be transmitted (The updated list of foreign countries is 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 [redacted];

(xiii) In case of genetic data processing, any possible finding, also with regard to unexpected findings that might be disclosed on account of the processing of the genetic data.

5.11.8 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.
- 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.
- The measures to keep patients' identification data separated from biological materials and genetic information are indicated in § 5.11.4 and 5.11.5.
- 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).

5.11.9 Transfer of patients' data outside the European Union

The study performance entails transferring patients' personal data (coded data) outside the EU. To this extent, the Sponsor, the Site, the Principal Investigator, the Centralised Laboratories, 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.

5.11.10 Exercise of patients' data privacy rights

Each study patient has the right to contact the Sponsor, Site, Principal Investigator, Centralised Laboratories and 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, namely: knowing whether or not any data referring to his/her is being processed in the context of the study; accessing his/her data; verifying the data's content, origin, exactness, location (including, where applicable, the non EU countries where the data might be); obtaining a copy of the data including their transmission to another entity indicated by the patient; asking that the data are supplemented, updated, amended; in the circumstances set forth by the law, asking that the processing of data is restricted, that data are anonymised or frozen; opposing 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 as inappropriate.

Each study patient is free to withdraw from the study at any time. In such case, each study patient may ask the Sponsor, the Site, the Principal Investigator, the Centralised Laboratories, 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.
Specific rights in relation to the processing of genetic data apply. Please refer to § 5.11.8.
If the Site, the Principal Investigator, the Centralised Laboratories, and/or the CRO receive a request for data privacy rights exercise, the concerned recipient shall immediately inform the Sponsor DPO by e-mail at [redacted]
The request shall be fulfilled within the term set forth by the applicable privacy laws (normally 30 days). The Sponsor, the Site, the Principal Investigator, the Centralised Laboratories, and the CRO shall implement adequate organisational measures to reply to patients within the above mentioned deadline.

5.11.11 Future research

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 drugs.
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.

6. BACKGROUND INFORMATION

6.1 ACUTE MYELOID LEUKAEMIA

Acute myeloid leukaemia (AML) is predominantly a disease of the elderly, with an age-adjusted incidence rate of 3 to 4/100 000 in Western countries (1-3) and the median age at diagnosis of approximately 70 years (3-5).

It is now recognized that AML is a highly heterogeneous disease or set of diseases in terms of morphology, cytochemistry, immunophenotype, cytogenetics, and molecular abnormalities (either mutations or gene overexpression) of the leukemic cell population. Since the morphology of the leukemic cells (blasts) in the bone marrow may not be sufficient to determine lymphoid or myeloid origin, cytochemistry and/or immunophenotyping is an essential part of the diagnosis. Chromosomal abnormalities occur in 50% to 60% (6-7) of patients and are highly prognostic for the outcome of first-line therapy and also after relapse, and are widely used to assess the treatment strategy in individual cases.

Recently, molecular characterization has added a further layer of prognostic insight within the cytogenetic strata, and in particular patients harboring some mutations (particularly those related to FLT3 IDH1 and IDH2) have molecularly targeted approach available.

AML is an aggressive disease that is rapidly fatal without specific therapy, and achievement of CR is a prerequisite for long-term survival. Curative treatment was not available until the late 1960s, when chemotherapy with Daunorubicin plus cytosine Arabinoside (DA) was introduced (8-9). The combination of an anthracycline, usually given over 3 days and cytarabine given over seven days (the so called 7+3 regimen) can induce CR in the majority of AML patients and in a proportion with favourable prognostic factors. A long-term survival is possible after appropriate post-remission therapy. Although numerous drugs have been tested either in monotherapy or in combination, no alternative induction regimens have proven to be more effective. Therefore, 7+3 remains the cornerstone of AML induction treatment, with the addition of Midostaurin in FLT3 mutated patients. Newly diagnosed patients who are unfit for standard induction chemotherapy are treated with non-intensive options, basically the hypomethylating agents (HMAs) Decitabine and Azacitidine or low-dose Cytarabine; recent data have shown that the addition of the BCL-2 inhibitor Venetoclax to the above agents or that of the hedgehog pathway inhibitor Glasdegib to low dose Cytarabine do improve the outcome of the single agent front line treatment (10-12). Venetoclax and Glasdegib, in combination with HMAs/LDAC or LDAC, respectively, have been approved by the US FDA for the front-line treatment of AML patients who are unfit for standard induction chemotherapy.

Since all patients will eventually relapse (usually within a matter of weeks) after responding to induction treatment alone, post-remission therapy is essential to achieve long term disease control. This can take the form of high dose consolidation chemotherapy (10-16) or in suitable patients'

allogeneic haematopoietic stem cell transplantation (allo-HSCT). Both of them can reduce the risk of relapse and improve long term disease control. In general, however, allo-HSCT offers the best possibility of increasing overall survival and can be curative in a minority of patients with the most favourable prognostic features (17-19).

Overall therefore, post remission therapy can prolong the period of time patients remain in remission following initial induction therapy, although long term survival is only achieved in 40% to 50% and 10% to 15% of younger and older patients, respectively (20). Furthermore, post-remission therapy is associated with a significant and debilitating burden of toxicity and also a treatment related mortality of 10-15 % within the first two months of therapy.

Whilst a minority experience long lasting disease control, the vast majority of patients in remission (approximately 80 per cent) will eventually relapse again and most of these will do so within six to twelve months of achieving a complete response. Furthermore, approximately 30 per cent of AML patients will fail to respond to induction therapy at all and, hence, demonstrate refractory disease from the outset.

Relapsed or refractory AML is an exceptionally intractable disease state and, if untreated, the overall survival is only about eight to ten weeks.

The treatment of AML at disease relapse or in refractory patients is highly unsatisfactory as demonstrated by the lack of any widely accepted standard of care approach. In general, salvage treatment consists of either high dose Cytarabine or combination regimens such as FLAG-IDA (Idarubicin, Fludarabine, Cytarabine and GCSF) or MEC (Mitoxantrone, Etoposide and Cytarabine), followed by allo-HSCT when possible for those patients achieving an initial remission. For specific subsets of AML patients (i.e. those harboring FLT3, IDH1 or IDH2 mutations), the US FDA has approved targeted treatments at disease relapse, yet the medical need in this indication remains largely unmet.

For those patients not receiving HSCT, responses to salvage therapy are dismal, with a median overall survival of about seven months at best. Even after HSCT, outcomes are significantly inferior to those of patients in first remission.

Hence, new effective approaches are urgently needed and inclusion in clinical investigational trials of novel experimental agents (such as the current study of the anti-CD157 antibody MEN1112) is still one of the best options for such patients.

Bst1/CD157, a GlycosylPhosphatIdylinosotol (GPI)-anchored transmembrane protein of 318 amino acids belonging to the Adenosine DiPhosphatase (ADP)-ribosyl cyclase family (21) previously described as bone marrow stromal antigen-1 (Bst-1) (22), is expressed on monocytes, granulocytes and macrophages matured in vitro (23) and it has been identified as a novel antigen expressed on AML blasts. Two separate studies demonstrated that the prevalence of the Bst1/CD157 expression on blast cells was almost 100% in peripheral and bone marrow blood samples obtained from AML

patients, either at the disease diagnosis or relapse (for the details of both studies, refer to the Investigator's Brochure).

Like CD33 (a cell surface target which has formed the basis of a number of antibody approaches to AML), Bst-1/CD157 is a cell surface antigen expressed on blasts and normal blood cells such as granulocytes and monocytes but, differently from CD33, it is not internalized. Hence, it represents a valuable antigen to be targeted by antibodies such as MEN1112, a humanized de-fucosylated monoclonal antibody (MoAb) which has shown activity against leukemic cells lines and *ex vivo* primary AML blasts.

In the context of haematological diseases, the therapeutic efficacy of MoAbs targeting surface antigens and acting through Antibody Dependent Cell-mediated Cytotoxicity (ADCC) has been proven in Non-Hodgkin's Lymphomas (NHLs) and Chronic Lymphocytic Leukaemia (CLL) with the approval of first generation antibodies such as rituximab and alemtuzumab. However, this approach has as yet been unsuccessful in AML. In part, this may be due to the fact that earlier strategies targeting CD33 may have been sub-optimal, due to a partial internalization and shedding of CD33, making it an inappropriate antigen for targeting by MoAbs acting through ADCC.

Furthermore, it is now widely recognized that the core fucose of Fc-linked oligosaccharides greatly affects the ADCC efficacy of therapeutic antibodies, with the removal of fucose markedly enhancing the ADCC through improved FcγRIIIa binding without altering antigen binding (24); ADCC enhancement technology is, therefore, expected to play a key role in the development of next-generation therapeutic antibodies with improved clinical efficacy. This may be particularly relevant in the context of AML, as the disease is characterized by an impairment of immune effector cells mainly involved in ADCC such as NK cells, monocytes and macrophages, thus making ADCC less effective (24-28). Therefore, the use of new generation of Fc engineered MoAbs such as MEN1112 could be expected to show significantly greater clinical efficacy than has been seen with antibodies of an earlier era. Indeed, Mogamulizumab, a new defucosylated MoAb, has shown to be active in Adult T leukaemia/lymphoma (ATL) (29-30) and was approved in Japan for the treatment of relapsed/refractory ATL. Compared to earlier antibody approaches in AML, MEN112 therefore possesses significant potential advantages in terms of both novelty of the leukaemic target and also structural superiority of the antibody construct. The current trial is intended to explore the extent to which these pre-clinical points of differentiation translate into clinical efficacy in patients with advanced AML who lack any existing established treatment options.

6.2 THE INVESTIGATIONAL PRODUCT: MEN1112

6.2.1 Physical, Chemical and Pharmaceutical Properties and Formulation

MEN1112 is a recombinant humanized antibody originated by engineering of a murine monoclonal antibody raised against the Bst1/CD157 antigen. [redacted]

MEN1112 drug substance is a solution containing the recombinant humanized antibody MEN1112 dissolved in a buffered and isotonic saline solution. [redacted]

The drug product MEN1112 consists of 10 mL of a sterile [redacted] solution containing 5.0 mg monoclonal antibody/mL in single-use glass vials as concentrate for solution for infusion. [redacted]

For drug product administration, the required volume of MEN1112 5.0 mg/mL concentrate for solution for infusion will be withdrawn from the vials and administered as IV infusion over 6 hours in 250 mL sterile 0.9 % sodium chloride solution.

6.2.2 Non-Clinical Data

6.2.2.1 Non Clinical Pharmacology

6.2.2.1.1 Mechanism of Action – in vitro

MEN1112 is a defucosylated humanized monoclonal antibody directed against Bst1/CD157. The Bst1/CD157 antigen shows an extremely low mRNA expression profile in healthy tissues, but it is highly expressed in monocytes, CD33+ cells and leukaemia cell lines. MEN1112 exhibits high and specific affinity for the Bst1/CD157 antigen in the range of 0.4-1 nM. After binding to Bst1/CD157 expressed on cell surface, MEN1112 is poorly internalized remaining localized at the cell membrane, making the targeting of Bst1/CD157 suitable for an ADCC approach. ADCC is one of the major clinical mechanisms of action of therapeutic antibodies against cell surface targets expressed on tumour cells. The antibody uses patients' innate immune cells (NK, monocytes, and macrophages) to kill target antigen-positive tumour cells. The activity is primarily triggered by: 1) a direct interaction of the Fc domain of the antibody with the corresponding FcγR receptors (CD16A) expressed on effector immune cells; 2) the interaction of the antigen binding domain of the Fab portion of MEN1112 with Bst1/CD157 expressed on blasts of AML. The defucosylation of Fc in MEN1112 should enhance ADCC potency allowing also the interaction with low affinity (158 F) allele of

CD16A. [redacted]

Indeed, MEN1112 promotes very efficiently ADCC in a concentration dependent manner on various cell lines expressing Bst1/CD157.
However, MEN1112 has per se no antiproliferative/proliferative activities and it is not able to mediate complement-dependent cytotoxicity (CDC).

6.2.2.1.2 Translational Research

Flow cytometric studies on human healthy donor whole blood using MEN1112 confirmed that Bst1/CD157 is highly expressed on neutrophils/monocytes, while eosinophils showed only a low-moderate expression of the antigen.
To evaluate prevalence of Bst1/CD157 antigen in primary human AML cells, extensive ex vivo investigations with patient-derived samples were conducted. Xenotransplantation studies are commonly employed and they are a useful approach to study the efficacy of anticancer therapeutics. However, translational research, that takes into consideration the heterogeneity of cancer, can add important information for the development of targeted therapies. In particular, it has been demonstrated, for AML, that mouse xenografts cannot represent the clonal architecture of leukaemia. However, primary samples of human AML tissue can be extremely useful for compound activity profiling and they reflect individual patient disease biology.
Two different studies, performed by flow cytometry, demonstrated that: 1) Bst1/CD157 is expressed in nearly 100% of AML patient samples analyzed (including samples at primary diagnosis or at relapse) both in bone marrow and in peripheral blood; 2) Bst1/CD157 expression levels varied to some degree between samples by intensity.
Similar results were also obtained in the bone marrow of AML patients.
Moreover, the expression of Bst1/CD157 on the compartment with a high percentage of leukemic stem cells was analyzed in 20 AML samples. Bst1/CD157 was expressed in 20/20 patients in the leukemic stem cell subpopulation of patient samples.
The correlation of Bst1/CD157 expression to FAB classification and cytogenetic markers was analyzed and the level of expression for Bst1/CD157 was found to vary to some degree between the different FAB subtypes, in particular the antigen is significantly higher in FAB M4/M5 compared to the other subtypes. When evaluating for cytogenetic prognostic markers, a significantly higher expression of Bst1/CD157 was observed in patients with Mixed Lineage Leukemia (MLL) rearrangements. For NPM1 and FLT-ITD mutations, no significant correlation could be shown.

Higher expression in patient samples of the European Leukemia Net prognostic system (ELN) adverse risk group was also observed.

The activity/potency of MEN1112 in determining blast depletion was also evaluated examining various E:T ratios and evaluating the role of NK activity/function, which is known to be impaired in AML patients. Interesting, even if heterogeneous, activity of MEN1112 was observed on: 1) primary AML blasts and healthy donor NK cells as effector cells; 2) NK cells isolated from AML patients at time of remission after intensive chemotherapy on cell lines used as target cells.

Through Fluorescence Activated Cell Sorting (FACS) analysis, the blast depletion activity was analyzed in peripheral whole blood and bone marrow from 26 and 23, respectively AML patients.

MEN1112 showed promising functional activity, independently of Fc γ receptor phenotype and the percentage of NK cells present. [redacted]

Additionally, the presence of soluble Bst1/CD157 was also evaluated in the AML patient serum samples, compared to healthy donors since antigens shed in the sera might limit the efficacy of a therapeutic antibody. However, no significant additional Bst1/CD157 shedding was observed in AML patients compared to healthy controls.

[redacted]

6.2.2.3 Toxicology

[redacted]

[redacted]

6.2.2.3.2 Cross-reactivity of MEN1112 with human tissues

Tissue cross-reactivity investigations were carried out to investigate the extent of binding MEN1112 in a panel of 42 human tissues and to identify target-specific and off-target binding. Binding of Fluorescein-labeled Antibodies (FITC) conjugated MEN1112 reported on cell membranes appeared to be specific and detected only in tissues known to express the target protein CD157. There was, therefore, no particular evidence for off-target binding.

[redacted]

[redacted]

6.2.3 Rationale for a Phase I Study and Selection of a Safe Starting Dose

In order to identify the starting dose for the first administration in humans, a repeat-dose toxicity study by i.v. administration has been carried out in Cynomolgus monkey (§ 6.2.2.3.1). [redacted]

6.2.4 Clinical Experience

This is the first in human study with MEN1112. The data and information related to the ARMY-1 study described in this section and in its respective paragraphs are included in the MEN1112 Investigator's Brochure (IB).

6.2.4.1 Patient disposition and reasons for withdrawal

As of 28 March 2019 (data cut-off date, unclean data) a total of 57 patients have been screened in the ARMY-1 study, 47 of whom have been treated, all using the "*one-shot*" schedule of administration, as tabulated below. Patient disposition at the cut-off date is provided below:

Table 1: Patient disposition in the ARMY-1 study

Number of Patients	Cohort 0.1 mg/kg N=4	Cohort 0.3 mg/kg N=7	Cohort 0.6 mg/kg N=6	Cohort 1.0 mg/kg N=8	Cohort 1.7 mg/kg N=17*	Cohort 2.5 mg/kg N=5	Overall N=47
Screened	7	8	7	10	20	5	57
Screening failure	3	1	1	2	3	0	10
Safety population	4/(100.0%)	7/(100.0%)	6/(100.0%)	8/(100.0%)	17/(100.0%)	5/(100.0%)	47/(100.0%)
DLT population	3/(75.0%)	6/(85.7%)	6/(100.0%)	7/(87.5%)	7/(41.2%)	5/(100.0%)	34/(72.3%)
Efficacy population	2/(50.0%)	4/(57.1%)	5/(83.3%)	4/(50.0%)	5/(29.4%)	2/(40.0%)	22/(46.8%)
Early withdrawal	4/(100.0%)	7/(100.0%)	6/(100.0%)	8/(100.0%)	10/(58.8%)	5/(100.0%)	40/(85.1%)

Note: Percentages calculated using the total number of patients enrolled as the denominator
* Includes 8 patients treated in the Step 2 of the study, all using the *"one-shot"* schedule

The majority of patients were early withdrawn from the study. The most frequently reported reason for withdrawal from study were disease progression and Investigator judgement (29.8% and 21.3%, respectively).

6.2.4.2 Overview of safety

Using the *"one-shot"* schedule of administration, treatment-related TESS occurred in the majority (95.7%) of study patients: 44.7% and 36.2% of patients experienced grade ≥ 3 treatment-related TESS and treatment-related serious TESS, respectively; the incidence of grade ≥ 3 treatment-related TESS was clearly increased in the Cohort 2.5 mg/kg, in which all patients experienced such events; the 2.5 mg/kg dose level also retained the highest incidence of treatment-related serious TESS (60%). Moreover, in this latter dose level, 2 out of 5 patients experienced DLT events, hence leading to the stop of the dose escalation phase as well as to the definition of the immediately lower dose level, namely 1.7 mg/kg, as the MTD. Treatment-related deaths occurred in two patients overall (4.3%), one in Cohort 1.0 mg/kg and one in Cohort 1.7 mg/kg. [redacted]. Treatment-related TESS leading to temporary study drug administration interruption occurred in 63.8% of study patients; although there is not a clear dose-relationship for such events, the highest incidence was found in the 2.5 mg/kg dose level. The incidence of TESS leading to temporary study drug administration interruption and reported as serious ranged between 0 and 25.0% through all the cohorts, without a clear dose trend.

The most frequently reported treatment-related grade < 3 TESS across all cohorts were *infusion-related reaction* (38.3% of patients), *disseminated intravascular coagulation* (17.0%), *chills* (14.9%) and *pyrexia* (12.8%); while for the latter two types of TESS there was no dose trend, the incidence of *disseminated intravascular coagulation* was clearly higher in Cohort 2.5 mg/kg - 60.0% of patients experiencing such TESS - than in all the previous cohorts (0-17.6% of patients reported to experience such TESS). With regard to *infusion related reaction*, the highest incidence (75.0%) was found at the 0.1 mg/kg dose level, which however was run using the one hour infusion duration and without the standardized premedication encompassing the mandatory use of dexamethasone and

methylprednisolone that was implemented thereafter. The 2.5 mg/kg dose level retained the second highest incidence (60%) of grade < 3 TESS *disseminated intravascular coagulation*, and it was almost double in respect of that in dose levels 0.6-1.7 mg/kg (25.0-33.3%), which were run using the same infusion duration – and, for the majority of patients, also the same premedication – used in dose level 2.5 mg/kg.

Six patients in total experienced TESS which - according to the drug causality assessment and severity grade reported by the investigator- met the definition of DLT as reported in the protocol version in force at the time of event occurrence

-

[redacted]

The most frequently reported grade ≥ 3 treatment related TESS were those pertaining to the *Blood and lymphatic system disorders* and *Investigations* by System Organ Class, both occurring in 21.3% of study patients. TESS pertaining to *Blood and lymphatic system disorders* did not show a clear dose trend; with regard to TESS pertaining to *Investigations*, the incidence of these events was clearly higher in the cohort 2.5 mg/kg than in any other dose level. The only grade ≥ 3 treatment related TESS reported in at least 10% of patients in any cohort was *febrile neutropenia* (10.6% of all study patients, without clear dose trend).

6.2.4.3 Overview of clinical pharmacokinetics

MEN1112 serum concentrations from Cohort 0.1 mg/kg to Cohort 1.7 mg/kg of ARMY-1 study were measured and an interim PK analysis was performed for 38 subjects after a single IV infusion and for 8 subjects after six consecutive IV infusions. The pharmacokinetics of MEN1112 in human were characterised by a dose-dependent behaviour after both single and repeat dose administration, as shown by a more than proportional increase in $AUC_{0\text{-}inf}$ in the dose-range 0.1-2.5 mg/kg. MEN1112 was slowly cleared from the body, with a mean half-life ranging from 10.8 to 41.8 hr and from 12.8 to 146.4 hr after single and repeat dose, respectively. The values obtained for volume of distribution at steady state were similar to total blood volume (i.e. 5 L). Estimates of clearance were also low (0.02 - 0.9 L/hr) and in the range of those reported for other monoclonal antibodies. The magnitude of inter-individual variability in MEN1112 disposition is large in the explored dose-range of 0.1-2.5 mg/kg.

6.3 RISK BENEFIT ASSESSMENT

The medical need for AML and MDS is yet highly unmet and new treatments are urgently needed for either disease.

MEN1112 is a defucosylated Monoclonal Antibody with high affinity binding to Bst1/CD157 antigen, which is expressed at high prevalence on both AML and MDS cells.

Due to its ability to deplete AML and MDS blasts, even in the presence of low NK cells percentage, MEN1112 is considered to have the potential to represent a new targeted therapeutic opportunity in both AML and MDS patients. the single agent activity of MEN1112 is under clinical investigation in patients with relapsed or refractory AML in the ARMY-1 trial. In this trial, the MTD of the "*one-shot*" administration schedule has been identified at 1.7 mg/kg following the occurrence of two DLT events in two patients treated at 2.5 mg/kg dose level [redacted]. The Sponsor therefore performed an in-depth review of the safety

profile of MEN1112, with a particular focus on the four patients [redacted] who, throughout the study, experienced DLT events that clearly started during the infusion and that were characterized by increased transaminases, with or without severe coagulation derangements and multiorgan failure [redacted] A panel of widely acknowledged AML experts was also called to advice on the pathophysiology of the above events as well as on the next steps for the prosecution of the clinical development of MEN1112 in AML. The experts concluded that the pathophysiology of the severe events observed so far in the above patients may involve cytokine storm and/or monocytic-macrophage activation, as well as massive lysis of target cells and that, to possibly prevent the occurrence of such events or limiting their severity, general safety measures should be applied. Based on the experience with other compounds (e.g. Blinatumomab, Venetoclax) and on the fact that the above toxicities did develop either at the first or the second dose during the first cycle of treatment, a "*ramp-up*" approach during Cycle 1 was concluded to be the most appropriate one. Therefore, the dose escalation will be resumed from the 1.7 mg/kg dose level (i.e. from the MTD achieved using the "*one shot*" schedule per Protocol V4.1), under the 3+3 design and using a "*ramp-up*" approach during the first two MEN1112 administrations of Cycle 1. If no DLT occurs, additional dose levels will be explored at 2.0 mg/kg, 3.0mg/kg and 5.0mg/kg. [redacted]

Additional intermediate dose levels may be also explored, under a 3+3 design, upon recommendation of the iDSMB that will be appointed to guide dose escalation decisions. In addition, as the clinical data collected so far are not sufficient to adequately design a maintenance treatment phase, starting from protocol version 6.1/6.2 the study will no longer encompass a maintenance phase, which is replaced by a follow-up period for safety and efficacy assessments. To serve the best interest of the patients, for those achieving at least a partial response according to protocol-defined criteria, the Sponsor commits to consider providing MEN1112 to allow the prosecution of the infusions at the frequency recommended by the iDSMB on an individual basis and after discussion with the treating Investigator and the Medical Monitor.

A mechanistic Target-Mediated Drug Disposition (TMDD) population PK model has been developed from free circulating MEN1112 concentration from ARMY-1 study (MEN1112-PK-01). The TMDD model was used in simulation to explore different *"ramp-up"* dosing schedule scenarios. Upon the aforementioned PK modelling simulations, a 3-day "*ramp-up"* approach was chosen. The "*ramp-up*" dosing escalation and the whole treatment plan will thus be as following:

DOSE LEVEL	CYCLE 1	CYCLE 2
1.7 mg/kg	Visit 1/Day 1: 0.1 mg/kg Visit 2/Day 2: 0.6 mg/kg Visit 3/Day 3: 1.0 mg/kg Visit 8/Day 8: 0.1 mg/kg Visit 9/Day 9: 0.6 mg/kg Visit 10/Day 10: 1.0 mg/kg Visit 12/Day 15: 1.7 mg/kg	Visit 16/Day 22: 1.7 mg/kg Visit 20/Day 29: 1.7 mg/kg Visit 24/Day 36: 1.7 mg/kg
2.0 mg/kg	Visit 1/Day 1: 0.1 mg/kg Visit 2/Day 2: 0.7 mg/kg Visit 3/Day 3: 1.2 mg/kg Visit 8/Day 8: 0.1 mg/kg Visit 9/Day 9: 0.7 mg/kg Visit 10/Day 10: 1.2 mg/kg Visit 12/Day 15: 2.0 mg/kg	Visit 16/Day 22: 2.0 mg/kg Visit 20/Day 29: 2.0 mg/kg Visit 24/Day 36: 2.0 mg/kg
[redacted]		
3.0 mg/kg	Visit 1/Day 1: 0.2 mg/kg Visit 2/Day 2: 1.0 mg/kg Visit 3/Day 3: 1.8 mg/kg Visit 8/Day 8: 0.2 mg/kg Visit 9/Day 9: 1.0 mg/kg Visit 10/Day 10: 1.8 mg/kg Visit 12/Day 15: 3.0 mg/kg	Visit 16/Day 22: 3.0 mg/kg Visit 20/Day 29: 3.0 mg/kg Visit 24/Day 36: 3.0 mg/kg
5.0 mg/kg	Visit 1/Day 1: 0.3 mg/kg Visit 2/Day 2: 1.7 mg/kg Visit 3/Day 3: 3.0 mg/kg Visit 8/Day 8: 0.3 mg/kg Visit 9/Day 9: 1.7 mg/kg Visit 10/Day 10:3.0 mg/kg Visit 12/Day 15: 5.0 mg/kg	Visit 16/Day 22: 5.0 mg/kg Visit 20/Day 29: 5.0 mg/kg Visit 24/Day 36: 5.0 mg/kg

The TMDD model simulations confirm that the simulated exposure at 24 and 48 hours with 2.0 mg/kg and 3.0 mg/kg with the new proposed schedule of administration are lower than those with 1.7 mg/kg administered with *"one-shot"* schedule. [redacted]

[redacted]

The "*ramp-up*" schedule is expected to be safer in respect of the dosing schedule in force up to protocol version 4.1 ("*one-shot*"), which has been extensively demonstrated to be tolerable up to 1.7 mg/kg as confirmed by the data collected in the 17 patients treated so far at this dose level between the dose escalation and the cohort expansion steps of the study. Therefore, the treatment of study patients will not be staggered. The "*ramp-up*" dosing also allows to stop earlier the administration of the intended full dose in case of infusion-related symptoms and/or detection of laboratory adverse events and allows a better safety profile since lower exposure are achieved with the *"ramp-up"* schedule up to 48 hours from the start of infusion – when the majority of severe toxicities occurred during the study – compared to those achieved with 1.7 mg/kg given "*one-shot*". Eventually, the following additional safety measures are implemented in the amended ARMY-1 study:

- Prior to the MEN1112 administration at Cycle 1 (Visit 1/Day 1, Visit 8/Day 8 and Visit 12/Day 15), WBC count should be $\leq 10 \times 10^9$/L; hydroxyurea can be used to achieve such count (a shift of +1 day of the *"ramp-up"* administration visit is allowed, if needed).
- Specific rules are provided in this protocol to manage the MEN1112 administration in case of severe infusion-related toxicities (see §8.4.7).
- In case of grade 3 or 4 cytokine release syndrome (CRS), it is recommended to consider the use of high dose corticosteroids. Intensive care supportive therapy should be considered for severe or life-threatening CRS, tumor lysis syndrome and/or disseminated intravascular coagulation.

Moreover, in order to independently assess the safety of the "*ramp-up*" schedule of administration, during both its dose escalation and cohort expansion steps, an iDSMB is implemented. The iDSMB, made by independent AML experts, will review patients' data at the end of each dose escalation

cohort, and will take-over the same applicable roles and responsibilities previously assigned to the Cohort Review Committee. The iDMSB will review the safety, efficacy and PK data collected with the "*ramp-up*" schedule, and the Sponsor will follow the iDSMB recommendation for any dose escalation decision.

[redacted]

Although neither complete nor partial responses have been documented so far in the ARMY-1 study, four patients – two of whom treated at the MTD dose level identified with the "*one-shot*" schedule of administration, namely 1.7 mg/kg – showed signs of a treatment-induced TLS, which represents a potential sign for potent antileukemic activity. Overall, these data support to continue the investigation of the clinical activity of MEN1112 given as single agent in AML patients with relapsed/refractory disease, and to investigate the new administration schedule ("*ramp-up*") aiming at exploring additional dose levels in the ARMY-1 study following the iDSMB recommendation for any dose escalation decision.

Therefore, considering a) the fair tolerability of MEN1112 at the MTD dose level (1.7 mg/kg) identified using the "*one-shot*" schedule, b) the possibility to further increase the MTD dose level by the mean of the new "*ramp-up*" schedule, c) the implementation of an iDSMB, as well as d) the potentially promising antitumour activity of MEN1112 (as proven by the four reported TLS cases, two of which at the 1.7 mg/kg dose level using the *"one-shot"* schedule), and eventually e) its potential use in combination studies using the "*ramp-up*" schedule of administration, the risk-benefit is assessed to be in favour of continuing MEN1112 clinical investigation and development as above described.

7. STUDY OBJECTIVES

7.1 PRIMARY OBJECTIVES

To identify the DLT and MTD of MEN1112 when given intravenously during Cycle 1 in patients with relapsed or refractory AML.

7.2 SECONDARY OBJECTIVES

The following will be assessed/determined:

- Safety and tolerability of MEN1112.
- Pharmacokinetic profile after single and repeat doses of MEN1112 following IV

administration.

- Potential of MEN1112 immunogenicity.
- Clinical activity of MEN1112.
- Correlation of baseline patient's and disease characteristics with clinical activity of MEN1112

[redacted]

8. INVESTIGATIONAL PLAN

8.1 OVERALL STUDY DESIGN AND PLAN DESCRIPTION

In protocol versions from 1.0 to 4.1 n=3 Dose Limiting Toxicity (DLT) evaluable patients per cohort (expanded to n=6 DLT evaluable patients in case of DLT occurrence, with the exception of cohort 0.3 mg/kg which was expanded to n=6 DLT evaluable patients regardless of DLT occurrence) were treated with MEN1112 at escalating doses of 0.1, 0.3, 0.6, 1.0, 1.7, and 2.5 mg/kg using *"one-shot"* infusions.

Starting from protocol version 6.1/6.2, n=3 Dose Limiting Toxicity (DLT) evaluable patients per cohort (expanded to n=6 DLT evaluable patients in case of DLT occurrence) will be treated with MEN1112 at escalating doses of 1.7, 2.0, 3.0, 5.0 mg/kg per each dose cohort using a modified schedule of administration that will include a *"ramp-up"* approach at Cycle 1. Additional intermediate dose levels may be explored, under a 3+3 design, upon recommendation of the independent Data Safety Monitoring Board (iDSMB) that will be appointed to guide dose escalation decisions in place of the Cohort Review Committee (CRC) that was appointed for this role up to Protocol Version 4.1. [redacted]

Step 2 (cohort expansion phase): Under Protocol Version 4.1, two patients experienced DLTs at the dose level of 2.5 mg/kg using the *"one-shot"* schedule of administration in Cycle 1. Therefore, the 1.7 mg/kg dose level was defined as the maximum tolerated dose (MTD) for the schedule of administration encompassing the *"one-shot"* infusion since Cycle 1; as a consequence, the expansion phase was opened to enrol up to 25 patients with MEN1112 given as *"one-shot"* infusions since Cycle 1.

Starting from protocol version 6.1/6.2, up to 30 patients will be treated with MEN1112 given at the MTD identified in Step 1 using the modified schedule of treatment, i.e. encompassing the *"ramp-up"* approach during Cycle 1. The iDMSB, already implemented for Step 1 will also be appointed to assess the data collected during the Step 2 of the study. See section 8.4.5 for the treatment plan details.

Starting from protocol version 6.1/6.2, Cycle 1 and Cycle 2 will constitute the Treatment period, followed by a 4-week End of Treatment period and a Follow-up period. During the Follow-up periods, only safety and/or efficacy assessments are scheduled; however, to serve the best interest of the patients, for those achieving at least a partial response according to protocol-defined criteria, the Sponsor commits to consider providing MEN1112 to allow the prosecution of the infusions at the frequency recommended by the iDSMB on an individual basis and after discussion with the treating Investigator and the Medical Monitor.

8.2 SELECTION OF STUDY POPULATION

The study population of this phase I trial will consist of relapsed or refractory AML patients who meet all of the inclusion criteria and none of the exclusion criteria, providing written informed consent.

8.2.1 Inclusion criteria

Inclusion criteria will be evaluated during Screening Period, with the exception of inclusion criteria 3 and 4, which will be evaluated at Visit 1/Day 1; inclusion criteria 5 and 6 will be re-evaluated prior to the first study drug administration (Visit 1/Day 1).

1. Male or female patients aged ≥ 18 years.
2. Documented definitive diagnosis of AML (according to World Health Organization (WHO) criteria, 2008) that is relapsed /refractory to standard treatment, for which no standard therapy is available or the patient refuses standard therapy. For the purpose of this study, refractory AML is defined as following:
   Failure to achieve CR/CRi (IWG criteria, 2003) following at least 1 cycle of cytotoxic chemotherapy (or hypomethylating agents if unsuitable for cytotoxic chemotherapy) and unlikely, as per Investigator's judgement, to achieve CR/CRi with further cytotoxic chemotherapy (or hypomethylating agents if unsuitable for cytotoxic chemotherapy).
3. WBC count ≤ 10 x 109/L at Visit 1; hydroxyurea is allowed to lower WBC count.
4. ECOG performance status of 0 to 2 at Visit 1/Day 1.
5. Life expectancy of at least 2 months.
6. Adequate renal and hepatic laboratory assessments:
   - AST, ALT, ALP ≤3.0 × ULN, unless considered due to leukemic organ involvement.
   - Total Bilirubin ≤2.0 × ULN.
   - Serum creatinine ≤2.0 × ULN.

7. A female of childbearing potential may be enrolled providing she:
   - has a negative pregnancy test during screening period and
   - is routinely using an effective method of birth control 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, associated with inhibition of ovulation, intrauterine device, total sexual abstinence or bilateral tubal occlusion) until 6 months from the last study drug administration
   - undergoes a monthly pregnancy test until 6 months from the last study drug administration.
8. Able to give written informed consent before any study related procedure.

8.2.2 Exclusion criteria

Exclusion criteria will be evaluated during Screening Period, with the exception of exclusion criteria 6, 7, 8 and 9, which will be evaluated at Visit 1/Day 1; exclusion criteria 4 and 5 will be re-evaluated prior to the first study drug administration (Visit 1/Day 1).

1. Acute promyelocytic leukaemia (FAB M3 classification).
2. Active central nervous system involvement.
3. Haematopoietic stem cell transplantation (HSCT) performed within 3 months prior to Screening Period. Patients with prior allogeneic HSCT performed more than 3 months prior to Screening Period are eligible with Medical Monitor approval.
4. Active infection requiring intravenous antibiotics.
5. Life-threatening illnesses other than AML, uncontrolled medical conditions or organ system dysfunction which, in the investigator's opinion, could compromise the patient's safety or interfere with the patient's ability to comply with the study activities.
6. Anti-tumour therapy within 14 days of study Visit 1, excluding hydroxyurea.
7. Prior participation in an investigational study (procedure or device) within 21 days of study Visit 1.
8. Major surgery within 28 days of study Visit 1/Day 1.
9. Radiotherapy within 28 days prior to study Visit 1 or scheduled along the study conduct.
10. Known history of HIV or active infection with HCV or HBV.
11. Known hypersensitivity to MEN1112 excipients.
12. Other active malignancies. History of malignancy in the last 12 months (except for basal cell or squamous cell skin cancer or carcinoma in situ of the cervix or breast or non-melanoma skin cancer).
13. Pregnant or breast-feeding women.

8.2.3 Withdrawal of patients from therapy or assessment

Participation in the study is strictly voluntary and patients have the right to withdraw from the study at any time without explanation. This will not affect his/her rights for future medical care. Treatment should be discontinued also if this is in the best interest of the patient upon Investigator judgement and/or in case of any of the following:

- Non-compliance of the patient or investigator with the protocol
- Disease progression
- DLTs
- Infusion toxicities requiring permanent treatment discontinuation (see §8.4.7)
- Treatment-related grade 3 not haematological toxicity lasting more than 7 days occurring after the first cycle, excluding common complications of AML (in particular infections, bleedings, fatigue)
- Treatment-related grade ≥ 4 not haematological toxicity occurring after the first cycle, excluding common complications of AML (in particular infections, bleedings, fatigue)
- Life threatening related Serious Adverse Event (SAE)
- Patient receives other treatment for AML (including HSCT)
- Occurrence of pregnancy

The Investigator is ultimately responsible for the safety and well-being of the patients and, if at any time during the study it is believed that the constraints of this protocol are detrimental to the patient's health, the patient may be withdrawn from the study.

Withdrawal of a patient must be notified to the study monitor, the reason(s) of withdrawal should be documented in the e-CRF and follow-up should be reported. For patients who withdraw from study, End of Study Visit has to be performed at the time of withdrawal.

If a patient prematurely terminates the study, data already collected will be used and analysed for the purpose of the study. In regard to biological samples already collected, in case of Informed Consent withdrawal, the patient may choose if samples not yet analysed, shall be analysed or destroyed.

8.3 IDENTITY OF THE INVESTIGATIONAL PRODUCT

8.3.1 Description of Investigational Medicinal Product

The drug product MEN1112 5.0 mg/mL concentrate for solution for infusion consists of 10 mL of a [redacted] solution containing 5.0 mg MoAB/mL as concentrate for solution for infusion [redacted].

Composition:

Ingredient	Quality	Function
MEN1112	Internal Specification	API

[redacted]

[redacted]

8.3.2 Packaging, labelling, and storage

The packaging and labelling of IMP will be performed [redacted]

Primary packaging: The drug product MEN1112 (OBT 357) 5.0 mg/mL concentrate is primary packaged in 20 mL [redacted] vials [redacted]

Secondary Packaging: The IMP is provided to the clinical sites in center boxes containing 8 vials and a leaflet detailing the instructions on how to administer the drug product. The IMP center boxes are accompanied with the corresponding batch certificate and the certificates of analysis and the form "Handing over and delivery receipt of Investigational Medicinal Product".

Labelling: Each of the vials (primary packaging) and the IMP center boxes (secondary packaging) are labelled in compliance with the current valid international and corresponding national requirements. The labels of the vials bear the unique vial number. These vial labels have a peel-off section which has to be attached to the corresponding section in the drug accountability log upon dispensing of the IMP at visits. The peel-off part reports the number of the vial and the IMP batch number. The fixed section of the vial label reports the contents of the vial and the instructions how to administer and

store the IMP in the respective national language. The label of the IMP center box is multilingual and reports the contents of the center box (quantity and unique numbers of vials) and the instructions how to administer and store the IMP in the respective national language.

Storage: [redacted]. The IMP must be kept in a secure area, out of reach and sight of children and inaccessible to unauthorised individuals.

8.3.3 Drug accountability

Upon receipt of all IMP, study site personnel or the designated pharmacist will open the shipment package, verify the contents as stated on the enclosed shipping form, and confirm the receipt by filling in and sending the form "Handing over and delivery receipt of Investigational Medicinal Product" [redacted]

The Investigator will be responsible for documenting the dispensing of the IMP to the patient by entering the unique vial number in the source documents and in the e-CRF.

The amount of administered drug product will be documented by the Investigator in the source documents and in the e-CRF in order to allow drug accountability.

In addition, the sites will maintain paper drug accountability forms to document dispensed IMP per patient. The peel-off labels of the vials will be stuck on these paper drug accountability forms.

[redacted] The infusion solution must be kept in a secured area, inaccessible to any unauthorised individuals.

8.3.4 Destruction of surplus medication

Throughout the study course and at the end of the study, all remaining IMP will be reconciled under the responsibility of the Investigator at the site. [redacted]. In case the return is not possible, the IMP can be destroyed locally, provided that the order for destruction is authorised by the Sponsor.

8.4 TREATMENT ADMINISTRATION- FREQUENCY AND DURATION OF APPLICATION

8.4.1 TLS risk assessment and prophylaxis

At the first *"ramp-up"* dose (Visit 1/Day 1), prior to study drug administration, TLS risk shall be assessed (see *Appendix I: TLS Manual for Investigator* for details) and, during Cycle 1, TLS prophylaxis has to be given prior to each study drug administration, as detailed in the TLS Manual for Investigator.

8.4.2 Premedication

On the first day of each *"ramp-up"* administration visit (i.e. Visits 1 and 8/Days 1 and 8), as well as on each "one shot" administration visit, premedication shall consist of:

- Dexamethasone 8 mg (os or IV) at 12 hours prior to the start of infusion
- Dexamethasone 8 mg (os or IV) to be repeated at 3 hours prior to the start of infusion
- Methylprednisolone 100 mg IV at 1-2 h prior to the start of infusion
- An antihistaminic and an antipyretic agent at 30 to 60 minutes prior to the start of infusion

On the second and the third day of each *"ramp-up"* administration visit (Visit 2, 3, 9 and 10/Day 2, 3, 9 and 10), premedication shall consist of:

- Methylprednisolone 100 mg IV at 1-2 h prior to the start of infusion
- An antihistaminic and an antipyretic agent at 30 to 60 minutes prior to the start of infusion

In case the *"ramp-up"* administration visit is stopped due to infusion-related toxicities:

- If *"ramp-up"* is resumed after ≥2 days, the premedication at *"ramp-up"* resumption should follow the whole scheme above, i.e. with dexamethasone on the day of *"ramp-up"* resumption and without dexamethasone on the following *"ramp-up"* day(s), if any.
- If *"ramp-up"* is resumed the day after the interruption, premedication without dexamethasone should be given on the day of *"ramp-up"* resumption and on the following *"ramp-up"* day(s), if any.
- If *"ramp-up"* is resumed on the same day of interruption, no additional premedication is needed at *"ramp-up"* resumption.

8.4.3 Step 1 Dose escalation method and cohort management

MEN1112 doses are to be administered to cohorts of 3 patients each. If no Dose-Limiting Toxicity (DLT) is observed in a cohort of three patients at a given dose level, the next cohort of 3 new patients

will be treated with the next higher dose. If a DLT is experienced by one of the three patients at any dose, three additional patients will be treated at the same dose level.

If two or more patients at a given dose level exhibit DLTs, this dose will be defined as the MAD. The MTD is defined as one dose level below the MAD, i.e. one dose level below the one at which ≥ 2 DLTs out of 6 treated patients occur.

In protocol versions from 1.0 to 4.1 n=3 Dose Limiting Toxicity (DLT) evaluable patients per cohort (expanded to n=6 DLT evaluable patients in case of DLT occurrence, with the exception of cohort 0.3 mg/kg which was expanded to n=6 DLT evaluable patients regardless of DLT occurrence) were treated with MEN1112 at escalating doses of 0.1, 0.3, 0.6, 1.0, 1.7, and 2.5 mg/kg using "*one-shot*" infusions.

Starting from protocol version 6.1/6.2, n=3 Dose Limiting Toxicity (DLT) evaluable patients per cohort (expanded to n=6 DLT evaluable patients in case of DLT occurrence) will be treated with MEN1112 at escalating doses of 1.7, 2.0, 3.0, 5.0 mg/kg per each dose cohort using a modified schedule of administration that will include a *"ramp-up"* approach at Cycle 1. Additional intermediate dose levels may be explored, under a 3+3 design, upon recommendation of the independent Data Safety Monitoring Board (iDSMB) that will be appointed to guide dose escalation decisions in place of the Cohort Review Committee (CRC) that was appointed for this role up to Protocol Version 4.1. [redacted].

8.4.3.1 Dose-level escalation assessment

In place of the Cohort Review Committee (CRC), which was appointed to guide dose escalation decisions up to Protocol Version 4.1, starting from Protocol Version 6.1/6.2, the decision as to whether, or how, to proceed through the dose levels during Step 1 are guided by the iDMSB which will be comprised of independent AML experts.

The iDSMB will meet by telephone to review the latest safety, PK and Pharmacodynamics (PD) (if any) data prior to dose-escalation to a subsequent cohort, and at any time if needed. Appropriate representatives of the Sponsor and the coordinating CRO will also attend and minute the meeting. Decisions of the iDMSB will be documented and sent to the sites.

The iDSMB is empowered to:

- Review the safety data from the first cycle of each cohort during the dose escalation phase of the study and make dose-escalation (or de-escalation) decisions according to the protocol or making adjustments, as needed. AEs occurring in Cycle 2 which meet the definition of a DLT or are considered clinically significant may also be considered in making dose escalation decisions.

- Consider other AEs, or possible trends in AEs, during the dose escalation phase which may provide relevant information for the dose escalation.
- Confirm the MTD or the maximum dose judged to be tolerable for evaluation in Step 2.
- Review safety data for additional patients recruited at the MTD or the maximum dose judged to be tolerable (at least every 2 months).
- Recommend future dose level and dose schedule administration during the study conduct; advise on premedication, concomitant medication and on any individual patient dose adjustments.

Roles and responsibilities of iDSMB as well as meeting schedule and format of information will be set forth in a separate iDSMB Charter prior to start administrating the drug to the first patient under protocol version 6.1/6.2.

8.4.4 Step 2- Cohort expansion

Under Protocol Version 4.1, two patients experienced DLTs at the dose level of 2.5 mg/kg using the *"one-shot"* schedule of administration in Cycle 1. Therefore, the 1.7 mg/kg dose level was defined as the maximum tolerated dose (MTD) for the schedule of administration encompassing the *"one-shot"* infusion since Cycle 1; as a consequence, the expansion phase was opened to enrol up to 25 patients with MEN1112 given as "*one-shot*" infusions since Cycle 1.

Starting from protocol version 6.1/6.2, up to approximately 30 patients will be treated with MEN1112 given at the MTD identified in Step 1 using the modified schedule of treatment, i.e. encompassing the *"ramp-up"* approach during Cycle 1. In place of the CRC, which was appointed to assess the data collected during Step 2 up to Protocol Version 4.1, under Protocol Version 6.1/6.2 and following amendments the iDMSB, already implemented in Step 1 will be appointed also to assess the data collected during the Step 2 of the study.

8.4.5 Treatment regimen and duration

MEN1112 is to be administered intravenously for two treatment cycles.

Up to Protocol Version 4.1, MEN1112 was administered by intravenous *"one-shot"* weekly infusions for two 21-day cycles, followed by *"one-shot"* monthly infusions in patients demonstrating clinical benefit (as per Investigator's judgement) as long as such benefit was maintained. Starting from protocol version 6.1/6.2, MEN1112 will be administered for two 21-day cycles; the first two infusions of Cycle 1 will be given using a *"3-day ramp-up"* schedule of administration**,** i.e. the complete MEN1112 dose will be split in three days. Starting from the third infusion of Cycle 1 onwards, MEN1112 will be administered as *"one-shot"* infusions. The treatment plan by dose level will be therefore as following:

DOSE LEVEL	CYCLE 1	CYCLE 2
1.7 mg/kg	Visit 1/Day 1: 0.1 mg/kg Visit 2/Day 2: 0.6 mg/kg Visit 3/Day 3: 1.0 mg/kg Visit 8/Day 8: 0.1 mg/kg Visit 9/Day 9: 0.6 mg/kg Visit 10/Day 10: 1.0 mg/kg Visit 12/Day 15: 1.7 mg/kg	Visit 16/Day 22: 1.7 mg/kg Visit 20/Day 29: 1.7 mg/kg Visit 24/Day 36: 1.7 mg/kg
2.0 mg/kg	Visit 1/Day 1: 0.1 mg/kg Visit 2/Day 2: 0.7 mg/kg Visit 3/Day 3: 1.2 mg/kg Visit 8/Day 8: 0.1 mg/kg Visit 9/Day 9: 0.7 mg/kg Visit 10/Day 10: 1.2 mg/kg Visit 12/Day 15: 2.0 mg/kg	Visit 16/Day 22: 2.0 mg/kg Visit 20/Day 29: 2.0 mg/kg Visit 24/Day 36: 2.0 mg/kg
[redacted]		
3.0 mg/kg	Visit 1/Day 1: 0.2 mg/kg Visit 2/Day 2: 1.0 mg/kg Visit 3/Day 3: 1.8 mg/kg Visit 8/Day 8: 0.2 mg/kg Visit 9/Day 9: 1.0 mg/kg Visit 10/Day 10: 1.8 mg/kg Visit 12/Day 15: 3.0 mg/kg	Visit 16/Day 22: 3.0 mg/kg Visit 20/Day 29: 3.0 mg/kg Visit 24/Day 36: 3.0 mg/kg
5.0 mg/kg	Visit 1/Day 1: 0.3 mg/kg Visit 2/Day 2: 1.7 mg/kg Visit 3/Day 3: 3.0 mg/kg Visit 8/Day 8: 0.3 mg/kg Visit 9/Day 9: 1.7 mg/kg Visit 10/Day 10:3.0 mg/kg Visit 12/Day 15: 5.0 mg/kg	Visit 16/ Day 22: 5.0 mg/kg Visit 20/ Day 29: 5.0 mg/kg Visit 24/ Day 36: 5.0 mg/kg

During Cycle 1, patients must be treated and monitored in-hospital up to at least 24 hours after each study drug administration visit. [redacted]

The total dose calculated for the first study drug administration can be applied also for the following ones providing that actual patient's weight is within ±10% of the weight measured prior to the first study drug administration. Otherwise, the total dose to be given shall be calculated based on the weight measured at the corresponding visit.

The individual study period (including the follow-up) is six months (except for female patients of childbearing potential, who will be required to undergo a monthly pregnancy test until 6 months from the last study drug administration).

8.4.6 Treatment compliance

The assessment of patients' compliance to IMP administration is not required as the investigational drug is infused at site by the Investigator.

8.4.7 Dosage modification and management of infusion toxicities

No dose adjustment is allowed.

The following instructions are provided for the management of infusion toxicities:

Toxicity	CTCAE v.4.03 Grade (duration)	Occurrence	Action on MEN1112 infusion	Action for toxicity
Cytokine release storm and/or Tumor lysis syndrome	3 (≤7 days)	First (during *"ramp-up"* administration)	Interrupt MEN1112 until resolved to grade 0, then: - If ≤20% of the ramp-up infusion dose (i.e. ≤50 mL of the total 250 mL infusion solution) was missed, restart MEN1112 at the next scheduled study drug administration. - If >20% (i.e. >50 mL of the total 250 mL infusion solution) of the ramp-up infusion was missed, as soon as feasible (upon resolution to grade 0) restart MEN1112 to complete the residual ramp-up dose (e.g. if the dose was interrupted when 120 mL of the second ramp-up dose had been administered, complete the second ramp-up dose with 130 mL of infusion solution, then administer the full 250 mL infusion solution of the third ramp-up dose on the day after). If the infusion cannot be completed within 24 hours from dilution, a new infusion solution shall be prepared. If applicable, postpone the next scheduled study drug administration (i.e. the first infusion of the following 3-day ramp-up	**Tumor lysis syndrome (TLS)**[1]: • Consider multidisciplinary approach with involvement of nephrologists and intensive care physicians. • Potassium must not be added to the hydration fluid. • In the absence of contraindications, it is recommended rasburicase at a dose of 0·2 mg/kg/day (duration determined according to the clinical response) • Symptomatic hypocalcaemia is recommended to be treated with a short infusion of calcium gluconate • In patients with potassium levels ≥6 mmol/l or with ≥ 25% increase from baseline, cardiac monitoring is recommended • Intractable fluid overload, hyperkalaemia, hyperuricaemia, hyperphosphataemia or

Toxicity	CTCAE v.4.03 Grade (duration)	Occurrence	Action on MEN1112 infusion	Action for toxicity
			dosing) to ensure an interval of 5 days between any study drug administration is guaranteed.	hypocalcaemia are indications for renal dialysis. • Consider intensive care unit admittance for severe (grade 3-4) TLS cases **Cytokine release storm**[2]: paracetamol and high dose steroids (dexamethasone) are recommended. Consider intensive care unit admittance for severe (grade 3-4) cases **Disseminated intravascular coagulation (DIC)**[3]: • In patients with DIC and active bleeding, it is recommended the use of platelet transfusion to maintain the platelet count above $50x10^9$/L • In patients with DIC and active bleeding, it is suggested transfusion of fresh frozen plasma (15–30 mL kg-1) with careful clinical monitoring to decide on dose adjustments. • In actively bleeding cases with persistently low fibrinogen values (below 1.5 g L-1) despite these supportive measures, it is suggested transfusion of two pools of cryoprecipitate (whenever available) or fibrinogen concentrate
	3 (≤7 days)	First (during *"one shot"* administration)	Interrupt MEN1112 until resolved to grade 0, then: - If ≤20% of the infusion (i.e. ≤50 mL of the total 250 mL infusion solution) dose was missed, restart MEN1112 at the next scheduled study drug administration. - If >20% (i.e. >50 mL of the total 250 mL	

Toxicity	CTCAE v.4.03 Grade (duration)	Occurrence	Action on MEN1112 infusion	Action for toxicity
			infusion solution) of the infusion was missed, as soon as feasible (upon resolution to grade 0) restart MEN1112 to complete the residual dose (e.g. if the dose was interrupted when 120 mL had been administered, complete the dose with 130 mL of infusion solution). If the infusion cannot be completed within 24 hours from dilution, a new infusion solution shall be prepared. If applicable, postpone the next scheduled study drug administration to ensure an interval of 7 days between any study drug administration is guaranteed.	• Routine use of tranexamic acid is not recommended. If therapy-resistant bleeding dominates the picture in hyperfibrinolytic DIC, tranexamic acid may be considered • It is recommended regular clinical and laboratory surveillance of the patient, to detect the development of complications including organ failure, and to ensure the underlying condition is being adequately treated • Consider intensive care unit admittance for severe (grade 3-4) cases **Infusion related reaction (IRR)**[4]: • Stop the administration of medication • Maintain the i.v. access and assess the patients level of consciousness • Position: - In the case of hypotension, the patient should be placed in the Trendelenburg position. - In the case of respiratory distress, sitting up. - If unconscious, in recovery position. • Administrate oxygen, if needed
	3 (≤7 days)	Second	Discontinue MEN1112 permanently	
	3 (>7 days)	Any		
	4 (any)	Any		
Elevated transaminase(s), disseminated intravascular coagulation, and/or other clinically relevant (as determined by treating physician) adverse reactions	3 (≤7 days)	First	Interrupt MEN1112 until the toxicity improves to grade ≤1, then follow the instructions provided above for grade 3 cytokine release storm/tumor lysis syndrome lasting ≤7 days at the first occurrence (either during ramp-up or one shot administration, as applicable).	
	3 (≤7 days)	Second	Discontinue MEN1112 permanently	
	3 (>7 days)	Any		
	4 (any)	Any		
Any	2	Any	Interrupt MEN1112 until the toxicity improves to grade ≤1, then follow the instructions provided above for grade 3 cytokine release storm/tumor lysis	

Toxicity	CTCAE v.4.03 Grade (duration)	Occurrence	Action on MEN1112 infusion	Action for toxicity
			syndrome lasting ≤7 days at the first occurrence (either during ramp-up or one shot administration, as applicable)	• In case of anaphylaxis: o It is recommended to administer adrenaline (0.01 mg/kg intramuscularly); this can be repeated every 5–15 min. Failure of a prompt response should be followed by administration of i.v. adrenaline o Fluid resuscitation: a rapid infusion of 1–2 litres of normal saline at a rate of 5–10 mL/kg in the first 5 min is recommended. o Vasopressors: dopamine (400 mg in 500 mL of 5% dextrose water) administered at 2–20 mg/kg/min and titrated to increase systolic blood pressure might be required if adrenaline and fluid resuscitation have failed to alleviate hypotension. Vasopressin and norepinephrine may also be used in anaphylaxis that is unresponsive to adrenaline o Antihistamines: the combined use of H1 and H2 antagonists is superior to the use of either alone. Diphenhydramine (1–2 mg/kg or 25–50 mg) may be given slowly i.v. in combination with ranitidine (50 mg) i.v. over 5 min o Corticosteroids: effective in preventing biphasic reactions, but not critical in the management of anaphylaxis. If given, the
Any	1	Any	At Investigator's discretion, either continue the scheduled infusion or interrupt it until the toxicity is resolved; in this latter case follow the instructions provided above for grade 3 cytokine release storm/tumor lysis syndrome lasting ≤7 days at the first occurrence (either during ramp-up or one shot administration, as applicable).	

Toxicity	CTCAE v.4.03 Grade (duration)	Occurrence	Action on MEN1112 infusion	Action for toxicity
				dosing of i.v. corticosteroids is recommended to be equivalent to 1–2 mg/kg of (methyl)prednisolone every 6 h o For bradycardia, it is recommended atropine 600 µg i.v. **Elevated transaminases:** it is recommended to rule out possible alternative/contributing causes. For grade 3 or 4 events, monitoring of liver function tests is recommended to be carried out on a daily basis.

[1] *Adapted from Coiffier et al, J Clin Oncol. 2008 Jun 1;26(16):2767-78 and from Jones et al, Br J Haematol. 2015 Jun;169(5):661-71*

[2] *Adapted from Frey and Porter, Hematology Am Soc Hematol Educ Program. 2016 Dec 2;2016(1):567-572*

[3] *Adapted from Thachil et al, J Thromb Haemost2015;13: 671–5.*

[4] *Adapted from Roselló et al, Ann Oncol (2017) 28 (suppl 4): iv100–iv118*

In case an infusion is interrupted due to drug-related toxicities (not meeting permanent treatment withdrawal criteria), when the infusion is resumed and/or at all subsequent infusions, the infusion duration shall be prolonged to 8 hours (total infusion time), using a constant infusion rate.
In case of grade 3 or 4 Cytokine Release Syndrome (CRS), it is recommended to consider the use of high dose corticosteroids. Intensive-care supportive therapy should be considered for severe or life-threatening CRS, tumour lysis syndrome and/or disseminated intravascular coagulation.

8.4.8 Concomitant Medication

During the study, patients are not allowed to receive:

- Any other investigational agent.
- Any active agent in AML setting (hydroxyurea is allowed throughout the whole duration of the first induction cycle in case of need for WBC count reduction).

Concomitant and prior (i.e. within 30 days before enrolment) medications shall be carefully checked since the use of the above reported medications may represent an exclusion criterion and make the patient ineligible to participate in the study. Furthermore, the regular and occasional use of any concomitant medication has to be recorded starting from Screening until the End of Study Visit.

8.5 STUDY PROCEDURES AND ASSESSMENTS

8.5.1 Study Procedures

Approximately 40 study visits are scheduled for screening, treatment and for assessment of safety, efficacy and pharmacokinetics as depicted in the study flow chart (see §2.2) and summarised below. The End of Study Visit is scheduled 180 days after Visit 1/Day 1.

Written Informed Consent has to be obtained PRIOR to performing any study assessment, as described below:

Screening Period (Day -7 to 0)

- Check of Inclusion/Exclusion Criteria
- Demographic data collection
- Medical and medication general history
- AML history, i.e. date of onset of AML, relapsed or refractory status following the last AML treatment, de novo or secondary AML status, number and category of previous AML treatments (including autologous and allogeneic HSCT), and duration of last CR (for relapsed patients), and disease features when available (i.e. AML karyotype, NPM1 and/or FLT3-ITD mutational status, FAB subtype)
- Physical examination, including vital signs (i.e. blood pressure [BP], heart rate [HR], breathing rate [BR], body temperature [T])
- Weight measurement
- Performance Status (PS) evaluation
- 12-lead ECG
- Blood sampling and urine collection for safety lab tests, including pregnancy test (if applicable)
- Blood sampling for anti-HIV antibodies, anti-HBcAg antibodies, HBV-DNA, HCV-RNA
- [redacted]

- [redacted]
- Blood sampling for immunogenicity assessment
- [redacted]
- Bone marrow aspirate for morphologic assessment, [redacted]
- Recording of AEs and change in concomitant medication

NOTE: Results of laboratory tests for anti-HIV antibodies, anti-HBcAg antibodies, HBV-DNA, HCV-RNA which have been performed within 3 months prior to Screening Period in the context of the standard patient's management (either in the local lab or in a different lab, provided that they comply with local standard procedures) can be reported in the e-CRF under Screening Period procedures and added in the patient file as source documents. In such case, there is no need to repeat the above mentioned tests.

TREATMENT PHASE

CYCLE 1

Visit 1/Day 1, first 3-day *"ramp-up"* dose

Prior to study drug administration

- Re-check inclusion/exclusion criteria and confirmation of patient's eligibility prior to start treatment
- Physical examination, including vital signs
- Weight measurement
- PS evaluation
- 12-lead ECG
- Blood sampling and urine collection for safety lab test
  NOTE: Check that WBC count is $\leq 10 \times 10^9$/L; hydroxyurea is allowed to lower WBC count.
- Blood sampling for PK [redacted] (pre-infusion)
- Recording of AEs and change in concomitant medications
- TLS risk assessment (see *Appendix I: TLS Manual for Investigator*)
- TLS prophylaxis (see *Appendix I: TLS Manual for Investigator*)
- Premedication (see §8.4.2)

Study drug administration

- Study drug administration, given as a 6 h infusion with constant infusion rate
- Blood sampling for safety lab test at following time points after start of infusion: 2h, 4h, 8h, 12h.
- Vital signs every 15 minutes during the first hour of study drug administration and then at the same time points of blood sampling for safety lab test

- 12-lead ECG at the end of infusion
- Blood sampling for PK [redacted] (at the end of infusion, and 6h after the end of infusion)
- Recording of AEs and change in concomitant medications

Visit 2/Day 2(one day after the completion of Visit 1) and Visit 3/Day 3 (one day after the completion of Visit 2)

Prior to study drug administration

- Physical examination, including vital signs
- PS evaluation
- 12-lead ECG
- Blood samplingfor safety lab test
- Blood sampling for PK [redacted] (pre-infusion)
- Recording of AEs and change in concomitant medications
- TLS prophylaxis (see *Appendix I: TLS Manual for Investigator*)
- Premedication (see §8.4.2)

Study drug administration

- Study drug administration, given as 6h infusion with constant infusion rate
- Blood sampling for safety lab test at the following time points after start of infusion: 2h, 4h, 8h, 12h
- Vital signs every 15 minutes during the first hour of study drug administration and then at the same time points of
  blood sampling for safety lab test
- 12-lead ECG at the end of infusion
- Urine collection at the end of infusion (ONLY at Visit 3)
- Blood sampling for PK [redacted] at the end of infusion, 6h after the end of infusion (ONLY at Visit 2), 14h after the end of infusion (ONLY at Visit 3)
- Recording of AEs and change in concomitant medications

Visit 4/Day 4, one day after the completion of the entire first *"ramp-up"*

- Physical examination, including vital signs
- PS evaluation
- Blood sampling for safety lab test
- [redacted]
- Blood sampling for PK [redacted] 24h after the end of last *"ramp-up"* dosing infusion
- Bone marrow aspirate for morphologic assessment, [redacted]

- Recording of AEs and change in concomitant medications

Visit 5-6/Day 5-6, one and two days after Visit 4, respectively

- Blood sampling for PK [redacted] (44h and 68h after the end of last *"ramp-up"* dosing infusion)
- Recording of AEs and change in concomitant medications

Visit 8/Day 8 (five days after the completion of Visit 3), Visit 9/Day 9 (one day after the completion of Visit 8) and Visit 10/Day 10 (one day after the completion of Visit 9), second 3-day *"ramp-up"* administration

Prior to study drug administration

- Physical examination, including vital signs
- Weight measurement (ONLY at Visit 8/Day 8)
- PS evaluation
- Blood sampling for safety lab test
  NOTE: Check that WBC count is ≤ 10 x 10^9/L (**ONLY at Visit 8/Day 8**); hydroxyurea is allowed to lower WBC count.
- Blood sampling for PK [redacted] (pre-infusion)
- Recording of AEs and change in concomitant medication
- TLS prophylaxis (see *Appendix I: TLS Manual for Investigator*)
- Premedication (see §8.4.2)

Study drug administration

- Study drug administration, given as a 6h infusion with constant infusion rate
- Blood sampling for safety lab test at the following time points after start of infusion: 2h, 4h, 8h, 12h
- Vital signs every 15 minutes during the first hour of study drug administration, after then at the same time points of blood sampling for safety lab test
- Blood sampling for PK [redacted] at the end of infusion)
- Recording of AEs and change in concomitant medications

Visit 11/Day 11, one day after the completion of the entire second *"ramp-up"*

- Physical examination, including vital signs
- PS evaluation
- Blood sampling for safety lab test including pregnancy test, if applicable
- Recording of AEs and change in concomitant medications

Visit 12/Day 15, five days after Visit 10, first *"one-shot"* infusion

Prior to study drug administration

- Physical examination, including vital signs
- Weight measurement
- PS evaluation
- Blood sampling for safety lab test

  NOTE: Check that WBC count is $\leq 10 \times 10^9$/L; hydroxyurea is allowed to lower WBC count.
- Blood sampling for PK [redacted] (pre-infusion)
- Recording of AEs and change in concomitant medications
- TLS prophylaxis (see *Appendix I: TLS Manual for Investigator*)
- Premedication (see §8.4.2)

Study drug administration

- Study drug administration, given as a 6h infusion with constant infusion rate
- Blood sampling for safety lab test at the following time points after start of infusion: 2h, 4h, 8h, 12h
- Vital signs every 15 minutes during the first hour of study drug administration, after then at the same time points of blood sampling for safety lab test
- Blood sampling for PK [redacted] (at the end of infusion)
- Recording of AEs and change in concomitant medications

Visit 13-15/Day 16-18, one, two and three days after Visit 12

- Physical examination including vital signs
- PS evaluation
- Blood sampling for safety lab test (at 24h, 48h and 72 h after start of infusion)
- Recording of AEs and change in concomitant medications

CYCLE 2

Visit 16/Day 22, seven days after Visit 12

Prior to study drug administration

- Physical examination including vital signs
- Weight measurement
- PS evaluation
- Blood sampling for safety lab test
- [redacted]
- Blood sampling for PK [redacted] (pre-infusion)
- Bone marrow aspirate for morphologic assessment, [redacted]
- Recording of AEs and change in concomitant medications
- Premedication (see §8.4.2)

Study drug administration

- Study drug administration, given as a 6h infusion with constant infusion rate
- Vital signs every 15 minutes during the first hour of study drug administration and at 15 minutes after end of infusion
- Blood sampling for PK [redacted] (at the end of infusion)
- Recording of AEs and change in concomitant medications

Visit 17-19/ Day 23-25, one, two and three days after the completion of Visit 16, respectively

- Physical examination including vital signs
- PS evaluation
- Blood sampling for safety lab test
- Recording of AEs and change in concomitant medications

Visit 20/Day 29, seven days after the completion of Visit 16

Prior to study drug administration

- Physical examination including vital signs
- Weight measurement
- PS evaluation
- Blood sampling for safety lab test
- Blood sampling for PK [redacted] (pre-infusion)
- Recording of AEs and change in concomitant medication
- Premedication (see §8.4.2)

Study drug administration

- Study drug administration, given as a 6h infusion with constant infusion rate
- Vital signs every 15 minutes during the first hour of study drug administration and at 15 minutes after end of infusion
- Blood sampling for PK [redacted] at the end of infusion
- Recording of AEs and change in concomitant medications

Visit 21-23/Day 30-32, one, two and three days after the completion of Visit 20, respectively

- Physical examination including vital signs
- PS evaluation
- Blood sampling for safety lab test
- Recording of AEs and change in concomitant medications

Visit 24/Day 36, seven days after the completion of Visit 20

Prior to study drug administration

- Physical examination including vital signs

- Weight measurement
- PS evaluation
- Blood sampling for safety lab test
- Blood sampling for PK [redacted] (pre-infusion)
- Recording of AEs and change in concomitant medications
- Premedication (see §8.4.2)

Study drug administration

- Study drug administration, given as a 6h infusion with constant infusion rate
- Vital signs every 15 minutes during the first hour of study drug administration and at 15 minutes after end of infusion
- Blood sampling for PK [redacted] (at the end of infusion and at 1h and 6h after the end of infusion)
- Recording of AEs and change in concomitant medications

Visit 25-27/Day 37-39, one, two and three days after the completion of Visit 24, respectively

- Physical examination including vital signs
- PS evaluation
- Blood sampling for safety lab test including pregnancy test (only at Visit 27, if applicable)
- Blood sampling for PK [redacted] (24h, 48h and 72h after the end of infusion)
- Recording of AEs and change in concomitant medications

Visit 28-29/Day 40-41, one and two days after Visit 27, respectively

- Blood sampling for PK [redacted] (96h and 120h after the end of infusion)
- Recording of AEs and change in concomitant medications

Visit 30/Day 42, the day after Visit 29

- Physical examination including vital signs
- PS evaluation
- Blood sampling for safety lab test
- [redacted]
- Blood sampling for PK [redacted] (144h after the end of infusion)
- Bone marrow aspirate for morphologic assessment, [redacted]
- Recording of AEs and change in concomitant medications

NOTES:

- During Cycle 1, under the *"ramp-up"* dosing scheme, an administration visit will encompass the three *"ramp-up"* infusions (to be split in up to four days, in case of specific infusion-related toxicities, see §8.4.7) to complete the administration of MEN11112.
- Prior to start MEN1112 infusion, results of the safety lab tests (including hepatic function tests) should be duly checked by the Investigator to confirm that eligibility criteria are met (Visit 1/Day 1, prior of infusion) or no treatment withdrawal/dose interruption criteria are met (any subsequent infusion).
- One of the following adjustments is allowed:
  - +1 day for any *"ramp-up"* administration visit in case of WBC count >$10x10^9$/L on the first day of such visit, in order to lower the WBC count using hydroxyurea. This is applicable also to the *"one-shot"* infusion visit of Cycle 1 (Visit 12/Day 15).
  - + 1 day for each study drug administration visit (i.e. first *"ramp-up"* and *"one-shot"* administration visit).
- In case of study visit re-schedule due to infusion related toxicities (see §8.4.7), WBC count recovery, or any other reasons, the interval of 5 days (Cycle 1) or 7 days (Cycle 2) between the end of any study drug administration visit and the start of the following one should be guaranteed.
- Moreover, at each infusion during the study conduct, in case of interruption due to drug-related toxicities:
  - The infusion duration will be prolonged [redacted] using a constant infusion rate; this infusion duration will then be applied to every subsequent infusions.
  - In case the interruption lasts >24 hours, the safety assessments will be repeated when the infusion is resumed according to the time-points scheduled for the original visit.
  - If any interruption occurs during Cycle 1 and the 3rd infusion of Cycle 2, blood sampling for PK & exploratory tests will also be taken at the time of each infusion interruption and just before each infusion resumption.
- During Cycle 1, under the *"ramp-up"* dosing scheme, prior to start each administration visit WBC count should be ≤ 10 x 10^9/L. In case the *"ramp-up"* administration visit is split due to infusion-related toxicities, WBC count should be ≤ 10 x 10^9/L also prior to start the second part of the *"ramp-up"* administration visit.
- During Cycle 1, patients must be treated and monitored as in-patients up to at least 24 hours after each study drug administration visit. [redacted]
- As the consumption of fibrinogen is a marker of disseminated intravascular coagulation, the Investigator shall carefully monitor the fibrinogen decrease rate and consider prompt

treatment with fresh frozen plasma even in the presence of fibrinogen values within normal range.

END of TREATMENT

Visit 31-34/Day 43/50/57/64, one week, two weeks, three weeks and four weeks after Visit 24, respectively)

- Blood sampling for PK [redacted]
- Blood sampling for immunogenicity assessment (ONLY at Visit 34)
- Recording of AEs and change in concomitant medications

NOTE: During the End of Treatment, a time-frame of + 1 day is allowed at any visit, however the scheduled time of the following visits should be maintained.

FOLLOW-UP PERIOD

Visit 35-38/Day 65/85/121/149, one, twenty-nine, fifty-seven and eighty-five days after Visit 34, respectively

- Physical examination, including vital signs
- PS evaluation
- Blood sampling for safety lab test including pregnancy test (if applicable)
- Bone marrow aspirate for morphologic assessment on Visit 35 and Visit 37 only in patients showing peripheral blood labs consistent with CR/CRi/PR
- Recording of AEs and change in concomitant medications.

NOTES:

- To serve the best interest of the patients, for those achieving at least a partial remission, the Sponsor commits to consider providing MEN1112 to allow the prosecution of the infusions at the frequency recommended by the iDSMB on an individual basis and after discussion with the treating Investigator and the Medical Monitor. In this case, premedication and safety assessments will resemble those already described for study drug administration visits, unless differently advised by the iDSMB.
- During Follow-up Period, a time-frame of + 2 days each is allowed at any visit, however the scheduled time of the following visits should be maintained.

END OF STUDY

End of Study Visit (180 days after Visit 1/Day 1)

- Physical examination and vital signs
- PS evaluation
- Blood sampling for safety lab test including pregnancy test (if applicable)
- [redacted]

- Bone marrow aspirate for morphologic assessment, [redacted]
- Recording of AEs and change in concomitant medications

NOTES:

- At the End of Study Visit, a time-frame of + 5 days is allowed.
- All patients shall undergo the End of Study Visit at the scheduled date or at the time of study withdrawal. Unscheduled assessments showing disease progression and leading to patient's withdrawal can replace the End of Study Visit provided that all assessment/procedures scheduled for this visit are completed.
- In case the patient is discontinued from the study within the treatment period, the End of Study Visit bone marrow aspirate is highly recommended to be performed.

GENERAL NOTES:

- For each safety lab test, blood sampling for PK [redacted] (except for those to be collected at the end of infusion) and for vital signs, a window of +/- 5% of the required time interval is allowed.
- The total dose calculated for the first study drug administration can be applied also for the following ones providing that actual patient's weight is within ±10% of the weight measured prior to the first study drug administration; otherwise, the total dose to be given shall be calculated based on the weight measured at the corresponding visit.
- Any effort aimed at preserving patient's safety and/or further clarifying an adverse event is recommended, including unscheduled assessments (e.g. additional safety lab sampling, additional safety lab parameters). The anonymized documentation of the above unscheduled assessment shall be then provided to the Sponsor.
- It is strongly recommended not to start the treatment on the day prior to -or on- weekends/holidays, unless the treatment is deemed not deferrable by the Investigator in view of the specific patient's clinical situation. In such case, the site shall anyway guarantee the actual availability of site personnel as well as the actual feasibility of ALL study procedures as required by the protocol.

8.5.1.1 Sample Analyses

In order to perform safety, pharmacokinetics, immunogenicity, [redacted] from approximately 4 mL to 90 mL (this highest volume taken only during the administration visits of Cycle 1) of whole blood volume needs to be collected per visit.

[redacted]

Details on samples collection, handling and shipment will be provided in separate Laboratory Manuals.

Bone marrow morphologic assessment will be performed on bone marrow blood smears.

[redacted]

- Bone marrow morphologic assessment will be performed locally.

[redacted]

8.5.2 Assessment of Safety

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

- Incidence, severity, seriousness, and treatment related causality of TESS.
- Frequency of clinically significant changes in:
  - Physical examination and vital signs
  - PS Evaluation
  - Safety laboratory tests
  - 12-lead-ECG.

8.5.2.1 Medical History

Complete medical history will be collected during the Screening Period in order to obtain all the information necessary to confirm the study inclusion and exclusion criteria.
General medical history shall include all the diseases (excluding AML) and conditions, either chronic or not, which are needed to assess the compliance with inclusion/exclusion criteria and those which are relevant according to the Investigator.
The AML specific medical history will include: date of onset of AML, relapsed or refractory status following the last AML treatment, *de novo* or secondary AML status, number and category of previous AML treatments (including auto- and allo-HSCT, if any), duration of the last CR/CRi (relapsed patients), AML karyotype (if available), NPM1 mutational status (if available), FLT3-ITD mutational status (if available), FAB subtype (if available) and previous patient's participation in clinical trials (if any).
General medical history shall be collected starting from 30 days prior to screening.
AML specific medical history shall be collected starting from AML onset date.

8.5.2.2 Physical Examinations and Vital signs

A complete physical examination will be performed at each study visit from Screening to End of Study Visit, except at Visit 5-6, Visit 28-29 and during the End of Treatment period; it includes a general appearance observation and a complete exam of the following body systems/areas: Head, Eyes, Ears, Nose and Throat (HEENT)/Neck, Lymph Nodes, Thyroid, Abdomen, Skin, Cardiovascular, Respiratory, Gastrointestinal, Neurological and Musculoskeletal/Extremities.
Vital signs will be recorded throughout the study at each visit except at Visit 5-6, Visit 28-29/ and during the End of Treatment period. At each study drug administration during Cycle 1, vital signs should be measured prior to study drug administration and following the same time points of blood sampling for safety lab tests (see 14.3). At Cycle 2, they should be measured prior to study drug administration, every 15 minutes during the first hour of study drug administration and 15 minutes after the end of infusion. The following parameters will be measured:

- Heart rate (HR, beats / min)
- Blood pressure (BP, systolic and diastolic, mmHg)
- Breathing rate (BR, breaths / min)
- Body temperature (T, °C).

8.5.2.3 Weight measurement

Body weight (to the nearest 0.1 kilogram [kg] in indoor clothing, but without shoes) will be measured during screening period and at study drug administration visits (during Cycle 1 only prior to the first *"ramp-up"* dose and at Visit 12/Day 15).

8.5.2.4 PS evaluation

Performance Status evaluation will be performed throughout the study at each visit except at Visit 5-6, Visit 28-29 and during End of Treatment period. The ECOG scale will be used.

8.5.2.5 12-Lead ECG

12-Lead ECGs will be performed locally, using standard equipment available at the study sites, during Screening Period and at Visit 1/Day 1, Visit 2/Day 2 and Visit 3/Day 3 (prior to and at the end of the study drug infusion).

Standard 12-Lead ECG will be performed at rest in the supine position. All ECG print-outs should be identified with patient number, year of birth and gender, as well as with the date and time of recording. All print-outs should be assessed, dated and signed by the Investigator and stored in the patient's record.

8.5.2.6 Clinical laboratory evaluation

Safety laboratory assessments will be performed at each study visit except at Visit 5-6, Visit 28-29 and during End of Treatment. Pregnancy test will be performed, if applicable, during Screening Period, at Visit 11, at Visit 27, at Visits 35-38 and at the End of Study Visit. In addition, female patients of childbearing potential are required to undergo a monthly pregnancy test until 6 months from the last study drug administration. Urinalysis will be assessed prior to and at the end of the first *"ramp-up"* administration visit (Visit 1/Day 1, Visit 2/Day 2 and Visit 3/Day 3). The assessment of anti-HIV antibodies, anti-HBcAg antibodies, HBV-DNA and HCV-RNA will be performed ONLY during the Screening Period. Safety tests will be performed by the local laboratory of participating sites in order to ensure prompt patient management. For the same reason, tests for anti-HIV antibodies, anti-HBcAg antibodies, HBV-DNA and HCV-RNA will be performed by the local laboratory of participating sites according to local standard procedures. Results of laboratory tests for anti-HIV antibodies, anti-HBcAg antibodies, HBV-DNA, HCV-RNA which have been performed within 3 months prior to Screening Period in the context of the standard patient's management (either in the local lab or in a different lab, provided that they comply with local standard procedures) can be reported in the e-CRF under Screening Period procedures. In such case, there is no need to repeat the above mentioned tests.

Laboratory values have to be transcribed into the e-CRF, except for the urinalysis where only the judgment will be reported; the Sponsor will be provided by the site laboratories with the currently valid version of the respective normal ranges (any update of reference ranges needs to be notified on an ongoing basis).

The lab print-outs should be identified with the patient number. All print-outs should be dated and signed by the Investigator and stored in the patient's record. Any out of range value shall be clinically assessed by the Investigator.

The volume of blood to be drawn for each battery of safety lab tests will amount to approximately 15 mL.

The following tests will be performed:

Table 3: *Serum, Blood and Urine Sample Analyte Listing*

SERUM CHEMISTRY	SERUM VIROLOGY	HAEMATOLOGY	URINALYSIS
Creatinine	Anti-HIV antibodies	Haemoglobin	pH
Uric acid	Anti-HBcAg antibodies	Haematocrit	Density
Potassium	HBV-DNA	RBC count	
Phosphorus	HCV-RNA	Platelet count	
		MCV	
Calcium		WBC count and differential (absolute and %):	Nitrite
BUN/Urea		neutrophil	Protein
Albumin		lymphocyte	Glucose
Alkaline phosphatase		eosinophil	Ketones
Glucose		basophil	RBC
Total proteins		monocytes	WBC
Total bilirubin and Direct bilirubin		blasts	Epithelial cells
ALT and AST			Casts
LDH			Bacteria
GGT			Yeast
INR			Crystals
Prothrombin time and/or prothrombin activity			
Partial thromboplastin time			
Fibrinogen			
D-dimer			
Amylase			
Sodium			
Chloride			
Beta-HCG (if applicable)			

8.5.2.7 Adverse Events/Serious Adverse Events – Definitions

8.5.2.7.1 Adverse Event (AE)

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. An AE can, therefore, 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.

8.5.2.7.2 Adverse Drug Reaction (ADR)

All 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.

8.5.2.7.3 Intensity (severity) of an Adverse Event / Adverse Drug Reaction

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 14.4). The highest intensity grade reached in a given cycle should be reported in the e-CRF:

- **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.

NOTE: ***In case of an AE/ADR consisting of a laboratory abnormality, its intensity (severity) should be ranged based on the level of abnormality of the out –of-range value and/or its interference on patient ability to perform daily routine activities, as above defined.*** *A severe AE, as defined by the above grading scale, is NOT the same as serious AE which is defined in §8.5.2.7.4.*

* *Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0. Published: May 28, 2009 (v4.03: June 14, 2010). U.S.DEPARTMENT OF HEALTH AND HUMAN SERVICES National Institutes of Health National Cancer Institute (please refer to Appendix IV).*

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

Any untoward medical occurrence or effect that at any dose:

- results in death.
- is life-threatening.

NOTE: *the term life-threatening in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.*

- requires patient hospitalisation or prolongation of existing hospitalisation.
- results in persistent or significant disability/incapacity.
- is a congenital anomaly/birth defect.
- is an 'important medical event' that may jeopardise the patient or may require an intervention to prevent one of the above characteristics/consequences.

NOTE: *Hospitalisation lasting less than 24 hours or pre-planned hospitalisation for medical intervention, such as chemotherapy administration, shall not qualify as SAE.*

Any other AE/ADR which is not included in the above definitions will be considered as non-serious.
The Investigator should also promptly report all the SAEs to the Sponsor's Drug Safety Manager (DSM, see §8.6).

8.5.2.7.5 Unexpected Adverse Drug Reaction

An ADR, the nature or intensity of which is not consistent with the applicable product 'safety reference information (e.g. IB for an unauthorised investigational product or summary of product characteristics (SmPC) for an authorised product).
Any other ADR which is not included in the above definition will be considered as expected.

NOTE: *In this study, the reference document is the MEN1112 IB, last version approved..*

8.5.2.7.6 Algorithm for Causality Assessment of Adverse Events

The causality (causal relationship to the study drug) of AEs will be assessed based on the following algorithm:
1. Certainly related: An AE, including a laboratory test abnormality assessed as CS, is considered certainly related to a drug when it occurs in a plausible time relation to the administration of the drug, and which cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (de-challenge) should be clinically plausible. The event must be definitely related, pharmacologically or phenomenologically, using a satisfactory re-challenge procedure if necessary.
2. Probably related: An AE, including a laboratory test abnormality assessed as CS, is considered probably related to a drug when it occurs in a reasonable time relation to the administration of the drug, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (de-challenge). Re-challenge information (AE reappearance after drug reintroduction) is not required to fulfil this definition.
3. Possibly related: An AE, including a laboratory test abnormality assessed as CS, is considered possibly related to a drug when it occurs in a reasonable time relation to the administration of the drug, or it could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal (de-challenge) may be lacking or unclear.
4. Unlikely related: An AE, including a laboratory test abnormality assessed as CS, is considered unlikely related to a drug when other drugs, chemicals or underlying disease provide plausible explanations and/or the temporal relation to the administration of the drug makes a causal relation improbable.

5. Not related: An AE, including a laboratory test abnormality assessed as CS, is considered not related to the use of a drug in case of existence of a clear alternative explanation and/or unreasonable temporal relationship, and/or non plausibility.
6. Unassessable/unclassifiable: The relationship between drug and AE, including a laboratory test abnormality assessed as CS, is considered unassessable/unclassifiable when a report, suggesting an AE, cannot be judged because information is insufficient or contradictory and cannot be supplemented or verified.
An AE in which the relationship is ranked 1, 2, 3 or 6 is defined as an ADR. AEs ranked 4 or 5 are not considered as ADRs.

8.5.2.8 Monitoring and Recording of Adverse Events

The Investigator is responsible for the detection and documentation of events meeting the definition of AE, as provided in this protocol (see § 8.5.2.7.1).
All AEs, whether or not thought to be drug related, must be actively followed-up and recorded by the Investigator (or designee) in the source documents and in the appropriate section of the e-CRF throughout the whole study duration, starting from the Informed Consent signature to the End of Study Visit or 70 days after last study drug administration whichever occurs last.
***NOTE*:** An AE will be considered as **'Treatment-Emergent Signs and Symptoms (TESS)'** if it occurs for the first time or if it worsens in terms of seriousness or severity after the first study drug intake (Visit 1).

8.5.3 Pharmacokinetic Evaluation

Blood samples for MEN1112 serum concentration measurements will be taken during Treatment phase and End of Treatment as depicted in § 14.2. If any interruption occurs during Cycle 1 and the 3rd infusion of Cycle 2 (i.e. where the PK is evaluated), blood sampling for PK & exploratory tests will be taken at the time of each infusion interruption and just before each infusion resumption.

[redacted]

C_{max}	Maximum observed serum concentration.
t_{max}	Time to C_{max}.
C_{last}	Last quantifiable serum concentration.
t_{last}	Time to C_{last}.
C_{trough}	Pre-dose serum concentration.
C_{avg}	AUC from dose time to τ (i.e. dosing interval) divided by τ

k_e	Apparent terminal elimination rate constant, estimated by log-linear regression analysis on serum concentrations visually assessed to be on the terminal log-linear phase.
$t_{½}$	The terminal serum half-life, calculated according to the following equation: $t_{1/2} = \frac{0.693}{k_e}$
$AUC_{(0\text{-}t)}$	Area under the serum concentration-time curves from time zero (pre-dose) to the time of the last quantifiable concentration, calculated by means of the linear-log trapezoidal method.
$AUC_{(0\text{-}\infty)}$	Area under the serum concentration-time curve from time zero to infinity, calculated according to the following equation: $AUC_{(0\text{-}\infty)} = AUC_{(0-t)} + \frac{C_{last}}{k_e}$
$\%AUC_{ex}$	The percentage of $AUC_{(0\text{-}\infty)}$ obtained by extrapolation calculated as follows: $AUC_{ex}(\%) = \frac{AUC_{(0-\infty)} - AUC_{(0-t)}}{AUC_{(0-\infty)}} \cdot 100$
CL	Systemic clearance, calculated according to the following equation: $CL = \frac{Dose}{AUC_{(0\text{-}\infty)}}$
V_{ss}	Volume of distribution at steady state, calculated according to the following equation: $V_{ss} = CL \cdot MRT$
V_d	Volume of distribution based on the terminal phase, calculated according to the following equation: $V_d = \frac{Dose}{k_e \cdot AUC_{(0\text{-}\infty)}}$
$AUMC_{(0\text{-}\infty)}$	The area under the first moment curve from zero to infinity calculated using the equation: $AUMC_{(0\text{-}\infty)} = \sum_{i=0}^{n-1} \frac{t_{i+1} - t_i}{2}(C_i t_i + C_{i+1} t_{i+1}) + \frac{tlast \cdot Clast}{k_e} + \frac{Clast}{k_e^2}$ $+ \frac{t \cdot C_t}{\lambda_z} + \frac{C_t}{\lambda_z^2} + \frac{t \cdot C_t}{\lambda_z} + \frac{C_t}{\lambda_z^2} + \frac{t \cdot C_t}{\lambda_z} + \frac{C_t}{\lambda_z^2}$
MRT	Mean residence time (for drug given with a constant infusion rate over a period T_{inf}) was calculated as: $MRT = \frac{AUMC_{(0\text{-}\infty)}}{AUC_{(0\text{-}\infty)}} - \frac{T_{inf}}{2}$
Ro	Accumulation ratio calculated as: $Ro = \frac{1}{\lvert 1 - e^{-k_e \tau} \rvert}$

PK parameters will be calculated, as data permit, following each of the three doses of the first *"ramp-up"* administration visit during Cycle 1 and following the third *"one-shot"* administration visit during Cycle 2.

The following PK variables will be assessed following the 1st and 2nd dose of the first *"ramp-up"* administration visit during Cycle 1:

- C_{max}, t_{max}, C_{trough}, C_{avg}, $AUC_{(0-t)}$

The following PK variables will be assessed following the 3rd dose of the first *"ramp-up"* administration visit during Cycle 1:

- C_{max}, t_{max}, C_{trough}, C_{avg}, C_{last}, t_{last}, $AUC_{(0-t)}$, $AUC_{(0-\infty)}$, $\%AUC_{ex}$, k_e, $t_{1/2}$, CL, V_{ss}, Vd, $AUMC_{(0-\infty)}$, MRT.

Total AUC following the first *"ramp-up"* administration visit during Cycle 1 will be calculated as the sum of $AUC_{(0-t)}$ related to each dose.

The following pharmacokinetic variables will be assessed following the 3rd *"one-shot"* administration visit during Cycle 2:

- C_{max}, t_{max}, C_{trough}, C_{avg}, C_{last}, t_{last}, $AUC_{(0-t)}$, $AUC_{(0-\infty)}$, $\%AUC_{ex}$, k_e, $t_{1/2}$, CL, V_{ss}, Vd, $AUMC_{(0-\infty)}$, MRT, accumulation ratio (Ro).

Actual PK sampling times will be used in the derivation of PK parameters. Alternatively, it is also acceptable to consider the planned sampling times if they do not deviate by more than 5% from the actual. Planned sampling times may be used as a replacement for unknown or missing actual times.

The calculation of the parameters listed above and others will depend upon the results of the drug concentration assay and the duration of drug infusions.

For the calculation of individual pharmacokinetic parameters, values Below the Lower Limit Of Quantification (BLLOQ) will be handled as follows:

1. BLLOQ values located before the t_{max} of their affiliating curve will be transformed to zero.
2. If a BLLOQ value located after the t_{max} falls between two quantifiable concentrations, it will be omitted from the pharmacokinetic analysis.
3. If, within a dosing interval, two or more BLLOQ values occur in succession after quantifiable concentrations, the profile will be deemed to have terminated at the first BLLOQ value and any subsequent concentrations in that dosing interval will be omitted from the non-compartmental analysis.
4. In some circumstances, when a pharmacokinetic rationale exists, BLLOQ values may be set to some other values, e.g., half of the Lower Limit of Quantification (LLOQ).

Concentrations reported as >LLOQ at time zero, when the subject has not previously been dosed, will be set to zero.

[redacted]

8.5.4 Pharmacokinetic and Safety Endpoints

8.5.4.1 Primary Endpoints

- Identification of **DLT** defined as an adverse event occurring during the first treatment cycle, judged to be related to MEN1112 and meeting any of the following criteria:
    - Grade 3 non-haematological toxicity lasting more than 7 days
    - Grade ≥ 4 non-haematological toxicity.

  Note: Common complications of AML (in particular infections, bleedings, fatigue) will not contribute to DLT assessment.
- Identification of **MTD** defined as one dose level below the Maximum Administered Dose (i.e. one dose level below the one at which ≥ 2 DLTs out of 6 treated patients occur).

8.5.4.2 Secondary Endpoints

- **Immunogenicity Evaluation Criteria:** Incidence of anti-MEN1112 autoantibodies.
- **Clinical Evaluation Criteria:**
    - Complete remission (CR) rate at any time point, where CR is defined as: bone marrow blasts <5%, absence of extramedullary disease, absolute neutrophil count >1 x 10^9/L and platelet count > 100 x 10^9/L.
    - Composite complete remission (CRc) rate at any time point, defined as the proportion of patients having either CR or CRi (where CRi is defined as: all criteria for CR except residual thrombocytopenia [platelets <100 x 10^9/L] and/or neutropenia [absolute neutrophil count <1 x 10^9/L]).
    - Best response rate, defined as the best observed response at any time point between CR, CRi and partial remission ([PR]: all haematologic criteria for CR with bone marrow blasts 5-25% and decrease of pre-treatment bone marrow blast percentage by at least 50%).
    - Duration of CRc: number of days between the date of CR/CRi achievement and the date of the last assessment confirming CR/CRi.
    - Overall Survival (OS), defined as the number of days between the first study drug administration and death from any cause.
    - Correlation of baseline characteristics with clinical activity of MEN1112.

[redacted]

8.5.4.4 Safety Endpoints

- Incidence, severity, seriousness and treatment related causality of Treatment Emergent Signs and Symptoms (TESSs).
- Frequency of clinically significant abnormalities in physical examination, safety laboratory tests, vital signs and 12-Lead ECG.

8.5.4.5 Pharmacokinetic Endpoints

PK parameters will be calculated, as data permit, following each of the three doses of the first *"ramp-up"* administration visit during Cycle 1 and following the third *"one-shot"* administration visit during Cycle 2.

The following PK variables will be assessed following the 1st and 2nd dose of the first *"ramp-up"* administration visit during Cycle 1: C_{max}, t_{max}, C_{trough}, C_{avg}, $AUC_{(0-t)}$.

The following PK variables will be assessed following the 3rd dose of the first *"ramp-up"* administration visit during Cycle 1: C_{max}, t_{max}, C_{trough}, C_{avg}, C_{last}, t_{last}, $AUC_{(0-t)}$, $AUC_{(0-\infty)}$, $\%AUC_{ex}$, k_e, $t_{1/2}$, CL, V_{ss}, Vd, $AUMC_{(0-\infty)}$, MRT. Total AUC following the first *"ramp-up"* administration visit during Cycle 1 will be calculated as the sum of $AUC_{(0-t)}$ related to each dose.

The following pharmacokinetic variables will be assessed following the 3rd *"one-shot"* administration visit during Cycle 2: C_{max}, t_{max}, C_{trough}, C_{avg}, C_{last}, t_{last}, $AUC_{(0-t)}$, $AUC_{(0-\infty)}$, $\%AUC_{ex}$, k_e, $t_{1/2}$, CL, V_{ss}, Vd, $AUMC_{(0-\infty)}$, MRT, accumulation ratio (Ro).

8.6 MANAGEMENT AND REPORTING OF ADVERSE EVENTS

8.6.1 Reporting of Serious Adverse Events to the Sponsors

All SAEs, whether or not deemed drug-related or expected, must be reported in the corresponding section of the e-CRF within 24 hours (one calendar day) of awareness. Once the information is saved, a notification e-mail will be automatically generated and sent to the Sponsor's DSM.

SAE Report Forms in paper support will be provided as a backup, to be used only in case of breakdown of the e-CRF System. In such case, the Investigator will be responsible for sending the SAE paper form and inserting the data in e-CRF as soon as the system works again.
Whenever paper SAE report forms are used, they must be submitted by e-mail to the Sponsor's DSM.

The initial SAE entry should include at least the following data:

- A short description of the AE.
- Reason why the AE is categorised as serious (seriousness assessment) according to criteria described in § 8.5.2.7.4.
- Causality assessment (according to the algorithm described in § 8.5.2.7.6).
- Study Code and Patient Identification (patient number) [If paper SAE Report Form is used].

If not already reported, the full description of the event and outcome must follow within 1 working day.

The Sponsor's confirmation of reception of the SAE report must be kept in the patient's records.

Any questions arisen during the processing and medical review of the SAE will be managed by means of electronic queries (i.e. queries in the e-CRF).

Any information provided by the Investigator as a query reply or as a follow-up SAE report will be processed in the same way as the initial SAE report within the required timeframe.
When relevant, the e-CRF pages concerning medical history, concomitant medication and laboratory tests will also be retrieved by the Sponsor's SDSM.
Any further significant information and supporting documentation that may become available (such as copies of laboratory reports, tests, procedures, autopsy evidence of the cause of death, etc.) shall

be provided to the Sponsor's SDSM by email no later than 24 hours after they become known by the Investigator.

8.6.2 Management of Suspected Unexpected Serious Adverse Reactions and other relevant safety issues

For each SAE, assessment of seriousness (according to § 8.5.2.7.4), causality (according to §8.5.2.7.6) will be provided by both, the reporting Investigator and the Sponsor. The assessment of expectedness (according to §8.5.2.7.5) will be done by the Sponsor.

NOTE: *The causality assessment given by the Investigator will not be downgraded by the Sponsor. If the Sponsor disagrees with the Investigator's causality assessment, the opinions of both, the Investigator and the Sponsor, will be provided.*

SUSARs (Suspected Unexpected Serious Adverse Reaction) are AEs which, cumulatively:

- have a reasonable possibility of causal relationship to the IMP
- are serious
- are unexpected

The Sponsor will ensure that all SUSARs occurred during the study are reported on an expedited basis (7 days or 15 days) to the concerned national CAs and ECs, according to European and/or country-specific legal requirements:

- For fatal and life-threatening SUSARs: the Sponsor should report at least the minimum information, as soon as possible, and in any case no later than 7 days after being made aware of the case. If the initial report is incomplete, the Sponsor is to submit a completed report based on the initial information within an additional 8 days.
- SUSARs which are not fatal and not life-threatening are to be reported within 15 days.
- The clock for expedited initial reporting (day zero) starts as soon as the information containing the minimum reporting criteria has been received by the Sponsor (or the Sponsor's delegate).
- If significant new information on an already reported case is received by the Sponsor, the clock starts again at day zero (i.e. the date of receipt of new information). This information should be reported as a follow-up report within 15 days.

The Sponsor will also inform all investigators. Whenever practicable, the information will be aggregated in a 6 monthly cumulative 'line listing' of SUSARs (with a brief safety assessment report), as required, per country regulations.

Apart from SUSARs, the following safety issues will be subjected 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 drug.

8.6.3 Management of Non-Serious Adverse Events (NSAES) and/or Laboratory Abnormalities

The Investigator must record all the available information concerning any NSAE (whether or not deemed related to the investigational drug) in the corresponding section of the eCRF: eCRF-AE pages, **within 5 calendar days** after the first knowledge of the occurrence of the event.

When relevant, e-CRF pages concerning medical history, concomitant medication and laboratory test will also be retrieved by the Sponsor's SDSM.

In addition, during the clinical study, abnormalities in laboratory tests (newly occurring after ICF signature or worsening of previously known abnormalities), which are considered clinically significant by the Investigator (such as values significantly above or under normal range or which require an intervention or diagnostic tests, or which may result in the IMP discontinuation), should be reported as AEs. Furthermore, all abnormalities in laboratory values should be collected and reviewed by Sponsor on a monthly basis.

8.6.4 Annual Safety Reporting

Once a year throughout the clinical trial, the Sponsor will provide the concerned national CAs and ECs with a safety report (Development Safety Update Report, DSUR), taking into account all new safety information received during the reporting period.

8.6.5 Breaking of the Randomisation Code

Not applicable.

8.6.6 Serious and Non-Serious Adverse Event Follow-Up

After the End of Study Visit or 70 days after last study drug administration whichever occurs last, the Investigator is not requested to actively follow-up the patient unless ongoing SAEs or non-serious AEs of special interest (as per CRC/iDSMB indication) are present. ***However, if the Investigator becomes aware of any SAE with a suspected causal relationship to the IMP after the end of the study, the Investigator shall, without undue delay, report the SAE to the Sponsor. These SAEs should be also recorded in the e-CRF as far as it is available. If the e-CRF is not available, the paper SAE form will be used as a backup.***

Patients who have discontinued the treatment for any reason will be followed up for at least 10 weeks after the last drug dose, or until recovery from all toxic effects or longer in case of expected delayed toxicity.

8.7 MANAGEMENT OF POSITIVE PREGNANCY TEST

Pregnancy tests will be performed, if applicable, during Screening Period, at Visit 11, at Visit 27, at Visits 35-38 and at the End of Study Visit. In addition, female patients of childbearing potential are required to undergo a monthly pregnancy test until 6 months from the last study drug administration. Pregnant women are excluded from the enrollment onto the study. In case a patient becomes pregnant during the study period, she shall be discontinued from treatment and the pregnancy followed up until the outcome.

The Investigator is expected to record in the provided "Pregnancy Exposure Report Form" any case of pregnancy occurring in a female patient participating in the study, during the treatment and until 6 months from the last study drug administration. The mentioned form will be sent by e-mail to the Sponsor's DSM within 5 calendar days after being made aware of the pregnancy. The "Pregnancy Exposure Report Form" is distributed to the sites to be used for this purpose.

The Investigator is requested to follow up each case of pregnancy exposure until the completion or termination of the pregnancy. If the pregnancy continues to term, the "Pregnancy Exposure Report Form" must be completed with the outcome (health status of the newborn infant) and sent to the Sponsor's SDSM again within 5 days after the outcome is known. If the pregnancy results in an abnormal outcome (miscarriage or new-born with congenital abnormality and/or stillbirth), in addition to completing the "Pregnancy Exposure Report Form", this will be recorded in the e-CRF as a SAE and managed as above described in § 8.6.1.

8.8 INDEPENDENT DATA SAFETY MONITORING BOARD

Starting from protocol version 6.1/6.2, an independent Data Safety Monitoring Board (iDMSB) made by a panel of independent AML experts is introduced. In the Step 1, the iDSMB will be

responsible to review dose escalation data and make dose escalation decisions; moreover, the iDSMB will review and assess the data collected during the Step 2 of the study.
Roles and responsibilities of the iDSMB are detailed in a separate DSMB Charter.

9. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

9.1 DETERMINATION OF SAMPLE SIZE

Due to the nature of the study, no formal sample size calculation is applicable. [redacted]

Starting from protocol version 6.1/6.2, up to approximately 6 DLT evaluable patients per dose level will be treated with MEN1112 during the dose escalation phase, while up to approximately 30 patients will be treated in the cohort expansion phase. Considering that the patients no-DLT evaluable during the dose escalation phase will be replaced, and assuming a drop-out rate of 30%, up to approximately 60 patients will be treated with MEN1112. This number might be higher in case additional intermediate dose levels will be investigated.

9.2 ANALYSIS POPULATIONS

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

- **Safety population:** all patients receiving study drug.
- **DLT population:**
  [redacted]
  Starting from protocol version 6.1/6.2 and following amendments:
  - All patients receiving at least 80% of the scheduled study drug administration during the first treatment cycle and with a safety follow-up of at least 6 days after the last administered dose or having experienced a DLT.
- **Efficacy population:** all patients completing the first treatment cycle and having a post-cycle peripheral blood lab test and bone marrow aspirate.
- **PP population:** all patients of the efficacy population excluding patients who experience major protocol violation(s).
- **PK population:** all patients receiving the study treatment and with reliable drug assay data relevant for the PK parameter of interest.

9.3 STATISTICAL ANALYSIS

9.3.1 Descriptive statistics

All study variables (with the exception of PK 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, standard deviation (SD), minimum, median, 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% CI, 3rd quartile, Kaplan-Meier survival curves and event rate every 21 days.

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

- Continuous variables: descriptive statistics for each time point and for the absolute/percentage differences to baseline.
- Discrete variables: descriptive statistics for each time point and shift tables to baseline.

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.

9.3.2 Efficacy Analysis

Efficacy analyses will be performed only through descriptive statistics.

9.3.3 Pharmacokinetic Analyses

The PK analysis will be run on the PK population. All PK variables (i.e. serum concentrations and parameters) will be summarized by cohort using the following descriptive statistics:

- Number of non-missing observations (N),
- Arithmetic mean and its 90% CI, SD, coefficient of variation (CV%) and standard error (SE),
- Geometric mean (GM) and its 90% CI and GM CV%,
- Minimum, median, maximum.

The concentration of MEN1112 will be summarized for each scheduled sampling time point (see *Appendix II: Timings of Blood sampling for PK* [redacted]) using descriptive statistics. Individual serum concentration data versus time will be presented in a data listing and visualized as

individual concentration-time plots. Additional analyses, if deemed appropriate, will be described in the statistical analysis plan.

For descriptive statistics, BLLOQ concentrations at time zero, when the subject has not previously been dosed, will be set to zero. All other BLLOQ values will be substituted by ½ LLOQ value before the calculation of the summary statistics.

9.3.4 Safety analysis

Safety and toxicity will be evaluated on the safety population by means of descriptive statistics during each study phase. Summary statistics (counts, %) will report the incidence of the AEs by CTC toxicity grade, dose level, cycle of therapy, relationship to study drug and overall. Counts and percentages will be produced for the results of the ECG, laboratory values, vital signs, physical examination, all classified as Normal/Abnormal NCS/Abnormal CS by dose level and therapy cycle.
Descriptive statistics will also be produced for the extent of exposure, overall drug(s) administration, drug(s) administration by dose(s) level, and dose(s) delay by dose(s) level.

9.3.5 Data Imputations

The missing values will not be imputed because, for all the analyses, an observed-cases approach will be applied.

9.4 PROTOCOL VIOLATIONS AND DATA REVIEW MEETING

Categories of protocol violations will be defined and will be integrated in the statistical analysis.
For the primary efficacy analysis, a Data Review Meeting (DRM) will take place at the end of the study in order to evaluate and accept the data management report, discuss remaining issues (outstanding queries, unresolved errors) and to confirm and approve relevant protocol violations. After this final DRM has taken place and the database is considered cleaned, the database will be locked.

9.5 STATISTICAL ANALYSIS PLAN

The SAP will be finalised before the lock of the study database. The SAP will describe in detail study endpoints and the statistical analyses, including the statistical analysis of the primary endpoint to be performed, including also additional endpoints and analyses not planned in the protocol. In case changes of the original primary endpoint or of the original primary analyses occur during the study, these changes will be the subject of a substantial protocol amendment.
Minor deviations (e.g. not involving changes in the primary endpoint and analysis) which might occur during the study will be detailed only in the SAP. All statistical analyses not pre-specified and run after data lock will be considered additional/exploratory analyses.

10. DATA QUALITY MANAGEMENT

10.1 DATA COLLECTION

Data collection activities will be carried out under the responsibility of the Sponsor. Patient data will be collected using an Electronic Data Capture system (EDC see §10.1.1). Patients will be identified by the patient study identification number (patient ID), assigned during the Screening Period.

[redacted]

Data will be collected, processed, evaluated, reviewed and stored in anonymous form in accordance with applicable data protection regulations.

10.1.1 Case Report Forms

Clinical data collected during the study at sites will be recorded in an electronic Case Report Form (e-CRF) using [redacted], which is a validated system. The Sponsor will be responsible for developing the e-CRF based on this study protocol and to review and perform the user acceptance test of the e-CRF in order to ensure protocol adherence.

The e-CRF will be made available to the study personnel by means of the [redacted] The accounts will be individual and password-protected.

The Investigator or designee will be responsible for entering study data into the e-CRF in accordance to the e-CRF Completion Guidelines provided by the Sponsor. In order to improve the quality of data collection and cleaning, data shall be entered into the e-CRF as closely as possible to the time when they become available and in any case within 5 working days.

The e-CRF data will not be considered as source data. The definition of the source data can be found in section 10.3.

Investigators will ensure the accuracy, completeness and consistency of data entered electronically signing the e-CRF using a personal password. An audit trail within the system will track all changes made to the data.

10.1.2 Central Laboratory/Examination data

The following Central Laboratories will be used during the study:

- [redacted]

[redacted]

10.1.3 Data capture systems versions and validation documentation

Versions of EDC system could change during the study. The Sponsor will maintain a list of the data capture system versions used and the validation documentation of each version. The list and the validation documentation will be provided to the site at the Site Initiation Visit (SIV) and will be updated at any EDC version change.

10.2 CLINICAL DATA MANAGEMENT

Data Management will be carried out under the responsibility of the Sponsor.

e-CRF data will be electronically verified through the use of automatic and manual checks. Discrepancies in the data will be resolved by means of electronic queries. Data will be frozen after source data verification by the Monitor, and they will be locked by the Data Managers when all activities for the trial, including medical and safety revision of the data, are complete and no more entries are expected.

Data from sources other than e-CRF will be provided to the Data Manager on an agreed scheduled basis. The Data Manager has the responsibility to reconcile data captured in the e-CRF with external data sources. Discrepancies found in the reconciliation of the data will be addressed by means of queries.

A clear overview of all clinical data management activities will be given in the Data Management Plan.

10.3 SOURCE DATA

Source data are defined as all data in original records and certified copies of original records of clinical findings, observations or other activities in a clinical trial that are necessary for the reconstruction and evaluation of the trial.

Original documents and data records include, but are not limited to, hospital/patients' medical records, laboratory notes, ECG records, patients' evaluation checklists, pharmacy dispensing records.

Study sites will also maintain paper drug accountability forms for the IMP to document dispensed and returned IMP per patient.

Source data should be held available for inspection by Sponsor representatives for the study or other authorised persons, such as auditors and inspectors of Regulatory Authorities.
Direct access to source data is defined as permission to examine, analyse, verify and reproduce any records and reports that are important for evaluation of a clinical trial. Any party allowed direct access to study source data and documents should take all reasonable precautions within the constraints of the applicable regulatory requirements to maintain the confidentiality of patient identity and sponsor proprietary information.
Data that are derived from the source documents should be consistent with the source documents and discrepancies, if any, should be explained in writing.
All the original documentation pertinent to the study procedures must be available for review in each patient's record.

10.4 QUALITY CONTROL/QUALITY ASSURANCE

10.4.1 Study Monitoring

This trial will be monitored in accordance with the ICH Note for Guidance on Good Clinical Practice. Monitoring and will be carried out by the CRO, [redacted] The site monitor will perform visits to the trial sites during the study conduct. At each monitoring visit, the facilities, study drug, storage conditions for immunogenicity, [redacted] and blood sampling for PK [redacted], storage area, e-CRF, patient's source data, and all other study documentation will be inspected/reviewed by the site monitor for adherence to the protocol and Good Clinical Practice. At each site visit, the monitor will review the e-CRFs for completion and accuracy. Accuracy will be checked by performing source data verification that is a direct comparison of entries made onto the e-CRFs against the appropriate source documentation. Any resulting discrepancies will be reviewed with the Investigator and his/her staff.
The Investigator agrees to allow access to all study related materials needed for the proper review of study conduct and to assist the monitor during the monitoring visits and during the data cleaning process. Monitoring procedures require that 100% of data are source data verified, particularly focusing on informed consents, adherence to inclusion/exclusion criteria, drug accountability, documentation of SAEs and the proper recording of efficacy and safety measurements.
All monitoring activities will be described in detail in the study-specific Monitoring Plan.

10.4.2 Quality Assurance

Independent study audit(s) and/or inspection(s) may take place at any time during or after the trial. The Independent audits/inspections can be carried by the Quality Assurance (QA) Department of the CRO, the independent Sponsor QA, or a Competent Authority. At all times, the confidentiality of patient related documents will be maintained.

11. PREMATURE TERMINATION OF THE WHOLE STUDY

The whole trial may be discontinued at the discretion of the Sponsor in the event of any of the following:

- New information leading to unfavourable risk-benefit judgement of the investigational products due to:
  - Occurrence of clinically significant unknown AEs or unexpectedly high severity or incidence of known AEs
  - New evidence of unfavourable safety or efficacy findings (from clinical or non-clinical examinations, e.g. toxicology)
- The Sponsors decision that continuation of the trial is unjustifiable for medical or ethical reasons
- Discontinuation of development of the IMP.

Competent Authorities and IRB/IECs will be informed about the discontinuation of the trial in accordance with applicable regulations.

12. END OF CLINICAL TRIAL AND ARCHIVING

The clinical trial 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.

12.1 ARCHIVING OF ELECTRONIC DOCUMENTATION/DATA

Duplicate electronic media [redacted] containing the patient data in PDF format (i.e. e-CRFs) for each site will be prepared by the Sponsor or a delegate for archiving purposes. [redacted]

Patient data relevant for each site will be distributed to the Investigator, who has to confirm the receipt of the material, verify whether the provided electronic media represent a copy of data generated during the study and sign a dedicate form provided by the Sponsor, the signed form has to be collected and archived at the Sponsor TMF.

[redacted] In addition, the Sponsor is responsible for creating 2 electronic media [redacted] containing an integrated [redacted] database with all study data (e.g.: e-CRF, central laboratory); [redacted]

Investigators and the Sponsor will be also responsible for refreshing their electronic media [redacted] to ensure long term archiving of files/data.

13. REFERENCES

1. Cancer Incidence in Sweden 2006. National Board of Health and Welfare. http://wwwsocialstyrelsense/NR/rdonlyres/AAD7CA00-CCE3-4E3EB998-1450BD7FB4A1/9428/20074216pdf. Accessed July 3, 2008.
2. National Cancer Institute, Surveillance Epidemiology and End Results. http://wwwseercancergov/aststats/selectionsphp?run&output_2&data_1&statistic_1&year_200802&race_1&sex_1&age 1&series_cancer&cancer_96#Output. Accessed July 3, 2008.
3. Phekoo KJ, Richards MA, Moller H, Schey SA. The incidence and outcome of myeloid malignancies in 2112 adult patients in southeast England. Haematologica. 2006;91:1400-1404.
4. Estey E, Dohner H. Acute myeloid leukaemia. Lancet. 2006;368:1894-1907.
5. Juliusson G, Billstrom R, Gruber A, et al. Attitude towards remission induction for elderly patients with acute myeloid leukaemia influences survival. Leukaemia. 2006;20:42-47.
6. Slovak M, Kopecky K, Cassileth PA, et al: Karyotypic analysis predicts outcome of preremission and postremission therapy in adult acute myeloid leukaemia: A Southwest Oncology Group/ Eastern Cooperative Oncology Group Study. Blood 96:4075-4083, 2000.
7. Grimwade D, Walker H, Oliver F, et al: The importance of diagnostic cytogenetics on outcome in AML: Analysis of 1,612 patients entered into the MRC AML: 10 Trial. Blood 92:2322-2333, 1998.
8. Ellison RR, Holland JF, Weil M, et al. Arabinosyl. cytosine: a useful agent in the treatment of acute leukaemia in adults. Blood. 1968;32:507-523.
9. Boiron M, Weil M, Jacquillat C, et al. Daunorubicin in the treatment of acute myelocytic leukaemia. Lancet. 1969;1:330-333.
10. Di Nardo et al, Blood 2019 133:7-17
11. Wei et al, Blood 2017 130:890
12. https://www.onclive.com/web-exclusives/fda-approves-glasdegib-for-frontline-aml
13. Burnett AK. Treatment of acute myeloid leukaemia in younger patients. Best Pract Res Clin Haematol. 2001;14:95-118.
14. Mayer RJ, Davis RB, Schiffer CA, et al. Intensive postremission chemotherapy in adults with acute myeloid leukaemia: Cancer and Leukaemia Group B. N Engl J Med. 1994;331:896-903.
15. Schiller G, Gajewski J, Territo M, et al. Long-term outcome of high-dose cytarabine-based consolidation chemotherapy for adults with acute myelogenous leukemia. Blood. 1992;80:2977-2982.
16. Ribeiro RC, Razzouk BI, Pounds S, Hijiya N, Pui CH, Rubnitz JE. Successive clinical trials for childhood acute myeloid leukaemia at St Jude Children's Research Hospital, from 1980 to 2000. Leukaemia. 2005;19:2125-2129.

17. Zittoun RA, Mandelli F, Willemze R, et al. Autologous or allogeneic bone marrow transplantation compared with intensive chemotherapy in acute myelogenous leukaemia: European Organization for Research and Treatment of Cancer (EORTC) and the Gruppo Italiano Malattie Ematologiche Maligne dell'Adulto (GIMEMA) Leukaemia Cooperative Groups. N Engl J Med. 1995;332:217-223.
18. Wahlin A, Markevarn B, Golovleva I, Nilsson M. Improved outcome in adult acute myeloid leukaemia is almost entirely restricted to young patients and associated with stem cell transplantation. Eur J Haematol. 2002;68:54-63.
19. Cornelissen JJ, van Putten WL, Verdonck LF, et al. Results of a HOVON/SAKK donor versus nodonor analysis of myeloablative HLA-identical sibling stem cell transplantation in first remission acute myeloid leukaemia in young and middleaged adults: benefits for whom? Blood. 2007;109:3658-3666.
20. Burnett AK. The treatment of AML: current status and novel approaches. Haematology. 2005; 10[suppl 1]:50-53.
21. Ortolan E, Vaisitti T and Aydin S. Evolution and Function of the ADP Ribosyl Cyclase/CD38 Gene Family in Physiology and Pathology. Physiol Rev.; 88: 841-86, 2008.
22. Kaisho T, Ishikawa J, Oritani K, Inazawa J, Tomizawa H, Muraoka O, Ochi T, and Hirano T. BST-1, a surface molecule of bone marrow stromal cell lines that facilitates pre-B-cell growth. PNAS , 91: 5325-5329, 1994.
23. Okuyama Y, Ishihara K, Kimura N, Hirata Y, Sato K, Itoh M, Ok LB, Hirano T. Human BST-1 expressed on myeloid cells functions as a receptor molecule. Biochem Biophys Res Commun. ; 228(3):838-45, 1996.
24. Satoh M, Iida S, Shitara K. Non-fucosylated therapeutic antibodies as next-generation therapeutic antibodies. Expert Opin Biol Ther. 2006;6:1161–1173.
25. Ho X, Fook-Chong S, Linn YC. Natural killer cell receptor repertoire is comparable amongst newly diagnosed acute myeloid leukaemia of different French-American-British subtypes, risk categories and chemosensitivities. Leuk Lymphoma. 2014 Feb;55(2):342-8.
26. Lion E, Willemen Y, Berneman ZN et al. Natural killer cell immune escape in acute myeloid leukaemia. Leukaemia. 2012 Sep;26(9):2019-26.
27. Stringaris K, Sekine T, Khoder A, et al. Leukaemia-induced phenotypic and functional defects in natural killer cells predict failure to achieve remission in acute myeloid leukaemia. Haematologica. 2014 May;99(5):836-47.
28. Fauriat C, Just-Landi S, Mallet F, et al. Deficient expression of NCR in NK cells from acute myeloid leukaemia: Evolution during leukaemia treatment and impact of leukaemia cells in NCRdull phenotype induction. *Blood.* 2007;109(1):323- 330.
29. Kazuhito Yamamoto, Atae Utsunomiya, Kensei Tobinai, Kunihiro Tsukasaki Phase I Study of KW-0761, a Defucosylated Humanized Anti-CCR4 Antibody, in Relapsed Patients With

Adult T-Cell Leukaemia-Lymphoma and Peripheral T-Cell Lymphoma J Clin Oncol 2010: 28:1591-1598.

30. Takashi Ishida, Tatsuro Joh, Naokuni Uike, Kazuhito Yamamoto Defucosylated Anti-CCR4 Monoclonal Antibody (KW-0761) for Relapsed Adult T-Cell Leukaemia-Lymphoma: A Multicenter Phase II Study J Clin Oncol 2012: 30:837-842.

14. APPENDICES

14.1 APPENDIX I: TLS MANUAL FOR INVESTIGATOR

Tumour Lysis Syndrome (TLS) Manual for Investigator [redacted] for ARMY-1 Clinical Study

First in man study with MEN1112, a CD157 targeted monoclonal antibody, in relapsed or refractory Acute Myeloid Leukemia

Table of Content

1. RISK ASSESSMENT FOR TUMOR LYSIS SYNDROME (TLS)

Patients due to receive the first cycle of treatment with MEN1112 should have a risk assessment for tumour lysis syndrome (TLS) according to the following algorithm:

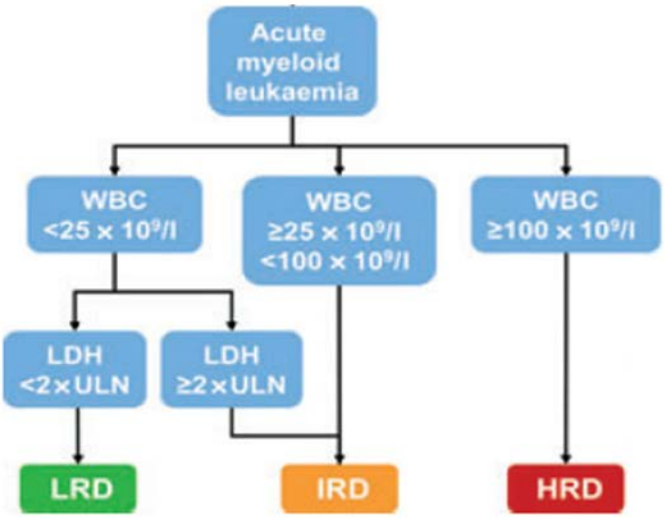


Figure adapted from Cairo M, Coiffier B, Reiter A and Younes A on behalf of the TLS Expert Panel. British Journal of Haematology 2010.

Important Note:

- Patients with LRD are intermediate-risk for TLS when renal dysfunction and/or renal involvement is present;
- Patients with IRD are high-risk for TLS when renal dysfunction and/or renal involvement is present OR when uric acid, phosphate and/or potassium levels are > ULN

Legend. *WBC= White Blood Count, LDH=Lactate Dehydrogenase, ULN= Upper Limit of Normal, LRD= Low Risk Disease, IRD= Intermediate Risk Disease, HRD= High Risk Disease.*

Important note: Although neither French-American-British subtype nor cytogenetics are included in the TLS risk assessment algorithm, it is worth considering that AML inv(*16*) / *t*(*16*;*16*) and the M4Eo cases are prone to demonstrate fulminant TLS under treatment, some of which have been reported to be fatal even despite optimal clinical patient management. Such TLS, which in other AML are usually only seen with very high peripheral blood counts, may show up in AML M4 inv(*16*) / *t*(*16*;*16*) patients even with low peripheral tumor cell counts, which is suspected to be linked to a very high fragility/sensitivity of the tumor cells to lysis/cell death induction. In this respect it is worth recalling that in the first in human ARMY study, a fulminant TLS leading to disseminated intravascular coagulation and consequent cerebral haemorrhage was the most likely cause for the fatal treatment-related case occurred in patient [redacted], who was indeed affected by relapsed AML M4 Eo with *t*(*16*;*16*).

2. TLS DIAGNOSTIC CRITERIA

Definition of Laboratory TLS (LTLS): LTLS is considered to be present if levels of 2 or more serum values of uric acid, potassium, phosphate or calcium are more than or less than normal at presentation or if they change by at least 25%, according to the following table.

Element	Value	Change from baseline
Uric acid	≥476 µmol/L (or 8 mg/dL)	25% increase
Potassium	≥6.0 mmol/L	25% increase
Phosphorus	≥1.45 mmol/L	25% increase
Calcium	≤1.75 mmol/L	25% decrease

Definition of clinical TLS (CTLS): CTLS requires the presence of LTLS in addition to 1 or more of the following significant clinical complications: renal insufficiency, cardiac arrhythmias/sudden death and seizures; the grade of CTLS is defined by the maximal grade of the clinical manifestation, according to the following table.

	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
LTLS	-	+	+	+	+	+
Creatinine[a,b]	≤1.5 x ULN	1.5 x ULN	>1.5-3.0 x ULN	>3.0-6.0 x ULN	>6.0 x ULN	death
Arrhythmia	none	Intervention not indicated	Non urgent medical intervention indicated	Symptomatic and incompletely controlled medically or controlled with device	Life-threatening	death
Seizure[b]	none	-	1 brief, generalized seizure; seizure(s) well controlled by anticonvulsants or infrequent focal motor seizures not interfering with activities of daily living	Seizure in which consciousness is altered; poorly controlled seizure disorder; with breakthrough generalized seizure despite medical intervention	Seizure of any kind which are prolonged, repetitive or difficult to control	death

Adapted from Cairo M and Bishop M. British Journal of Haematology 2004.

[a] Patient will be considered to have elevated creatinine if it is 1.5 times greater than the upper limit of normal (ULN).

[b] No directly or probably attributable to a therapeutic agent

3. PROPHYLAXIS OF TLS

LRD	IRD	HRD
Hydration	Hydration	Hydration
± Allopurinol	Allopurinol	Rasburicase

Important Note:

- Any patient with renal impairment or allergic to allopurinol should be considered for rasburicase despite their risk assignment based on tumor features, though those with low risk disease can often be managed using hydration alone
- Rasburicase should be avoided in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency. Such patients should be treated with fluids and allopurinol and monitored carefully

Hydration: The exact fluid volume required is not known but it seems reasonable to aim for 3 L/24 h, provided individual tolerability. Urinary output shall be carefully monitored. Alkalinization is not recommended.

Allopurinol: The standard recommended dosing schedule for allopurinol in prevention of TLS is 200–400 mg/m^2/day in 1–3 divided doses for adults, up to a maximum of 800 mg daily. In practice, most adult haematologists simply use 300 mg/day and, for the most part, this is effective but it may be prudent to increase the dose of allopurinol or, preferably, switch to rasburicase in the presence of deteriorating biochemical or clinical markers. Allopurinol doses may need to be adjusted in renal failure.

Rasburicase: Although the licensed dose of rasburicase is 0,2 mg/kg/day, a number of publications have explored lower doses and shorter courses of therapy. Taking these into account, and pragmatically considering available vial sizes, it has been recommend that, in the absence of established clinical or laboratory TLS, TLS can be prevented in the majority of adult patients using a single fixed dose of 3 mg rasburicase. It is essential to closely monitor for biochemical and clinical markers of TLS and if there is evidence of any progression then the dose should be repeated daily until markers of TLS have entirely returned to normal. In patients with a prior history of glucose-6-phosphate dehydrogenase (G6PD) deficiency, rasburicase is contraindicated and allopurinol should be utilized instead of rasburicase.

4. TREATMENT OF ESTABLISHED TLS

Management of this condition requires a multidisciplinary approach including haematologists, nephrologists and intensive care physicians. The following topics need to be addressed:

Fluid balance: There are no trials that demonstrate a particular rate of fluid delivery to be better than another but recent reports suggest 3 L/m^2 every 24 hours would be reasonable in adults, with the aim of maintaining a urine output of > 100 ml/m^2/h for older patients. Urine output should be measured at least hourly and a formal assessment of fluid balance should be undertaken at least 6 hourly. Care should be taken to document all fluid losses, such as vomiting or diarrhoea. Elderly patients and those with pre-existing cardiac and renal disease are at particular risk of fluid overload. Whilst furosemide 0.5 mg/kg intravenously can be a useful emergency treatment, the drug may promote tubular uric acid deposition and is likely to be less efficacious in the presence of renal tubular blockade. The presence of significant fluid overload requires nephrology advice. Alkalinization of the urine is not recommended.

Management of hyperuricaemia: Rasburicase is the drug of choice. Any patient who has been on allopurinol as a prophylactic measure should be switched to rasburicase if they develop clinical TLS, the exceptions being patients who have had previous allergic reactions to rasburicase and those in whom it is contraindicated due to G6PD deficiency. In those patients allopurinol should be continued but renal dialysis is more likely to be required. The standard recommended dose of rasburicase is 0.2 mg/kg/day given as a 30-min infusion. The current European Medicines Agency and US Food and Drug Administration recommendations include daily dosing for up to 5 days. Whilst there are some data to support short duration of rasburicase or reduced dose therapy in the context of prophylaxis there are no data, beyond those of the licensing authority, to guide dosing in the setting of established TLS. It seems reasonable to recommend rasburicase 0.2 mg/kg/day be given for 3–7 days with careful monitoring of electrolytes.

Management of hyperphosphataemia and hypocalcaemia: If the above measures do not prevent significant hyperphosphataemia, it can be hard to control phosphate levels other than by dialysis. The temporary use of aluminium hydroxide 50–150 mg/kg/day has been described but is slow to act and poorly tolerated, thus is not routinely recommended in this setting. Asymptomatic hypocalcaemia should not be treated as treatment can precipitate further calcium phosphate deposition in the kidneys. If corrected calcium levels drop below ≤1.75 mmol/L or there has been a 25% drop from baseline, then cardiac monitoring is recommended. Symptomatic hypocalcaemia (e.g. cardiac arrhythmia, seizure or tetany) should be treated with calcium gluconate in the standard doses for adults and children. The aim is to treat the symptoms but not to normalize the biochemical parameters.

Hyperkalaemia: It is recommended that patients with potassium levels ≥6 mmol/L or having experienced a 25% increase in potassium level from baseline should be offered cardiac monitoring. A potassium level ≥7 mmol/L constitutes a medical emergency and dialysis is likely to be required urgently. Effects of standard measures are temporary and dialysis is often required. Acute cardiotoxicity should be treated with a short infusion of calcium gluconate with continuous cardiac monitoring. Nebulized or intravenous salbutamol can be effective, as can intravenous infusion of insulin and glucose. Both strategies increase movement of potassium from the extracellular to the intracellular space.

Renal dialysis: When the measures described have failed to prevent renal deterioration and significant fluid overload, hyperkalaemia, hyperuricaemia, hyperphosphataemia or hypocalcaemia have developed, renal dialysis is indicated. Peritoneal dialysis is not recommended for this indication because clinical improvement is slower than with other forms of dialysis. There are no major trials comparing haemodialysis with haemofiltration or other extracorporeal therapies and all approaches appear to be effective. Given the continuous release of metabolites into the blood in the setting of TLS, some groups have suggested that daily dialysis may be the best strategy. In patients who are haemodynamically compromised, continuous renal replacement therapy can be helpful. Dialysis should continue until there is adequate recovery of renal function and urine output.

Important note: Any additional safety test is allowed when required to properly guide TLS prophylaxis/management and/or as per Investigator's judgment.

5. REFERENCES

- Jones GL, Will A, Jackson GH, et al. Guidelines for the management of tumour lysis syndrome in adults and children with haematological malignancies on behalf of the British Committee for Standards in Haematology. Br J Haematol. 2015 Jun;169(5):661-71
- Cairo MS, Coiffier B, Reiter A, et al. Recommendations for the evaluation of risk and prophylaxis of tumour lysis syndrome (TLS) in adults and children with malignant diseases: an expert TLS panel consensus. Br J Haematol. 2010 May;149(4):578-86
- Cairo MS, Bishop M. Tumour lysis syndrome: new therapeutic strategies and classification. Br J Haematol. 2004 Oct;127(1):3-11
- Seftel MD, Bruyere H, Copland M, et al. Fulminant tumour lysis syndrome in acute myelogenous leukaemia with inv(16)(p13;q22). Eur J Haematol. 2002 Oct;69(4):193-9
- Hijiya N, Metzger ML, Pounds S, et al. Severe cardiopulmonary complications consistent with systemic inflammatory response syndrome caused by leukemia cell lysis in childhood acute myelomonocytic or monocytic leukemia. Pediatr Blood Cancer. 2005 Jan;44(1):63-9.
- Dombret H, Hunault M, Faucher C, et al. Acute lysis pneumopathy after chemotherapy for acute myelomonocytic leukemia with abnormal marrow eosinophils. Cancer. 1992 Mar 15;69(6):1356-61.)

14.2 APPENDIX II: TIMINGS OF BLOOD SAMPLING FOR PK & EXPLORATORY TESTS

	STUDY VISIT	NR. Blood sampling for PK & exploratory tests	TIMING
CYCLE 1	1, 2	3 each Visit	Pre-infusion
			At the end of infusion
			6 h after the end of infusion
	3	3	Pre-infusion
			At the end of infusion
			14 h after the end of infusion
	4	1	24 h after the end of last ramp-up dosing infusion
	5	1	44 h after the end of last ramp-up dosing infusion
	6	1	68 h after the end of last ramp-up dosing infusion
	8, 9, 10	2 each Visit	Pre-infusion
			At the end of infusion
	12	2	Pre-infusion
			At the end of infusion
CYCLE 2	16	2	Pre-infusion
			At the end of infusion
	20	2	Pre-infusion
			At the end of infusion
	24	4	Pre-infusion
			At the end of infusion
			1 h after the end of infusion
			6 h after the end of infusion
	25	1	24 h after the end of infusion
	26	1	48 h after the end of infusion
	27	1	72 h after the end of infusion
	28	1	96 h after the end of infusion
	29	1	120 h after the end of infusion
	30	1	144 h after the end of infusion
End of Treatment	31	1	1 week after the end of infusion
	32	1	2 weeks after the end of infusion
	33	1	3 weeks after the end of infusion
	34	1	4 weeks after the end of infusion

NOTE: If any interruption occurs during Cycle 1 and the 3rd infusion of Cycle 2, blood sampling for PK & exploratory tests will also be taken at the time of each infusion interruption and just before each infusion resumption.

14.3 APPENDIX III: TIMINGS OF SAFETY BLOOD SAMPLING

	STUDY VISIT	NR. SAFETY SAMPLES	TIMING
	SCREENING	1	N/A
CYCLE 1	1, 2, 3	5 each Visit	Pre-infusion
			2h after the start of infusion
			4h after the start of infusion
			8h after the start of infusion
			12h after the start of infusion
	4	1	One day after the completion of the entire first ramp-up
	8, 9, 10	5 each Visit	Pre-infusion
			2h after the start of infusion
			4h after the start of infusion
			8h after the start of infusion
			12h after the start of infusion
	11	1	One day after the completion of the entire second ramp-up
	12	5	Pre-infusion
			2 h after the start of infusion
			4 h after the start of infusion
			8h after the start of infusion
			12 h after the start of infusion
	13, 14, 15	1 each Visit	24 h after the start of infusion
			48h after the start of infusion
			72 h after the start of infusion
CYCLE 2	16	1	Pre-infusion
	17	1	N/A
	18	1	N/A
	19	1	N/A
	20	1	Pre-infusion
	21	1	N/A
	22	1	N/A
	23	1	N/A
	24	1	Pre-infusion
	25	1	N/A
	26	1	N/A
	27	1	N/A
	30	1	N/A
FOLLOW-UP PERIOD	35-38	1	N/A
	End of study	1	N/A

14.4 APPENDIX IV: COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS (CTCAE) VERSION 4.0. PUBLISHED: MAY 28, 2009 (V4.03: JUNE 14, 2010). U.S.DEPARTMENT OF HEALTH AND HUMAN SERVICES - NATIONAL INSTITUTES OF HEALTH - NATIONAL CANCER INSTITUTE