I.R.I.S.

INSTITUT DE RECHERCHES INTERNATIONALES SERVIER

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%: Percent
ADME : Absorption Distribution Metabolism Excretion
AE : Adverse Event
ALP : ALkaline Phosphatase
ALT : ALanine aminoTransferase
AML : Acute Myeloid Leukaemia
aPTT : activated Partial Thromboplastin Time
AST : ASpartate aminoTransferase
ATC: Anatomical Therapeutic Chemical
AZA : Azacitidine
Bcl-2 : B-cell lymphoma 2 protein
BLRM : Bayesian Logistic Regression Model
BM : Bone Marrow
BNP : Brain Natriuretic Peptide
bpm : beats per minute (heart rate unit)
BR : Best Response
C : Cycle
CLcr : Creatinine CLearance
CPK : Creatine Phosphokinase
CPK-MB : Creatine PhosphoKinase Myocardial Band
CR : Complete Remission
CRi : Complete Remission with incomplete haematologic recovery
CSR : Clinical Study Report
Cx : Cycle x
D : Day
DBP : Diastolic Blood Pressure
DI : Dose Intensity
DLT : Dose Limiting Toxicity
DLTES : Dose-Limiting Toxicity Evaluable Set
DNA : Deoxyribonucleic Acid
e.g. : Exempli gratia (for example)
ECG : ElectroCardioGram
ECOG : Eastern Cooperative Oncology Group
eCRF : Electronic Case Report Form
EMA : European Medicines Agency
EoC : End of Cohort
EoT : End of Trial
EWOC : Escalation With Overdose Control
FAB: French-American-British

FU : Follow-Up
G/L : Giga (109) per litre
GGT : Gamma-Glutamyl Transferase (Gamma-Glutamyl Transpeptidase)
HbcAb : B virus core antibody
HbsAb : B virus surface antibody
HbsAg : Hepatitis markers B virus surface antigen
HBV : Hepatitis B Virus
HCV : Hepatitis C Virus
HDL : High-Density Lipoprotein
HEV : Hepatits E Virus
HMA : HypoMethylating Agents
HR : Heart Rate
i.e. : id est (that is)
ICF : Informed Consent Form
ICH : International Conference on Harmonisation
IME : Independent MedicalExam
IMP : Investigational Medicinal Product: a pharmaceutical form of an
active ingredient or placebo being tested or used as a reference
in a clinical trial i.e. S64315 and azacitidine
INR : International Normalized Ratio
I.R.I.S. : Institut de Recherches Internationales Servier
IS : Included Set
IU : International Unit
IV : IntraVenous (route)
kg : Kilogram
LDH : Lactate DeHydrogenase
LDL : Low-Density Lipoprotein
LID : Lead-In Dose
LLN : Lower Limit Normal of reference range
LVEF : Left Ventricular Ejection Fraction
Max: Maximum
MCL1 : HGNC Approved Gene Symbol for Myeloid Cell Leukaemia
Sequence 1
Mcl-1 : Induced myeloid leukaemia cell differentiation protein
MDS : MyeloDysplastic Syndrome
MDRD_GFR : Modification of Diet in Renal Disease Glomerular Filtration Rate
MedDRA : Medical Dictionary for Regulatory Activities
mg : Milligram
min : Minimum
mL : Millilitre
MLFS : Morphologic Leukaemia-Free State
mmHg : Millimetres of mercury

MPN : myeloproliferative neoplasms
MRD : Minimal (measurable) Residual Disease
msec: Milliseconds
MTD : Maximum Tolerated Dose
N : Number
NA : Not Applicable
NAE : Number of Adverse Events
NCI-CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events
NPD: Number of Protocol Deviations
PB : Periferal Blood
PCR : Polymerase chain reaction
PD : PharmacoDynamics
PDI : Planned Dose Intensity
PG : PharmacoGenomics
PK : PharmacoKinetics
PR : Partial response
PT : Preferred Term
PV : PharmacoVigilance
QTc : QT interval corrected for heart rate
QTcF : QTc interval corrected with Fridericia's formula
QW : Once Weekly
Q1 : First Quartile
Q3 : Third Quartile
RBC : Red Blood Cells
RDI : Relative Dose Intensity
RNA : Ribonucleic acid
RP2D : Recommended Phase II Dose
SAE : Serious Adverse Event
SAP : Statistical Analysis Plan
SBP : Systolic Blood Pressure
SC SubCutaneous (route)
SD : Standard Deviation
SI : Standard International
SOC : System Organ Class
SS : Safety Set
TEAE : Treatment Emergent Adverse Event
TLG : Tables, Listings and Graphs
TLS : Tumour Lysis Syndrome
TPN : Total parenteral nutrition
TSH : Thyroid Stimulating Hormone
ULN : Upper Limit Normal of reference range

WBC : White Blood Cells
WHO : World Health Organization
WHODD : World Health Organization, Drug Dictionary
WV : Withdrawal Visit

1. INTRODUCTION

This Statistical Analysis Plan (SAP) details the planned analyses to be performed, in accordance with the main characteristics of the study protocol V5.0 dated 14th of October 2022.
The shells for Tables, Listings and Graphs (TLG) are described in a separate document.

The study data will be analysed and reported in the Primary abbreviated Clinical Study Report (CSR) once the study is terminated (at the end-of-study, defined as the date of the last follow-up of the last patient, including a phone contact, or the date of the last contact attempt if the last patient is declared lost to follow-up). A statistical data review will be conducted prior to database lock. A limited number of outputs will be produced for the purpose of reviewing the data prior to authorizing the database lock.

The final analysis for the abbreviated CSR will be performed (and so the database locked) as soon as all safety data are available, and all the mandatory steps required for database lock have been performed.

Of note, this SAP does not cover the pharmacokinetic and pharmacodynamic profiling data analyses described in the study protocol. These analyses are covered in separate analysis plans written by I.R.I.S. Clinical Pharmacokinetics and Technologie Servier, respectively.

Given the abbreviated nature of the CSR, this SAP will cover the disposition, demographics and baseline characteristics of the study sample, the extent of exposure and treatment compliance to the investigational medicinal products (IMP)s, and the safety profile of the IMPs. Efficacy of IMPs and other observations related to patient follow-up will not be analysed.

1.1. Study objectives

The primary objective of the study is to determine the safety profile (including dose-limiting toxicity (DLT) and maximum tolerated dose (MTD)) and tolerability of S64315 in combination with azacitidine in patients with AML.

The secondary objectives (not addressed by this SAP) are:
- To determine the pharmacokinetics (PK) profile of S64315 and azacitidine administered in combination, and potential metabolites.
- To evaluate anti-leukemic activity of S64315 in combination with azacitidine.

The exploratory objectives of the study (not addressed by this SAP) are:
- To assess the minimal (measurable) residual disease (MRD) and clonal evolution after treatment with the combination of S64315 with azacitidine.
- To evaluate the pharmacodynamic (PD) profile of S64315 in combination with azacitidine in relation to:
  - The biological activity (target engagement).
  - The relationship between the expression level of B-cell lymphoma 2 protein (Bcl-2) family members (in blood, and bone marrow samples) and the anti-leukemic activity.
  - The relationship between the anti-leukemic activity, karyotypes and AML associated genes mutations or dysregulations.
- To explore PK/PD relationship for safety and efficacy.
- To explore relationship between the deoxyribonucleic acid (DNA) polymorphism for proteins involved in the absorption distribution metabolism excretion (ADME) and the variability of PK parameters.

1.2. Study endpoints

The **endpoints for the primary objective** are:

- The incidence of DLT(s) starting from the lead-in dose (LID) period to the end of each cycle of treatment of S64315 in combination with azacitidine.
- The incidence and severity of adverse events (AEs) and serious adverse events (SAEs) according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0.
- The recording of any change or addition of a new concomitant treatment.
- The laboratory tests: haematology with differential, blood biochemistry, thyroid function, blood coagulation, urinary analysis, hepatitis markers, Tumour Lysis Syndrome (TLS) monitoring, cardiac markers follow up.
- The complete physical examination, Eastern Cooperative Oncology Group (ECOG) performance status and vital signs measurements.
- The electrocardiogram (ECG) parameters and cardiac function assessment.
- The left ventricular ejection fraction (LVEF).
- The dose interruptions, reductions and dose intensity.

1.3. Study design

The study CL1-64315-004 is an international, multicentre, non-randomised, non-comparative, open label, phase I/II study of S64315 and azacitidine administered in combination, conducted in patients with AML.

This study was originally designed in two phases: Phase I for dose escalation and Phase II for dose expansion. Furthermore, the dose escalation phase I part was further planned to have 2 arms: Arm A evaluating the combination of S64315 with azacitidine (see Figure (1.3.2) 1), and Arm B evaluating the triplet regimen of S64315 with azacitidine and a Bcl-2 inhibitor. However, Phase I - Arm B and Phase II for dose expansion will not be conducted.

1.3.1. Dose administration schedule and escalation

The initial schedule (see Figure (1.3.2) 1) will consist of a lead-in period followed by 28-day cycles when S64315 will be administered in combination with azacitidine. S64315 will be administered via intravenous (IV) infusion over at least 2 hours once every week, azacitidine will be administered via subcutaneous (SC) injection once daily for 7 consecutive days.

The schedule will be as follows:

- A 2-week LID period with S64315 fixed LID1 of 25 mg on day -13 (D-13) and S64315 fixed LID2 of 50 mg on D-6, followed by

- 28-day cycles (Cx) of combination treatment period with S64315 administered on CxD2, CxD9, CxD16 and CxD23, and 75 mg/m² of azacitidine administered daily for 7 days from CxD1 to CxD7 followed by a rest period of 21 days.

On days of concomitant administration of S64315 and azacitidine (CxD2), azacitidine should be administered 2 hours (±10 min) prior to S64315. The starting dose of S64315 after the lead-in period will be 50 mg. A panel of doses (see Table (1.3) 1 from 25 mg (-1) and up to 250 mg could be explored according to the dose escalation process of the Bayesian Logistic Regression Model (BLRM).

During the dose escalation phase, at each new dose level, the IMPs will be firstly administered to one patient. If no medically important or life-threatening toxicity occurs during a 1 week observation period, the subsequent patients will be allowed to start treatment without further delays between subsequent patients. The dose increase between two dose levels will be guided by the observed toxicities.

An adaptive BLRM with overdose control (EWOC) will be used to guide the dose escalation of S64315 in combination with azacitidine. The dose escalation will only concern S64315. The purpose of the dose escalation phase I part is to determine the safety profile, the MTD, the DLTs and the recommended Phase II Dose (RP2D) in patients with relapsed/refractory AML. All available data on DLTs (assessed from the LID period and up to the end of cycle 1) will be used for updating the model. Before making a decision regarding dose escalation, the minimum number of patients required from a cohort must have been treated with one cycle of the combination and be fully evaluable for treatment-related toxicities according to the minimum requirements for inclusion in the Dose-Limiting Toxicity Evaluable Set (DLTES). If a patient is not eligible for inclusion in the DLTES, this patient must be replaced.

A maximum of 6 DLT-evaluable patients may be initially enrolled at a new dose level, and a minimum of 3 DLT-evaluable patients must be treated at a given dose level in order to begin treatment of patients at a new, higher dose level. To better characterize the safety, tolerability, PK, PD, or preliminary clinical activity of S64315 in combination with azacitidine, more than 6 DLT-evaluable patients may be treated in a cohort. If the starting dose of the combination is not well tolerated, a dose level -1 will be considered. Intermediate doses may be tested, if needed. A minimum of 6 DLT evaluable patients must have been evaluated at the dose considered to be the MTD, and before treating patients with this dose in the Phase II part of the study.

Table (1.3) 1 - Provisional dose levels of S64315

Dose level	Proposed dose*	Increment from previous dose
-1**	25 mg	-50%
1	50 mg	Starting dose
2	100 mg	100%
3	200 mg	100%
4	250 mg	25%

*It is possible for additional and/or intermediate dose levels to be added during the course of the study Cohorts can be added at any dose level below the MTD in order to better understand safety, PK or PD
**No dose reduction below dose level -1 is permitted for this study

Before testing a new dose level during the dose escalation phase, an end of cohort (EoC) meeting between the Sponsor (Centre for Therapeutic Innovation Oncology, Medical Safety Leader, Methodology Department and Clinical Pharmacokinetics department), the coordinator

and the investigators will take place to discuss the toxicities in terms of DLTs, safety data, the PK and available PD, and the preliminary efficacy data observed in all patients.

Of note, the dose escalation part was stopped by a joint decision from Servier and Novartis by taking into account the model estimations and a global assessment of the safety, PK, PD and preliminary activity data. No intra-patient dose escalation and no expansion part will be conducted for this study.

1.3.2. Study plan

The study start is defined as the date of the first visit of the first patient, corresponding to informed consent form (ICF) signature. It will be divided into the following periods for each patient of Arm A:

- **Screening visit**

The screening eligibility criteria will be checked after the patient informed consent is obtained.

- **Inclusion period**

The inclusion and exclusion criteria will be checked. The inclusion period can last up to 15 days before starting the LID period. The patient is included when he/she has met all the inclusion criteria.

- **S64315 lead-in dose period**

The lead-in dose period will last 2 weeks. S64315 LID1 will be administered on D-13 at 25 mg and LID2 on D-6 at 50 mg. LID1 and LID2 doses will be fixed all along the study.

- **Combination treatment period**

A treatment cycle will consist of 28 days for patients treated with S64315 in combination with azacitidine during the dose escalation phase I part:

- Weekly schedule for S64315 on CxD2, CxD9, CxD16 and CxD23.
- Daily schedule for azacitidine from CxD1 to CxD7 followed by a 21-day rest period.

The planned duration of combination treatment is until disease progression, unacceptable toxicity, treatment failure (defined as failure to achieve complete remission (CR), complete remission with incomplete haematologic recovery (Cri), partial response (PR), or morphologic leukaemia-free state (MLFS) after at least 6 cycles of study treatment) or patient/physician decision. In case of myelosuppression within the context of non-active AML, a 4-week interruption of administration of one or both IMP(s) will be allowed for bone marrow recovery at the investigator's discretion after discussion and approval from the Sponsor. If the patient is benefiting from the study treatment according to the investigator's judgement and if it is in the patient's best interest to continue the combination of S64315 with azacitidine, the patient may remain on study treatment. In case the patient becomes eligible for transplant, patient's treatment discontinuation should be left at the investigator's decision.

- **Withdrawal visit (WV):**

Up to 28 days after the last dose of IMP

- **Post-withdrawal follow-up**

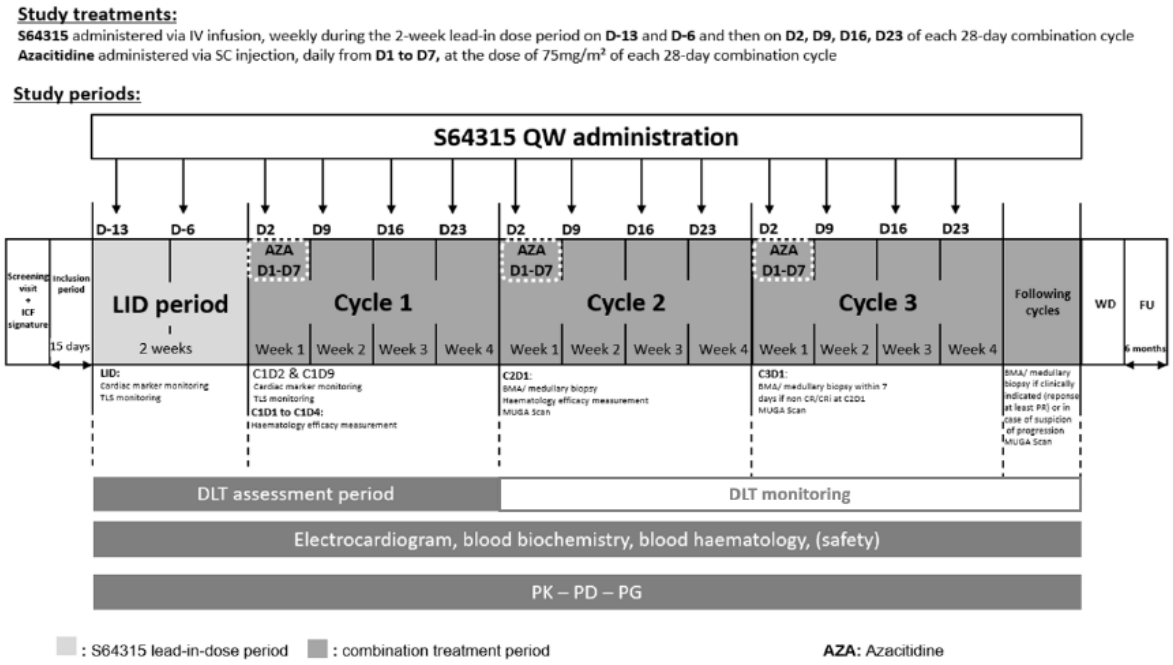
After the withdrawal visit, a contact or telephone call will be done for the patients:

- Every 3 months (±15 days) from the WV and up to 6 months, except in case of consent withdrawal for the dose escalation phase I part.

- **End of Trial (EoT)**

The EoT is defined as the date of the last follow-up of the last patient (including a phone contact), or the date of the last contact attempt if the last patient is declared lost to follow-up.

Figure (1.3.2) 1 - Study plan for S64315 administration schedule in combination with azacitidine (dose escalation phase I part – Arm A)



S64315 infusion on D-13, D-6, CxD2, CxD9, CxD16, CxD23
Azacitidine administration from CxD1 to CxD7
PK: pharmacokinetic measurements
PD: pharmacodynamics measurements
PG: optional pharmacogenomics measurements
WV: withdrawal visit

AZA: azacitidine
D: day
FU: post-withdrawal follow-up
LID: Lead-in dose
QW: Once Weekly
W: week

1.3.3. Type of randomisation

The assignment of a patient to a particular cohort will be coordinated by the Sponsor. No randomisation will be performed in this study.

1.4. Determination of sample size

No formal statistical power calculations to determine sample size were performed for this study. Overall, a maximum of 180 patients will be enrolled in the dose escalation phase I part of Arm A (up to 30 patients) followed by sub-arms A1and A2 (50 per sub-arms, up to 150 patients overall). However, due to the stop of the dose escalation phase, the expansion part to sub-arms A1 and A2 will not be conducted.

2. ANALYSIS SETS AND SUBGROUPS

2.1. Analysis sets and subgroups

- **Screened Set:**

All patients who signed the ICF, whether they are included or not at the end of the screening period.

- **Included Set (IS):**

All patients who have signed the ICF, whose eligibility was confirmed at the end of the screening period, and who were included in the dose escalation phase I part of the study.

- **Safety Set (SS):**

All patients who have signed the ICF and who received at least one dose of IMP (S64315 or azacitidine) during dose escalation phase I part of the study. It will be used for all safety analyses.

For the safety analysis, patients will be analysed according to the treatment combination and dose level received at C1D1 (for azacitidine) and C1D2 (for S64315). Patients who only received LID will be analysed according to the dose of S64315 planned to be administered.

- **Evaluable Set (DLTES):**

All patients from the SS who are evaluable for DLT according to the DLT assessment at the end of cycle 1. A patient is not considered evaluable for DLT if he/she:

- Permanently discontinued treatment before C1D28 for reasons other than DLT.
- Did not undergo a DLT assessment at the end of Cycle 1.
- Did not receive the minimum exposure criteria i.e., minimum number of doses according to the dose administration schedule of both IMPs prescribed from study entry to DLTs assessment visit (end of Cycle 1 D28), unless treatment was stopped for a DLT (see Table (2.1) 1).
- If a patient received more than the assigned IMP doses from study entry to DLT occurrence during the DLT assessment period, non-evaluability criteria will be reassessed by Sponsor and investigator (Table (2.1) 1).

Table (2.1) 1 - Minimum number of S64315 and azacitidine doses to meet minimum exposure until the end of cycle 1

Schedule description	Minimum of doses of S64315/azacitidine
S64315 during the 2-week LID period (LID1 on D-13 and LID2 on D-6)	2 out of 2
S64315 (D2, D9, D16 and D23 in 28-day cycle)	3 out of 4
azacitidine (D1 to D7 in 28-day cycle)	5 out of 7

3. STATISTICAL METHODS

3.1. General considerations

Descriptive statistics depending on the nature of the criteria and the number of patients by dose level combinations:

- For **qualitative data**, number of observed values, number and percentage of patients per class will be presented. Unless otherwise specified in the TLG, no class "Missing" is considered.
- For **quantitative data**, number of observed values, mean, standard deviation (SD), minimum (min) and maximum (max), median, first (Q1) and third (Q3) quartiles.

For **Event**:

- Number of patients (or cycles) having experienced the event (n).
- Number of events that occurred (for AE analyses only) (NAE).
- Number of patients (or cycles) at risk for the event (N).
- Global incidence rate (%),
  - calculated as the ratio between the number of patients (or cycles) having experienced the event (n) and the number of patients (or cycles) at risk at the beginning of the study (N).

Globally, mean, standard deviation and the percentage will be submitted only to the dose level combinations with sufficient number of patients.

3.2. Disposition and baseline characteristics

Description of disposition of patients (status, protocol deviations and analysis set), treatment duration and extent of exposure, as well as other baseline characteristics will be performed by dose level combination and overall.

Calculation rules for general definitions (such as value prior to treatment, under treatment, analysable value, IMP infusion date,…) are provided in Appendix 4.1.

Specific definitions on disposition of patients, baseline characteristics and patient follow-up are provided in Appendix 4.2.

3.2.1. Disposition of patients

Disposition of patients will be described overall for the Screened Set. Number of patients screened, included and not included, with relative reasons, will be presented.

Disposition of patients at the time of inclusion will also be described overall and by planned treatment dose for the IS. Number of patients included, with relative conformity to protocol, and withdrawn, with relative reasons, will be presented.

Furthermore, disposition of patients for the IS will also be described after inclusion, separately for LID period and for each cycle. Number of patients ongoing at the given LID period or cycle, and withdrawn, with relative reasons, will be presented.

3.2.2. Protocol deviations

Protocol deviations before or at inclusion, as well as after inclusion, will be described in the IS, overall and by category of deviations (based on International Conference on Harmonisation (ICH) E3 guideline and ICH E3 Q&A). Number of protocol deviations (NPD), number and percentage of patients with at least one protocol deviation will be presented.

3.2.3. Analysis sets and subgroups

The number of patients in each analysis set (studied analysis set and reference analysis set), and reasons for exclusion will be described.

Listings of patients with their membership, or not, of each analysis set and of excluded patients with reasons for exclusion will be provided.

3.2.4. Demographic data and other baseline characteristics

3.2.4.1. Demographic data

Descriptive summary statistics (n, mean, SD, median, min, max, median, Q1, Q3) will be provided for variables measured on a continuous scale, for patients of the IS:

- Age.

The frequency distribution (n, %) will be provided for patients of the IS by dose level combination and overall for variables measured on a nominal scale for the following classes:

- Age ([18-65[years, [65-85[years, ≥ 85 years).
- Gender (Female, Male).
- Race (Caucasian/White, Black/African American, American Indian/Alaska Native, Asian, Native Hawaiian/Other Pacific Islander, Other).
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino).

3.2.4.2. Pregnancy test

The frequency distribution (n, %) will be provided for female patients of the IS by dose level combination and overall for variables measured on a nominal scale for the following cases:

- Pregnancy test (Yes, No).
- Positive pregnancy test (Yes, No).
- Patient childbearing potential (Yes, No).

3.2.4.3. Disease history

Descriptive summary statistics (n, mean, SD, median, min, max, median, Q1, Q3) will be provided for variables measured on a continuous scale for:

- Disease duration (years).
- Treatment-free interval since previous AML treatment line (days).

- Treatment-free interval since previous (MyeloDysplastic Syndrome) MDS treatment line (days).

The frequency distribution (n, %) will be provided in patients of the IS by dose level combination and overall for variables measured on a nominal/ordinal scale according to the following classes:

- Disease duration (≤ 1 years,]1-2 years],]2-4 years] , > 4 years).
- Treatment-free interval since previous AML treatment line (≤ 30 days,]30-60 days], > 60 days).
- Treatment-free interval since previous MDS treatment line (≤ 30 days,]30-60 days], > 60 days).
- Patient with at least one progression during or after a previous treatment line for AML (Yes, No).
- Subtype of AML:
  - AML with recurrent genetic abnormalities.
  - AML with myelodysplasia-related changes.
  - Therapy-related myeloid neoplasms.
  - AML, not otherwise specified.
  - Myeloid sarcoma.
  - Myeloid proliferations related to Down syndrome.
- Disease status (In relapse, Refractory to previous treatment, Treatment-naïve for AML).
- Type of AML (De novo, Secondary).
- FAB: French-American-British (FAB) classification.
- Cytogenetics risk category (Favorable, Intermediate, Intermediate I, Intermediate II, Adverse, Not assessable).
- Red blood cell transfusion dependent (Yes, No).
- Platelets transfusion dependent (Yes, No).
- Presence of myelodysplasia.
- Gene Mutation research at diagnosis (No, Yes).
- List of genes tested (No, Yes).
- Presence of gene mutation (Absent, Present).

A listing of key demographic and disease characteristics will also be presented.

3.2.4.4. Previous therapies

Previous therapies for AML will be summarized for patients in the IS. The following categorical variables will be described by frequency distribution (n, %):

- Number of patients with at least one previous surgery, one previous radiotherapy, one previous drug treatment and one previous transplant.
- Number of patients by combination of previous therapies (drug treatment + radiotherapy, drug treatment + transplant, drug treatment + surgery, radiotherapy + transplant, radiotherapy + surgery, transplant + surgery, drug treatment + radiotherapy + transplant, surgery + radiotherapy + transplant, drug treatment + surgery + radiotherapy, drug treatment + surgery + transplant, drug treatment + surgery + radiotherapy + transplant).
- Number of patients by type of previous transplant (autologous stem cell, allogenic stem cell).
- Number of treatment lines by class (0, 1, 2, 3, 4-7, >7).
- Number of relapses (0, 1, 2, 3, 4-7, >7).

- Number of patients who received some specific treatments lines.
- Previous therapies by pharmacological class.

Descriptive summary statistics (n, mean, SD, median, min, max, median, Q1, Q3) will be provided for variables measured on a continuous scale including:

- Number of treatments lines.
- Number of relapses.

3.2.4.5. Signs and symptoms related to AML

The number and percentage of patients with signs and symptoms at baseline will also be summarized by System Organ Class (SOC) and Preferred Term (PT) in patients of IS.

3.2.4.6. Clinical laboratory baseline evaluation

Laboratory analysis as described in Section 3.4.4 will be analysed in patients of the IS by dose level combination and overall.

For Hepatitis markers B virus surface antigen (HbsAg), B virus surface antibody (HbsAb), B virus core antibody (HbcAb), hepatitis C virus (HCV) RNA-PCR, hepatits E virus (HEV) RNA-PCR: Descriptive statistics at baseline by classes (negative, positive).

Hepatitis B virus (HBV)-DNA tests: if HbsAg or HbcAb positive at baseline.

3.2.4.7. Initial disease assessments

The frequency distribution (n, %) will be provided in patients of the IS by dose level combination and overall. The following categorical variables will be described by frequency distribution (n, %):

- BM blasts (%)
- BM Auer rods
- Presence of Myelodysplasia
- Neutrophils
- Platelets
- PB Blasts (%)
- Platelets transfusion dependent
- Red blood cells transfusion dependent

3.2.4.8. Medical and surgical history not related to AML

Medical and surgical history other than for the AML will be summarized by SOC and PT according to the Medical Dictionary for Regulatory Activities (MedDRA) dictionary in patients of the IS.

3.2.4.9. Vital signs and clinical examination at baseline

Descriptive summary statistics (n, mean, SD, median, min, max, median, Q1, Q3) will be provided for variables measured on a continuous scale including:

- Weight (kg).
- Height (cm).
- Supine systolic blood pressure (SBP).
- Supine diastolic blood pressure (DBP).
- Supine heart rate (HR).

The frequency distribution (n, %) will be provided in patients of the IS by dose level combination and overall for variables measured on a nominal scale according to the following classes:

- ECOG (0, 1, 2, 3, 4).
- Supine SBP (< 90 mmHg , [90-140 mmHg[, ≥ 140 mmHg).
- Supine DBP(< 60 mmHg , [60-90 mmHg[, ≥ 90 mmHg).
- Supine HR (< 60 bpm , [60-100 bpm[, ≥ 100 bpm).

3.2.4.10. Centralised ECG at baseline

Descriptive summary statistics (n, mean, SD, median, min, max, median, Q1, Q3) will be provided for variables measured on a continuous scale including QT interval (uncorrected) and Fridericia QT interval corrected for heart rate (QTcF).

The frequency distribution (n, %) will be provided in patients of the IS by dose level combination and overall for variables measured on a nominal scale according to the following classes:

- Presence of ECG abnormalities (Yes, No).
- Presence of clinically significant ECG abnormalities (Yes, No).
- QT interval (uncorrected and Fridericia corrected) in classes (≤ 450 ms,]450-480] ms,]480-500] ms and > 500 ms).

3.2.4.11. LVEF at baseline

Descriptive summary statistics (n, mean, SD, median, min, max, median, Q1, Q3) will be provided for LVEF. The frequency distribution (n, %) will also be provided in patients of the IS by dose level combination and overall, according to the following classes:

- LVEF (< 50%, [50-70%], >70%).

3.2.4.12. Chest X-Ray

The frequency distribution (n, %) will be provided in patients of the IS by dose level combination and overall for Chest X-Ray, according to the following classes:

- Chest X-Ray performed (Yes, No).

3.2.4.13. TLS prevention

All concomitant treatments for TLS prevention taken at inclusion and before the treatment period will be described for each dose level combination and overall in the SS, by Anatomical Therapeutic Chemical (ATC) code into 4 levels (Pharmacological class, Pharmacological sub-class, therapeutic class, Preferred name). TLS risk category, type of hydration performed and anti-hyperuricaemic administration will also be presented.

3.2.5. Treatments of patients

3.2.5.1. Extent of treatment exposure and treatment compliance

Details concerning definition on extent of exposure, treatment compliance are provided in Appendix 4.2.1.5.

For S64315 and azacitidine separately the frequency distribution (n, %) or descriptive summary statistics (n, mean, SD, median, min, max, median, Q1, Q3) as applicable will be provided in

patients of the SS by planned dose level combination and overall for variables measured on a nominal scale according to the following classes:

- Extent of exposure*:
  - The global treatment duration (combined measure for S64315/azacitidine): summary statistics.
  - Treatment duration (weeks) overall and by treatment period (LID/Combination treatment).
  - Treatment duration (weeks) during combination treatment period (i.e., excluding LID) (< 4 weeks, [4-12[weeks, [12-24[weeks, [24-36[weeks, [36-48] weeks, >48 weeks).
  - LID duration (]0-1] week,]1-2] weeks and > 2 weeks).
  - Number of cycles (1 cycle, 2 cycles, 3-6 cycles, 7-10 cycles, > 10 cycles) during the combined treatment period.
  - Number of patients by cycle (LID, Cycle 1, Cycle 2, etc).
- Treatment compliance*:
  - Cumulative dose (mg) for S64315/ Cumulative dose (mg/m^2) for azacitidine overall, by cycle (including LID), and for combination treatment.
  - Dose intensity (DI) (mg/week) for S64315/ DI (mg/m^2/day) for azacitidine overall, by cycle (including LID), and for combination treatment.
  - Relative Dose Intensity (RDI) (%) for S64315/azacitidine overall, by cycle (including LID), and for combination treatment.
  - RDI for S64315(< 35%, [35-65[%, [65-100[%, ≥ 100%) overall, by cycle, and per treatment period (LID/Combination treatment).
  - RDI for azacitidine (< 62%, [62-85[%, [85-100[%, ≥ 100%) overall, by cycle, and per treatment period (Combination treatment).
  - Treatment interruption (Yes/No) during treatment period (including LID).
  - Reason of treatment interruption (Medical reason, Non-medical reason, Missing).
  - LIDLIDNumber of cycles with at least one treatment interruption for S64315 during treatment period (including LID).
  - Number of cycles with at least one treatment interruption for azacitidine during treatment period.
  - Cycle delayed (Yes/No) during treatment period (including LID).
  - Reason for cycle delayed (Medical reason, Non-medical reason, Missing).
  - Number of cycles delayed during treatment period (including LID).
  - Number of cycles delayed (1, 2, > 2) during treatment period (including LID).
- Specifically for S64315, the summary of treatment compliance will also will include:
  - Dose modified (Yes/No) during treatment period (including LID).
  - Number of dose modifications during treatment period (including LID).
  - Number of dose modifications (1, 2, > 2) during treatment period (including LID).
  - Time to first dose modification (days) during treatment period (including LID).
  - Partial dose administered (Yes/No) during treatment period (including LID).

  - Number of cycles with partial dose for S64315 during treatment period (including LID).
  - Number of cycles with partial dose for S64315 (1, 2, > 2) during treatment period (including LID).
- Specifically for azacitidine, the summary of extent of exposure will include:
  - Average number of days dosed per cycle with planned dose level for azacitidine overall.
  - Average number of days dosed overall.
  - Number of azacitidine interruption days.

* Applicable for both S64315 and azacitidine if not specified.

3.2.5.2. Concomitant treatments

Details concerning definition on concomitant treatments are provided in Appendix 4.2.1.6.
All concomitant treatments taken during the study period will be described for each administered dose level combination, and overall, in the SS, by ATC code into 4 levels (pharmacological class, pharmacological sub-class, therapeutic class and preferred name) and into 1 level (pharmacological class only). Concomitant treatments only during the study period are described because we will have an abbreviated CSR for the CL1-64315-004.

3.2.6. Other observations related to patient follow-up

We will have an abbreviated CSR for the CL1-64315-004, therefore, follow-up analysis is not applicable.

3.3. Efficacy analysis

We will have an abbreviated CSR for the CL1-64315-004, therefore, efficacy analysis is not applicable.

3.4. Safety endpoints

All safety analyses will be performed in the SS (resp. DLTES for DLT analysis) by treatment dose level combination and overall. The treatment period is defined from first IMP intake up to last IMP intake date + (*) days.
(*) 30 days for AE and death analysis, 28 days for clinical laboratory evaluation, vital signs and clinical examination, centralized ECG and LVEF analysis.

Qualitative data will be presented in number and percentage of patients per class, while quantitative data will be presented in mean, SD, min and max, median, Q1 and Q3.

Calculation rules for expressions of safety endpoints, as well as general definitions (such as value prior to treatment / under treatment, analysable value, first and last IMP intake dates…), are provided in Appendix 4.1.

Calculation rules for safety endpoints and other specific definitions are provided in Appendix 4.2.

3.4.1. Dose limiting toxicity

Number and percentage of patients with at least one DLT before the end of the first cycle, type of DLT and listing of PTs, verbatim and worst grade of AE declared as DLT will be provided in the DLTES.
Listing of patients with at least one DLT, type of DLT and PTs, verbatim will also be provided in the DLTES.

3.4.2. Adverse events

Number of events, number and percentage of patients reporting at least one event, presented by primary SOC and PT (depending on the analysis), will be provided for SAEs over the study period and for treatment emergent adverse events (TEAEs).

TEAE will be described according to the seriousness, the worst grade, the severity, the relationship, the action taken regarding the IMP(s), the requirement of added therapy and the outcome.

Of note, the seriousness and the relationship with the IMPs (S64315 and/or azacitidine) of the adverse event are based on the investigator's opinion, but it includes also the sponsor decision to upgrade the seriousness and/or the relation to IMP(s) (the causal relationship will not be upgraded for EudraCT analyses).

The National Cancer Institute Common Terminology Criteria for Adverse Events Common Terminology Criteria for Adverse Events (NCI-CTCAE) classification version 5.0 will be used to classify all adverse events.

3.4.3. Death

Number and percentage of deaths will be described on each period (during the treatment and follow-up period / during the treatment period / during the follow-up period). Reason of death on each period will be provided in terms of qualitative data. During treatment period, reason will be presented by SOC and PT, whereas during the follow-up period it will be presented in terms of either progressive disease or other reason.

3.4.4. Clinical laboratory evaluation

Descriptive statistics on quantitative value and value by grade at baseline and worst grade on treatment according to the grade at baseline will be provided for gradable parameters (see Table (3.4.4) 1).

Table (3.4.4) 1 – Gradable parameters

Parameter		**Worst Highest**	**Worst lowest**	**Gradable at baseline***
Blood biochemistry	Alanine aminotransferase (ALT)	High ALT	NA	No
	Albumin	NA	Low albumin	Yes
	Alkaline phosphatase (ALP)	High ALP	NA	No
	Amylase	High amylase	NA	Yes
	Aspartate aminotransferase (AST)	High AST	NA	No
	Bilirubin (total)	High total bilirubin	NA	No
	Cholesterol (total)	High cholesterol	NA	Yes
	Creatine phosphokinase (CPK)	High CPK	NA	Yes
	Gamma-glutamyl transferase (gamma-glutamyl transpeptidase) (GGT)	High GGT	NA	No
	Creatinine (serum)	High serum creatinine	NA	Yes
	Glucose	NA	Hypoglycemia	Yes
	Lypase	High lipase	NA	Yes
	Magnesium	Hypermagnesemia	Hypomagnesemia	Yes
	Potassium	Hyperkalemia	Hypokalemia	Yes
	Sodium	Hypernatremia	Hyponatremia	Yes
	Triglycerides	High triglycerides	NA	Yes
	Ionized calcium	High ionized calcium	Low ionized calcium	Yes
Blood haematology	Haemoglobin	High haemoglobin	Anemia	Yes for Low / No for High
	Lymphocytes	NA	Low lymphocytes	Yes
	Neutrophils	NA	Low neutrophils	Yes
	White blood cells (WBC)	NA	Low WBC	Yes

	Platelets	NA	Low platelets	Yes
Blood coagulation	Activated partial thromboplastin time (aPTT)	High aPTT	NA	Yes

Descriptive statistics on quantitative value and value by reference ranges at baseline and worst value on treatment according to baseline, with respect to the lower-limit notmal (LLN) and the upper-limit normal (ULN) or by classes (<LLN / [LLN-ULN] / >ULN or normal / mild / moderate / severe for creatinine clearance) will be provided for non-gradable parameters (see Table (3.4.4) 2) and for parameters gradable post-baseline but non-gradable at baseline, in which case only baseline values will be presented.

Table (3.4.4) 2 – Non Gradable parameters

Parameter		**Worst Highest**	**Worst lowest**
Blood biochemistry	Bicarbonates	NA	Low bicarbonates
	Uric acid	High uric acid	NA
	Calcium (total)	Hypercalcemia	Hypocalcemia
	Creatinine clearance (approximated by the Modification of Diet in Renal Disease Glomerular Filtration Rate (MDRD_GFR))	NA	Low creatinine clearance (Normal/mild/ moderate/severe)
	Direct bilirubin	High direct bilirubin	NA
	High-density lipoprotein (HDL)	High HDL	NA
	Lactate dehydrogenase (LDH)	High LDH	NA
	Low-density lipoprotein (LDL)	High LDL	NA
	Phosphorus	NA	Hypophosphatemia
	Troponin I	High troponin I	NA
	Troponin T	High troponin T	NA
	Urea	High urea	NA
	Urea nitrogen (blood) (BUN)	High BUN	NA
Blood haematology	Basophils	NA	Low basophils
	Eosinophils	High eosinophils	NA
	Haematocrit	High haematocrit	Low haematocrit
	Monocytes	High monocytes	NA
	Red Blood Cell (RBC) Count	High RBC	Low RBC
	Lymphocytes	High lymphocytes	NA

	White Blood Cell (WBC) Count	High WBC	NA
Thyroid function	T3 free	High T3 free	Low T3 free
	T4 free	High T4 free	LowT4 free
	Thyroid Stimulating Hormone (TSH)	High TSH	Low TSH
Cardiac markers	Creatine PhosphoKinase Myocardial Band (CPK-MB) activity	High CPK-MB activity	NA
	CPK-MB mass	High CPK-MB mass	NA
	Brain Natriuretic Peptide (BNP)	High BNP	NA
Blood coagulation	International normalized ratio (INR)	High INR	NA

For urinalysis parameters haematuria, glycosuria, proteinuria, ketonuria: Descriptive statistics at baseline and worst value on treatment period, by classes (negative, trace, positive).

3.4.5. Vital signs and clinical examination

Vital signs and clinical examination will be described, in terms of quantitative value and value by classes at baseline, worst (highest and/or lowest) value under treatment, and absolute and change (and relative change for weight as well) from baseline to worst (highest and/or lowest) value under treatment for:

- SBP (<90, [90-140[and ≥ 140 mmHg).
- DBP (<60, [60-90[, ≥ 90 mmHg).
- HR (<60, [60-100[and ≥ 100 bpm).
- ECOG status (0, 1, 2, 3, 4, 5).
- Weight (relative baseline change measured as <-10%, ≥ -10%).

3.4.6. Centralised ECG

QT interval (uncorrected and corrected Fridericia) during the treatment period will be described in terms of:

- Maximum absolute prolongation.
- Maximum change from baseline.

Values and changes from baseline of corrected QT interval will be described in classes, considering thresholds defined in ICH E14:

- Values: ≤ 450,]450-480],]480-500] and > 500.
- Changes: ≤ 30,]30-60] and > 60.

Emergent ECG and emergent clinically significant ECG abnormality during treatment period will be described.

3.4.7. LVEF

LVEF will be described, in terms of quantitative value:

- At baseline.
- Worst (*lowest*) post-baseline value under treatment.
- Change from baseline to worst (lowest) post-baseline value under treatment.

Moreover, values and change from baseline of LVEF will be described in classes:

- Values:<40 / [40-50[/ ≥ 50%.
- Change and relative change: ≤ -10% / > -10%.

The worst (lowest) value under treatment will also be described by grade according to NCI-CTCAE version 5.0 (Grade 0 / Grade 2/ Grade 3 / Grade 4).

3.5. Exploratory analysis

All exploratory biomarker analysis results will be presented in a separate report.

3.6. Interim analysis

N.A.

4. APPENDICES

4.1. General analytic definitions

Definitions below correspond to calculation rules for expressions defined in Section 3.2, 3.3, 3.4 as well as definition of value prior to treatment / under treatment, analysable value, first and last IMP intake dates and other general definitions.

4.1.1. Expressions

Reliable value

For biological and coagulation samplings:

Identified with flag BIOFG (“Non analysable value”) different from 1 and non-missing result.

For other panels:

Non-missing result.

Value at baseline is defined as the last reliable (i.e. last non-missing) value prior to treatment.

Note: In case of patient included but not treated (i.e. patients with treatment duration equal to 0): value at baseline is defined as the last analysable value prior to the LID (i.e. "Visit<C000").

Baseline value of cycle n is defined as the last reliable (i.e. last non-missing) value prior to first study treatment intake of cycle n.

Value at the Cycle n Day n is defined as the first reliable (i.e. first non-missing) value at the visit.

Post-baseline value is defined as available value after the first IMP intake or, in case of missing first intake, after the date visit superior (>) to last inclusion visit (A000).

End post-baseline value is defined as the last reliable post-baseline value of the criteria of interest during the treatment period.

Worst post-baseline value is defined as the worst reliable post-baseline value of the criteria of interest during the treatment period.

Lowest/highest post-baseline value is defined as the lowest/highest value during the treatment period.

Change from baseline to worst post-baseline value is calculated as:
Worst post-baseline value - Value at baseline.

Change from baseline to lowest/highest post-baseline value is calculated as:
Lowest/highest post-baseline value - Value at baseline.

Relative change from baseline to highest/lowest value (%) is calculated as:

$$\left(\frac{(Highest|Lowest\ value\ during\ the\ period\ of\ interest - Value\ at\ baseline)}{Value\ at\ baseline}\right) * 100.$$

4.1.2. First and last IMP intakes dates

For patients having taken at least one dose of IMP (S64315 or azacitidine), the dates of first and last IMP (S64315 or azacitidine) intake on the analysis period (including LID) will be defined as follows:

- The date of the first IMP intake within the analysis period (including LID).
- The date of the last IMP intake within the analysis period (including LID):
  max(last intake date of last cycle of S64315, last intake date of last cycle of azacitidine).

Note: For azacitidine, cycles with both missing first and last IMP intake dates and with administered dose missing or equal to 0 will not be taken into account.

After selection of the dates of first and last IMP intake as defined above, if these dates are missing or incomplete, the following substitution rules will be applied:

Table (4.1.2) 1 - Substitution rules of *IMP* intake dates

Date to substitute		Substituted date
First *IMP* (S64315 or azacitidine) intake	../mmm/yyyy	**Inclusion date** if complete with same month and year *Otherwise:* **01/mmm/yyyy**
	../…/yyyy	**Inclusion date** if complete with same year *Otherwise:* **01/JAN/yyyy**
	../.../….	**Inclusion date** if complete
Last *IMP* (S64315 or azacitidine) intake	../mmm/yyyy	**Last available date*** if same month and year *Otherwise:* **Last day of the month/mmm/yyyy**
	../…/yyyy	**Last available date*** if same year *Otherwise:* **31/DEC/yyyy**
	../.../….	**Last available date* Last available date****

Notes:
- *Missing dates will be substituted only for patients having taken at least one dose of study treatment:*
  ../mmm/yyyy = missing day.
  ../.../ yyyy = missing day and month.
  ../.../.... = totally missing date.

******* *Last available date (only for patients included) is defined as date of death if patient died, and as maximum date among completed dates relative to patient's information otherwise.*

4.1.3. Value prior to treatment / under treatment

Table (4.1.3) 1 - Time frame

Criteria	**Value prior to treatment if measured between (D1=) days before and (D2=) days after the first *IMP* intake** (D1 and D2 included)		**Post-baseline value on treatment period if measured between (D1=) days after the first *IMP* intake and until (D2=) days after the last *IMP* intake** (D1 and D2 included)	
Disease assessment	D1 = 21	D2 = Xsup	D1 = Xinf	D2 = 28
Biochemistry / haematology / thyroid function / coagulation / hepatitis markers	D1 = 21	D2 = Xsup	D1 = Xinf	D2 = 28
Vital signs	D1 = 21	D2 = Xsup	D1 = Xinf	D2 = 28
ECG/LVEF	D1 = 21	D2 = Xsup	D1 = Xinf	D2 = 28
Pregnancy Test	D1 = 21	D2 = Xsup	D1 = Xinf	D2 = 28
All other criteria (death and AE excepted)	D1 = 28	D2 = Xsup	D1 = Xinf	D2 = 28*

*Xsup: 0 and" Visit< "**".*
*Xinf: 0 and" Visit ≥"**".*
(*):30 days for AE and death analysis.
(**) Visit number depending on the panel

4.1.4. General duration derivation and conversion

In instances where duration or times-to-event are calculated, the convention to be used unless otherwise specified is [later date] – [earlier date] + 1 day.

When converting a number of days to other units, the following conversion factors will be used: 1 year = 365.25 days; 1 month = 30.44 days.

4.1.5. Analysable value

Table (4.1.5) 1 - Definition of analysable value

General definition Non missing value	
Specific definitions	
Laboratory parameters	Only reliable values are considered for analyses. Unreliable values are flagged into the database.
ECG parameters	For the analysis of QT criteria per measurement time, only values at each scheduled post-baseline visits will be analysed. All data obtained from triplicate ECGs are taken into account in the analysis. For ECGs, for each measurement time, the mean of available values is calculated and taken into account in the analyses. The measurement times of QT criteria will be those fulfilled in the database and transferred by Banook Group.
PB blasts BM blasts	Having at least 20% blasts in the BM or PB is used for diagnosis of AML. In normal BM the blast count is 5% or less, while PB usually doesn't contain any blasts. PB or BM blast percentages (%) are also monitored for diagnosis, management, and follow up of AML patients. All values [0, 100[are considered for analyses.

4.1.6. Management of other dates

The rules for substitution of missing or incomplete death date are as follows:

Table (4.1.6) 1 - Substitution rules of death date

Date to substitute		Substituted date
Death date	../mmm/yyyy	**Last available date*** if same month and year *Otherwise:* **01/mmm/yyyy**
	../…/yyyy	**Last available date*** if same year *Otherwise:* **01/JAN/yyyy**
	../.../….	**No substitution**

Notes:

../mmm/yyyy = missing day.
../.../ yyyy = missing day and month.
../.../.... = totally missing date.

- ** Last available date is defined as maximum date among completed dates relative to patient's information otherwise.*

If no specific management of dates is defined, missing information is substituted as defined below:

Table (4.1.6) 2 - Substitution rules of dates if no specific management is defined

Date to substitute		Substituted date
Date	../mmm/yyyy	01/mmm/yyyy
	../…/yyyy	01/JAN/yyyy
	../.../….	No substitution

Notes:

../mmm/yyyy = missing day.
../.../ yyyy = missing day and month.
../.../.... = missing date.

For assessments with time also collected and useful for the analysis, substitution rules are as follows:

Table (4.1.6) 3 - Substitution rules of dates and times if no specific management is defined

Date and time to substitute		Substituted date and time
Date	dd/mmm/yyyy hh-…	dd/mmm/yyyy hh:00
	dd/mmm/yyyy …-…	dd/mmm/yyyy 00:00
	../mmm/yyyy …-…	01/mmm/yyyy 00:00
	../…/yyyy …-…	01/JAN/yyyy 00:00
	../.../…. …-…	No substitution

Notes:

hh-... = missing minutes.
...-... = missing time.
../mmm/yyyy = missing day.
../.../ yyyy = missing day and month.
../.../.... = missing date.
(as seconds are not collected in the electronic case report form (e-CRF) they will always be substituted by 00).

4.2. Specific analytic definitions and data handling conventions

4.2.1. Study patients: Disposition, baseline characteristics and follow-up

4.2.1.1. Disposition of patients

All withdrawal reasons occurred in the study will be taken into account.

4.2.1.2. Protocol deviations

For the description of protocol deviations, the 6 following categories are considered in accordance with ICH E3 guideline and ICH E3 Q&A:

- Selection/inclusion criteria not fulfilled.
- Patient having withdrawal criteria but not withdrawn.
- Incorrect treatment or dose received.
- Forbidden concomitant treatment.
- Endpoint assessment possibly affected.
- Safety possibly affected.

4.2.1.3. Demographic data and other baseline characteristics

4.2.1.3.1. Demographic data

Age (years) is calculated in the ClinTrial database as:

(Date of inclusion – Date of birth)/365.25.

The result is truncated and not rounded. If the day and/or month of inclusion date and/or birth date is/are missing, the calculation is done by using the year.

4.2.1.3.2. History of AML

Disease duration

Disease duration (years) is calculated as:

(Inclusion visit date – Date of the first diagnosis)/365.25.

Treatment free interval

Treatment-free interval since previous AML treatment line (days) and Treatment-free interval since previous MDS treatment line (days) are defined as:

(Date of first IMP intake – Date of end of the last prior drug therapy).

Of note, in case of partial or incomplete dates:

Missing diagnosis date		Substituted diagnosis date
../mm/yyyy	⇨	Diagnosis date=**01**/mm/yyyy
../…/yyyy	⇨	Diagnosis date=**01/01/**yyyy
Missing end date of the last prior therapy		**Substituted end date of the last prior therapy**
../mm/yyyy	⇨	End date of the last prior therapy=start date of the last prior therapy + 1 day if same month and year *otherwise*: End date of the last prior therapy =01/mm/yyyy
../…/yyyy	⇨	End date of the last prior therapy=start date of the last prior therapy + 1 day if same year *otherwise*: End date of the last prior therapy=01/01/yyyy
../…/…	⇨	End date of the last prior therapy=start date of the last prior therapy + 1 day

Notes:

If start date of the last prior therapy is partially or completely missing, follow the substitution rules if no specific management is defined (Table (4.1.6) 2 - Table (4.1.6) 3).

../mm/yyyy = missing day.

../.../ yyyy = missing day and month.

4.2.1.3.3. Medical history and surgical or medical procedures history other than AML

The existence of a history (Yes/No) is defined from the presence, or not, of a primary SOC and/or PT, persistent or not at the time of study entry.

4.2.1.3.4. Signs and symptoms related to AML or prior therapies received for studied disease

The existence of a sign or symptom (Yes/No) is defined from the presence, or not, of a primary SOC and/or PT.

4.2.1.3.5. Previous therapies for AML

Of note, for patients entering the study with an AML secondary to MDS, previous therapies will be reported concerning AML treatment only.

The ATC classification (ATC code = 5 digits) is composed of 4 levels:

- The first (1 digit) represents the anatomo-physiological class.
- The second (2 digits) represents the pharmacological class.
- The third (1 digit) represents the pharmacological sub-class.
- The last (1 digit) represents the therapeutic class.

Previous treatment is defined as any treatment recorded in the eCRF page "Previous drug treatments for acute myeloid leukaemia (AML) or for previous myelodysplastic syndrome (MDS)".

The existence of a previous radiotherapy (Yes/No) is defined from the presence or not of a verbatim for the previous radiotherapy involved site at inclusion visit.

The existence of a previous drug treatment (Yes/No) is defined from the presence, or not of an "ATC classification" and/or a "preferred name" for the previous drug treatment at inclusion visit.

The existence of a previous transplant (Yes/No) is defined from the presence, or not of previous transplant date at inclusion date.

The existence of a previous surgery (Yes/No) is defined from the presence or not of a verbatim for the previous surgery at inclusion visit.

The number of treatment lines is calculated as the sum of all previous treatment lines received, since diagnosis date of the studied disease (regardless the type of therapy).

The number of relapses is calculated as the sum of all previous lines with CR (including CR MRD-, CR, CRi and Haematologic relapse responses) as best response received, since diagnosis date of the studied disease (regardless the type of therapy).

The specific treatment lines described with the corresponding code lists are the following:
- 3427.1 Cytarabine 20221(WHODDB3).
- 3601.2 Treatments containing fludarabine 20221 (WHODDB3).
- 3428.2 Anthracyclines and related substances 20221(WHODDB3).
- 4273.0 Hypomethylating agents (HMAs) for CL164315004 study 20221 (WHODDB3).
- 3430.1 Azacitidine 20221(WHODDB3).
- 3422.1 Decitabine 20221(WHODDB3).
- 3429.1 Lenalidomide 20221(WHODDB3).
- 3594.2 Investigational drugs 20221(WHODDB3).
- Stem cell transplant and bone marrow transplant (no code list associated – To refer to previous transplant section allograft or autograft)
- 1869.0 Systemic and local treatment containing glucocorticoids DDB320221.
- 1728.2 Treatments containing an alkylating agent DDB320221.
- 3600.2 Treatments containing cyclophosphamide 20221(WHODDB3).
- 3602.0 Treatments containing antimetabolites agents DDB320221.
- 3609.0 Treatments containing protein and tyrosine kinase inhibitors DDB320221.
- 3605.1 Treatments containing etoposide 20221(WHODDB3).
- 3914.0 Granulocyte colony stimulating factor 20221(WHODDB3).
- 4131.1 Treatments containing enasidenib 20221(WHODDB3).
- Gemtuzumab ozogamicin (Mylotarg®) (drug code: 15959801001, version WHODDB32022.1)
- Ivosidenib (Tibsovo®) (drug code : 09165501001, version WHODDB32022.1)

No substitution of missing or incomplete previous drug treatments are applied.

4.2.1.3.6. Initial disease assessment

PB blasts in blood expressed in SI unit (G/L) in “blood haematology” form will be converted to % unit by dividing by the corresponding WBC value.

Information concerning platelets transfusion-independence prior to LID1 and red blood cells transfusion-independence prior to LID1 (i.e. before the first IMP intake) will be retrieved from the “History of the Acute Myeloid Leukaemia” e-CRF form. The patients having received a transfusion prior to LiD1 will be considered as transfusion-dependent.

4.2.1.4. TLS prevention

TLS prevention treatment lines (anti-hyperuricemic therapy) are referenced in the code list n°3399.0 WHOODB3 20221.

4.2.1.5. Extent of exposure and treatment compliance

Global treatment duration

Global treatment duration (weeks) is defined as (min [max (last intake date of the last cycle azacitidine + 21 days, last intake date of S64315 + 6 days), death date, withdrawal date] - first *IMP* intake + 1)/7.

Treatment duration for S64315 including LID period (QW)

Treatment duration (days) for S64315 is defined as [(min (last infusion date + 6 days, death date, withdrawal date) - first S64315 infusion date) +1].

Treatment duration (weeks) for S64315 is defined as [(min (last infusion date + 6 days, death date, withdrawal date) - first S64315 infusion date) +1] /7.

Treatment duration for S64315 excluding LID period (QW)

Treatment duration (days) for S64315 is defined as [(min (last infusion date + 6 days, death date, withdrawal date) - first S64315 infusion date of cycle 1) +1].

Treatment duration (weeks) for S64315 is defined as [(min (last infusion date + 6 days, death date, withdrawal date) - first S64315 infusion date of cycle 1) +1] /7.

Treatment duration for azacitidine

Treatment duration (days) for azacitidine is defined as [min (last intake date of the last cycle + 21 days, death date, withdrawal date) - first azacitidine intake + 1].

Treatment duration (weeks) for azacitidine is defined as [min (last intake date of the last cycle + 21 days, death date, withdrawal date) - first azacitidine intake + 1]/7.

S64315 treatment duration in LID period:

S64315 treatment duration in LID period LID(days) is defined as [min (first S64315 infusion date of cycle 1-1, death date, withdrawal date) – first S64315 infusion date of LID1]+1.

Note: In case of missing first S64315 at cycle 1, S64315 treatment duration in LID period is defined as [min(last S64315 infusion date in LID +6, death date, withdrawal date) - first S64315 infusion date of LID]+1. LIDLID

LID period duration (weeks): LID period duration (days) / 7.

Cycle duration for S64315

Duration of cycle *i* (weeks) for S64315 is defined as [first *IMP* intake of cycle (*i+1*) – first *IMP* intake of cycle *i*] /7.
Note: The duration of the last cycle for S64315 will be estimated to be 4 weeks for the calculation of dose intensity and relative dose intensity at the last cycle.

Cycle duration for azacitidine

Duration of cycle *i* (weeks) for azacitidine is defined as [first *IMP* intake of cycle (*i+1*) – first *IMP* intake of cycle *i*] /7.

Of note,

- The duration of the last cycle for azacitidine will be defined as [(last intake of last cycle + 21 days) – first intake of last cycle + 1] /7.

Numbers of cycles for S64315/azacitidine

The number of cycles with study drug intake for S64315/azacitidine will be defined based on patient exposure data while on treatment excluding S64315 LID period. A patient is considered to enter in a cycle if there is at least one intake date.

Real administrated dose of S64315 will be recorded directly from S64315 infusion e-CRF page. For information, the administrated dose is recorded in mL within e-CRF. The conversion of the real administrated dose in mg is directly calculated by the data manager. Little variation between planned dose and real administrated dose can be expected due to feasibility (IMP preparation and injection).

Planned dose intensity (PDI) for S64315 (mg/week)

Planned dose intensity (PDI) for S64315 (mg/week)	**Schedule (QW)** *4* intakes per cycle /1 intake per LID week
Dose Level -1: ***25*** mg*	***25*** mg/ week*
Dose Level 1: ***50*** mg**	***50*** mg/ week**
Dose Level 2: ***100*** mg	***100*** mg/ week
Dose Level 3: ***200*** mg	***200*** mg/ week
Dose Level 4: ***250*** mg	***250*** mg/ week

* LID1 dose.
** LID2 dose

However, it is possible that intermediate or higher dose levels are added during the course of the study.

Cumulative dose for S64315

The cumulative dose (mg) for S64315 per patient in a time period (during the treatment period including LID or per cycle) is the sum of the total dose levels that the patient received within that period according to the compliance.

$$Cumulative\ dose\ (mg) = \sum_{timeperiod} \left(Real\ Administrated\ dose\ (mg)\right).$$

Dose intensity (DI) for S64315

The dose intensity (*mg/ week*) for S64315 per patient is defined as the cumulative dose (mg) received during the treatment period divided by the total treatment duration in weeks, including LID period.

$$DI\ \left(\frac{mg}{wk}\right) per\ patient\ = \frac{Cumulative\ dose\ (mg)}{Treatment\ duration\ (weeks)}.$$

The dose intensity (*mg/ week*) for S64315 per cycle is defined as the cumulative dose (mg) received during the cycle divided by the cycle duration in weeks.

$$DI\ \left(\frac{mg}{wk}\right) at\ cycle\ i\ =\ \frac{Cumulative\ dose\ (mg)\ received\ at\ cycle\ i}{Duration\ of\ cycle\ i\ (weeks)}.$$

The duration of the last cycle will be estimated to be *(*)* weeks.

(*): 4 weeks for regimen QW, 2 week for LID.

Relative dose intensity (RDI) for S64315

The RDI (%) for S64315 per patient measures the percentage of the total trial dose planned that was really administered. It is defined as the ratio of the dose intensity (mg/week) to the initial planned dose intensity (mg/week)

$$RDI\ (\%)\ per\ patient\ =\ \frac{DI\ (mg/wk)}{Planned\ dose\ intensity\ (mg/wk)} * 100.$$

The RDI (%) for S64315 per cycle is defined as the ratio of the dose intensity (mg/week) at cycle *i* (including LID cycles) to the planned dose intensity (mg/week).

$$RDI\ (\%)\ at\ cycle\ i\ =\ \frac{DI\ at\ cycle\ i\ (mg/wk)}{Planned\ dose\ intensity\ at\ cycle\ i\ (mg/wk)} * 100.$$

Treatment interrupted for S64315

A treatment interruption is defined according to the S64315 infusion e-CRF page (Did the patient receive the IMP infusion (Yes/No)).

Number of cycles with at least one treatment interruption for S64315 experienced by a patient over the treatment period will be calculated.

Cycle delay for S64315

A cycle delay is defined according to the S64315 infusion e-CRF page (infusion postponed (Yes/No) at D2 of the cycle *i* or of LID2). Moreover, a delay of LID2 will be also considered if the duration of the LID1 is higher than 7 days, while a delay of cycle *i* will be also considered if the duration of the cycle *i*-1 is higher than *(*)*. In case of missing cycle delay reason, reason of cycle delay will be considered as unknown. The delay in days will be derived, based on the dates of administration.

Delay (days) of cycle $_i$ = (first *IMP* intake of cycle *i*) – (first *IMP* intake of cycle *i-1 + x days*).

(*): 30 days for regimen QW (theoretical cycle duration + 2 days for potential technical or logistical difficulty). In the delay duration formulae above *x=30.*

(*) x=16 days if Cycle i-1 is the LID period.

Number of cycles delayed for S64315 experienced by a patient over the treatment period will be calculated among patients experiencing a cycle delay.

Dose modification for S64315

A dose modification is defined according to the S64315 infusion e-CRF page (Has the dose been modified since the last infusion (Yes/No), with a dose level different from the dose level at previous infusion).

Number of dose modifications for S64315 experienced by a patient over the treatment period will be calculated among patients experiencing a dose modification.

Time to first dose modification for S64315 will be calculated among patients experiencing a dose modification from the first study drug intake until the first dose modification.

Partial dose administered for S64315

A partial dose administered is defined according to the S64315 infusion e-CRF page (Was full dose administered ? (Yes/No))

Number of cycles with partial dose experienced by a patient over the treatment period will be calculated among patients.

Number of days dosed for azacitidine

The number of days dosed for azacitidine is defined as the total number of days with azacitidine intake (overall and by cycle).

Average number of days dosed per cycle for azacitidine

The average number of days dosed per cycle for azacitidine is defined as the total number of days dosed for azacitidine divided by the number of cycles according to the period of interest (i.e. for overall period: number total of cycles / for each cycle: 1):

$$Average\ days\ dosed\ per\ cycle\ = \frac{Total\ number\ of\ days\ dosed}{Number\ of\ cycles}.$$

Number of days dosed with planned dose level for azacitidine

The number of days dosed with planned dose level for azacitidine is defined as the total number of days with azacitidine intake corresponding to the planned dose level of 75 mg/m^2 (the actual dose administered is equal to 75mg/m^2 or within the interval 75 ±7.5 mg/m^2).

Average number of days dosed per cycle with planned dose level for azacitidine

The average number of days dosed with planned dose level for azacitidine per cycle is defined as the total number of days dosed with planned dose level for azacitidine divided by the number of cycles according to the period of interest (i.e. for overall period: number total of cycles / for each cycle: 1):

$$Average\ days\ dosed\ with\ planned\ dose\ level\ per\ cycle = \frac{Total\ number\ of\ days\ dosed\ with\ planned\ dose\ level}{Number\ of\ cycles}.$$

Real administrated dose of azacitidine will be recorded directly from azacitidine injection e-CRF page (Administered dose (mg)).

Planned dose intensity (PDI) for azacitidine:

Planned dose intensity (day): 75 mg/m^2/day (fixed).

Planned dose intensity (cycle or overall): (75 mg/m^2/day (fixed) * 7) / 28.

Cumulative dose for azacitidine

The cumulative dose (mg/m²) for azacitidine per patient during a time period (during the treatment period or per cycle) is the sum of the total dose levels that the patient received between the first and last treatment intake according to the compliance.

$$Cumulative\ dose\ (mg/m^2) = \sum_{timeperiod} \left(\frac{Real\ Administrated\ dose\ (mg)}{BSA\ (m^2)} \right).$$

Dose intensity (DI) for azacitidine

The dose intensity (mg/m²/day) for azacitidine per patient is defined as the cumulative dose (mg/m²) received during the treatment period divided by the overall treatment duration of azacitidine.

$$DI\left(\frac{mg/m^2}{day}\right) per\ patient\ = \frac{Cumulative\ dose\ (mg/m^2)}{Overall\ treatment\ duration\ of\ azacitidine}.$$

The dose intensity (mg/ day) for azacitidine per cycle is defined as the cumulative dose (mg) received during the cycle divided by the cycle duration of azacitidine.

$$DI\left(\frac{mg/m^2}{day}\right) at\ cycle\ i\ = \frac{Cumulative\ dose\ (mg/m^2)\ received\ at\ cycle\ i}{Cycle\ i\ duration\ of\ azacitidine}.$$

Relative dose intensity (RDI) for azacitidine

The relative dose intensity (%) for azacitidine per patient measures the percentage of the total trial dose planned that was really administered. It is defined as the ratio of the dose intensity (mg/m²/day) to the initial planned dose intensity (mg/m²/day).

$$RDI\ (\%)\ per\ patient\ = \frac{DI\ (mg/m^2/day)}{Planned\ dose\ intensity\ (mg/m^2/day)} * 100.$$

The relative dose intensity (%) for azacitidine per cycle is defined as the ratio of the dose intensity (mg/m²/day) at cycle *i* to the planned dose intensity (mg/m²/day).

$$RDI\ (\%)\ at\ cycle\ i\ = \frac{DI\ at\ cycle\ i\ (mg/m^2/day)}{Planned\ dose\ intensity\ at\ cycle\ i\ (mg/m^2/day)} * 100.$$

Treatment interruption for azacitidine

A treatment interruption is defined according to the azacitidine injection e-CRF page (Did the patient receive at least one azacitidine injection (Yes/No)).

Number of cycles with at least one treatment interruption for azacitidine experienced by a patient over the treatment period will be calculated.

Number of azacitidine interruption days experienced by a patient over the treatment period will be calculated among patients experiencing a treatment interruption.

The number of azacitidine interruption days is the number of days on which azacitidine was scheduled to be administered but was not actually administered.

Cycle delay for azacitidine

A cycle delay is defined according to the azacitidine injection e-CRF page (Was the injection day postponed (Yes/No) at D1 of the cycle). Moreover, a cycle delay of cycle *i* will be also considered if the duration of the cycle *i*-1 is higher than *(*)*. In case of missing cycle delay

reason, reason of cycle delay will be considered as unknown. The delay in days will be derived, based on the dates of administration.

For i>1, Delay (days) of cycle $_i$ = (first *IMP* intake of cycle *i*) – (first *IMP* intake of cycle *i-1* + *x days*)

(*): 30 days for regular cycle (theoretical cycle duration + 2 days for potential technical or logistical difficulty). In the delay duration formulae above *x=30.*

Number of cycles delayed for azacitidine experienced by a patient over the treatment period will be calculated among patients experiencing a cycle delay.

4.2.1.6. Concomitant treatments

The anatomical therapeutic chemical classification (ATC code = 5 digits) is composed of 4 levels:

- The first (1 digit) represents the anatomo-physiological class.
- The second (2 digits) represents the pharmacological class.
- The third (1 digit) represents the pharmacological sub-class.
- The last (1 digit) represents the therapeutic class.

The existence of a concomitant treatment (Yes/No) is defined from the presence, or not, of an ATC classification and/or preferred name.

The **periods** considered **for the analysis** are:

During the study period, for which the concomitant treatment:

- LIDstart date ≥ LIDinclusion date
- start date < inclusion date LIDand stop date ≥ LIDinclusion date or missing

At inclusion and before the treatment period, for which the concomitant treatment for tumour lysis syndrome prevention:

- start date < first S64315 infusion date (during the LID period) , or
- start date <= inclusion date and stop date >= inclusion date or is missing

The following **rules for substitution** of missing or incomplete start and stop dates are so that the concomitance period is maximised:

Table (4.2.1.6) 1 - Substitution rules of concomitant treatments intake dates

Date to substitute		Substituted date
Start date	../mmm/yyyy	If the year and the month are the same as the year and the month of inclusion, then Start date= **Inclusion date**, otherwise Start date=**01/mm/yyyy**
	../…/yyyy	If the year is the same as the year of inclusion, then Start date= **Inclusion date**, otherwise Start date=**01/01/yyyy**
	../.../….	If stop date is non-missing and inferior to inclusion date, then: **Stop date** Else: **Inclusion date**

Stop date	../mmm/yyyy	If patient died same month and year, then
		Date of death
		Else
		Last day of the month/mmm/yyyy

	../…/yyyy	If patient died same year, then
		Date of death
		Else
		31/DEC/yyyy

	../.../….	If patient died, then
		Date of death
		Else
		No substitution
		(i.e., treatment considered as still ongoing)

Note: ../mm/yyyy = missing day
../.../ yyyy = missing day and month
../.../.... = missing date

The following rules for substitution of totally or partially missing start and stop dates are used for concomitant treatments (only further anti-leukemic therapy):

Table (4.2.1.6) 2 - Substitution rules of further anti-leukemic therapy intake dates

Date to substitute		Substituted date
Start date	../mmm/yyyy	If the year and the month are the same as the year and the month of the last IMP intake date, then **Last IMP intake date** otherwise **01/mm/yyyy**
	../…/yyyy	If the year is the same as the year of the last IMP intake date, then **Last IMP intake date,** otherwise **01/01/yyyy**
	../.../….	**Last IMP intake date**

Stop date	../mmm/yyyy	If patient died same month and year, then
		Date of death
		Else
		Last day of the month/mmm/yyyy ,

	../…/yyyy	If patient died same year, then
		Date of death
		Else
		31/DEC/yyyy

	../.../….	If patient died, then
		Date of death
		Else
		No substitution
		(i.e., treatment considered as still ongoing)

Note: ../mm/yyyy = missing day
../.../ yyyy = missing day and month
../.../.... = completely missing date

4.2.1.7. Other observations related to patient follow-up

N.A.

4.2.2. Efficacy

N.A.

4.2.3. Safety

4.2.3.1. Dose Limiting Toxicity (DLT)

A DLT is defined as:

- A clinically significant adverse event graded according to the NCI-CTCAE version 5.0, observed following the administration of the test drugs.
- Assessed as unrelated to disease progression, intercurrent illness, or concomitant Medications.
- At least possibly related to the test drug(s) by the investigator and meeting any of the criteria included in Table (4.2.3.1) 1.

DLT will be reported based on investigator, using the *'Dose limiting toxicity (DLT)' / 'Adverse event'* e-CRF page, and not recalculated.

Table (4.2.3.1) 1 –Toxicity criteria

TOXICITY	DLT CRITERIA
Eye disorders: blurred vision; cataract; corneal ulcer; dry eye; eye pain	Grade ≥ 3 confirmed by an ophthalmologic examination
GI disorders	Grade ≥ 3 nausea, vomiting or diarrhoea resulting in hospitalization, tube-feeding or use of total parenteral nutrition (TPN)
	Grade 4 diarrhoea
Renal abnormalities	Grade ≥ 3 serum creatinine
Hepatic abnormalities	AST or ALT ≥ 3xULN along with a total bilirubin > 2.0xULN and confirmed Hy's law cases according to FDA guidance; For patients with elevated baseline AST or ALT or total bilirubin: [AST or ALT > 2.0xbaseline AND > 3.0xULN] OR [AST or ALT > 8.0xULN], whichever is lower, combined with [total bilirubin > 2.0 x baseline AND > 2.0xULN]
	Isolated Grade 3 AST or ALT which does not resolve within 7 days to Grade ≤1
	Isolated Grade 4 AST or ALT
For any Grade ≥3 hepatic toxicity which does not resolve within 7 days to Grade ≤ 1 level or baseline, an abdominal CT scan or hepatic echography must be performed.	
Pancreatic abnormalities	Grade ≥ 3 serum lipase and/or serum amylase
	Grade ≥ 3 pancreatitis
For any Grade 3 or Grade 4 pancreatic toxicity, which does not resolve within 7 days to Grade ≤1 level or baseline, an abdominal CT scan must be performed	
Creatine kinase (CK) / Creatine phosphokinase (CPK)	Grade ≥ 3 serum CK/CPK
	Grade 3 isolated electrolyte abnormalities (i.e. those occurring without clinical consequence) not recovered with or without intervention, to Grade < 2 level within 72 hours

Electrolyte abnormalities (including magnesium, calcium, phosphorus, etc.) **clinically significant**	Any Grade 4 electrolyte abnormality
Cardiac disorders	QTcF interval ≥ 501 ms or increase of > 60 ms from baseline on at least two separate ECG assessments (1 assessment = triplicate ECG)
	Asymptomatic, absolute decrease in LVEF of 10% or greater from baseline AND LVEF < 50%
	Asymptomatic, absolute decrease in LVEF of 20% or greater from baseline
	Troponin increase > 10xULN or a troponin increase consistent with the diagnosis of a myocardial infarction (Grade 3)
	Symptomatic congestive heart failure
Skin and subcutaneous tissue disorders	Grade ≥ 3 rash
Haematological abnormalities	Grade 4 neutropenia and/or thrombocytopenia persisting for 28 days after the start of azacitidine dosing in a cycle of therapy in the absence of active AML (< 5% blasts) or active MDS or myelofibrosis
Other AEs	Any Grade ≥ 3 AE
	Single event or multiple occurrences of the same event that lead to a dosing delay of > 7 days in a cycle may be considered to be DLT by the Investigators and the Sponsor, even if not Grade ≥ 3
	Failure to restart test drug administration at the same dose due to drug-related toxicity
	Failure to restart test drug administration at the same dose within one cycle (i.e. 28 days) of the first missed dose due to delayed recovery from drug-related toxicity
	Failure to initiate cycle 1 after completing the LID period or failure to receive LID2 after receiving the LID1, due to drug-related toxicity
NCI CTCAE v5.0 will be used for grading	

4.2.3.2. Adverse events

Each **medical concept of adverse events coded according to the internal "multiple medical concept" process** is taken into account as a single adverse event in the statistical analysis.

The modalities of the adverse event (onset and end dates, severity, seriousness, action taken, additional therapy, relationship, outcome...) replicated by default to each medical concept are also taken into account in the statistical analyses.

Emergent adverse events on treatment are defined as all adverse events:

- which occur between the first IMP intake date (included) and the last IMP intake date "+ (*) days",

or

- which was present before the first IMP intake date and which worsen (in terms of severity) or become serious according to the investigator opinion between the first IMP intake date (included) and the last IMP intake date "+ (*) days".

(*): 30 days for regimen QW.

Note: Adverse events occurring or worsening or becoming serious on the day of the first IMP intake (if any) is considered as emergent.

Serious adverse events are defined as all adverse events upgraded by the sponsor during the independent medical exam (IME) or PharmacoVigilance (PV) process (upgrade of seriousness) or considered as "serious" from investigator assessment.

Serious adverse events from investigator assessment are defined as all adverse events fulfilling at least one of the following seriousness criteria for immediate notification: death, hospitalisation, or prolongation of hospitalisation, medically important, life-threatening, disability/incapacity or congenital anomaly.

A fatal adverse event corresponds to an adverse event with “Fatal” as outcome.

Adverse events related to S64315 correspond to adverse events with relationship forced by the sponsor during the PV process (upgrade of relationship for adverse events assessed as serious according to investigator or sponsor opinion) or considered as "related" from investigator assessment. In other cases, the adverse events are considered as "not related to S64315".

Adverse events related to azacitidine correspond to adverse events with relationship considered as "related" from investigator assessment. In other cases, the adverse events are considered as "not related to azacitidine".

Adverse events related to S64315 and azacitidine from investigator assessment correspond to adverse events associated with the answer "Related" to the "Is this event related to S64315" question and “Related” to the “Is this event related to azacitidine” question.

The following information will be taken into account:

- For the analyses where the severity of the adverse event is considered, the worst severity from the day of emergence and during the studied period (i.e. between the first IMP intake date (included) and the last IMP intake date *"(*) days"* (included)) will be taken into account.
- The number of patients by worst grade: for each patient, SOC and PT, we analyse the worst grade of events.
- The number of events by worst grade: for each patient, SOC and PT, we analyse the worst grade of each event. The percentage will be calculated as the number of events of the PT concerned at grade X divided by the total number of events of the PT concerned.
- For the analyses where the action taken regarding the IMP (S64315 and/or azacitidine) and the additional therapy requirement are considered, all the actions taken, and additional therapy requirements recorded from the day of emergence and on the studied period will be taken into account.

  However, in case of an episode of an emergent adverse event leading to studied treatment withdrawal reported after the last IMP intake date "+ (*) days", the adverse event will be considered as leading to studied treatment withdrawal during the studied period.
- Seriousness is judged by event: if one episode is serious (whatever the time it occurs), the whole event will be considered as serious.
- A severe adverse event corresponds to an adverse event with NCI-CTCAE version 5.0 grade 3, 4 or 5.
- Any grade corresponds to an adverse event with NCI-CTCAE version 5.0 grade 1, 2, 3, 4 or 5.
- All multicoded events will be taken into account in the analyses.
- For the analysis of recovered emergent adverse event during / after treatment period, a TEAE is considered as recovered “during treatment period” (“after end of treatment period”,

respectively) if the associated outcome is recovered" or "recovered with sequelae" and occurs between the first IMP intake date and the last IMP intake date "+ (*) days"(included) (strictly after the last IMP intake date "+ (*) days", respectively).
(*): 30 days for regimen QW

The following rules are applied in case of missing severity:

Table (4.2.3.2) 1 – Emergence of adverse events in case of missing severity/grade (if any)

Severity/Grade			
Nearest before the first *IMP* intake date	**During the study period**		**Adverse event considered as**
Missing	Missing	→	Emergent
Missing	Grade 1	→	Non emergent
Missing	Grade 2, 3, 4 or 5	→	Emergent
Grade 1, 2, 3	Missing	→	Emergent
Grade 4	Missing	→	Non emergent

The rules for substitution of missing or incomplete episode date (onset date, dates of the six seriousness criteria and dates of change of severity and action taken) are as follows:

Table (4.2.3.2) 2 – Substitution rules of AE dates

Date to substitute	**Substituted date (Episode date)**
../mmm/yyyy	- If same month and year than first *IMP* intake date, then: **First *IMP* intake date** Else: **01/mmm/yyyy**
- ../…/yyyy	- If same year than first *IMP* intake date, then: **First *IMP* intake date** Else: **01/JAN/yyyy**
- ../…/….	- **First IMP intake date**

Notes:
../mm/yyyy = missing day.
../.../ yyyy = missing day and month.
../.../.... = missing date.

The rules for substitution of missing or incomplete recovery dates, in case of AE outcome "recovered" "recovered with sequelae" are as follows:

Table (4.2.3.2) 3 - Substitution rules of recovery date

Date to substitute	Substituted date
../mmm/yyyy	If same month and year than date of AE last information (*), then: **Date of AE last information** Else: **Last day of the month /mmm/yyyy**
../…/yyyy	If same year than date of AE last information (*), then: **Date of AE last information** Else: 31/DEC/yyyy
../.../….	**Date of AE last information***

Notes:
../mm/yyyy = missing day.
../.../ yyyy = missing day and month.
../.../.... = missing date.
** Date of AE last information is defined as the maximum between onset date, dates of change of severity and action taken and dates of the six seriousness criteria for this adverse event.*

Duration of AE (days): (recovery date (last episode) – onset date of AE) + 1.

4.2.3.3. Death

Death information are taken on 'Adverse Event' (serious criteria for immediate reporting = Death) and 'Post withdrawal follow-up (Patient status = Death) e-CRF pages.

In case of death reported on 'Adverse Event' page, the date of death is compared to the date of last intake + (*) days to classify occurrence on treatment or during follow-up.

(*): 30 days for regimen QW.

4.2.3.4. Clinical laboratory evaluation

Values

Only reliable values are considered for analyses. Unreliable values are flagged into the database.

WBC differentiation, including values of neutrophils, basophils, eosinophils, monocytes, lymphocytes and blasts, will be ignored if blast value is missing/not done or the differentiation is automated, as considered not reliable.

In case of **multiple samples**:

- Each post-baseline value (test, re-test, planned, unplanned) measured under treatment is taken into account for analyses.

Units

All parameters will be analysed in international units (IU).

Abnormal values

Abnormal values are described according to:

- Reference laboratory ranges for the non-gradable parameters.
- NCI-CTCAE version 5.0 grade for gradable parameters.

Laboratory reference limits and NCI-CTCAE version 5.0 grades are reported in the database.

For the parameters which are gradable according to CTCAE v5.0, the grades will be derived using the local laboratory reference limits in analysis datasets.

Table (4.2) 4 - Definition of CTCAE grade - Version 5.0 - Gradable parameters

Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Sodium (mmol/l) – Hypernatremia	]ULN;150]	]150;155]	]155;160]	>160
Sodium (mmol/l) - Hyponatremia	[130;LLN[	-	[120;130[	< 120
Potassium (mmol/l) – Hyperkalemia	]ULN;5.5]	]5.5;6]	]6;7]	> 7
Potassium (mmol/l) – Hypokalemia		[3.0;LLN[	[2.5;3.0[	< 2.5
Amylase (IU/L) - High	>ULN – 1.5 x ULN	>1.5 x ULN – 2 x ULN	>2 x ULN – 5 x ULN	> 5 x ULN
Triacylglycerol Lipase (IU/L) - High	>ULN – 1.5 x ULN	>1.5 x ULN – 2 x ULN	>2 x ULN – 5 x ULN	> 5 x ULN
Ionized calcium (mmol/l) - High	]ULN;1.5]	]1.5;1.6]	]1.6;1.8]	> 1.8
Ionized calcium (mmol/l) - Low	[1.0;LLN[	[0.9;1.0[	[0.8;0.9[	< 0.8
Magnesium (mmol/l) - Hypermagnesemia	]ULN;1.23]	-	]1.23;3.30]	> 3.30
Magnesium (mmol/l) - Hypomagnesemia	[0.5;LLN[	[0.4;0.5[	[0.3;0.4[	< 0.3
Albumin (g/l) - Low	[30; LLN[	[20; 30[	< 20	-
Glucose (mmol/l) - Hypoglycemia	[3.0;LLN[	[2.2;3.0[	[1.7;2.2[	< 1.7
Total cholesterol (mmol/l) - High	]ULN;7.75]	]7.75;10.34]	]10.34;12.92]	> 12.92
Triglycerides (mmol/l) - High	[1.71;3.42]	]3.42;5.7]	]5.7;11.4]	> 11.4
Serum creatinine increased (umol/L)	>ULN – 1.5 x ULN	>1.5 x baseline – 3.0 x baseline (if baseline available) OR >1.5 x ULN – 3.0 x ULN	>3.0 x baseline (if baseline available) OR >3.0 x ULN – 6.0 x ULN	>6.0 x ULN
Total bilirubin increased (umol/L)	>ULN – 1.5 x ULN if baseline is normal [≤ULN]; 1.0 x baseline – 1.5 x baseline if baseline is abnormal [>ULN]	>1.5 x ULN – 3.0 x ULN if baseline is normal [≤ULN]; >1.5 x baseline – 3.0 x baseline if baseline is abnormal [>ULN]	>3.0 x ULN – 10.0 x ULN if baseline is normal [≤ULN]; >3.0 – 10.0 x baseline if baseline is abnormal [>ULN]	>10.0 x ULN if baseline is normal [≤ULN]; >10.0 x baseline if baseline is abnormal [>ULN]
CPK (IU/l) - high	>ULN – 2.5 x ULN	>2.5 x ULN – 5 x ULN	>5 x ULN – 10 x ULN	> 10 x ULN
Haemoglobin (g/dl) increased	> ULN and increase from baseline]0 ;2] (g/dl)	> ULN and increase from baseline]2 ;4] (g/dl)	> ULN and increase from baseline > 4 (g/dl)	-
Haemoglobin (g/dl) - Anemia	[10;LLN[	[8;10[	< 8	-
White Blood Cells (g/l) - Low	[3.0;LLN[	[2.0;3.0[	[1.0;2.0[	< 1.0

Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Neutrophils (g/l) - Low	[1.5;LLN[	[1.0;1.5[	[0.5;1.0[	<0.5
Lymphocytes (g/L) - Low	[0.8;LLN[	[0.5;0.8[	[0.2;0.5[	<0.2
Platelets (g/L) - Low	[75;LLN[	[50;75[	[25;50[	<25
aPTT (sec) - High	>ULN – 1.5 x ULN	>1.5 x ULN – 2.5 x ULN	>2.5 x ULN	-
ALT increased (IU/L)	>ULN – 3.0 x ULN if baseline is normal [≤ULN]; 1.5 x baseline – 3.0 x baseline if baseline is abnormal [> ULN]	>3.0 x ULN – 5.0 x ULN if baseline is normal[≤ULN]; >3.0 x baseline – 5.0 x baseline if baseline is abnormal [> ULN]	>5.0 x ULN – 20.0 x ULN if baseline is normal [≤ULN]; >5.0 x baseline – 20.0 x baseline if baseline is abnormal [> ULN]	>20.0 x ULN if baseline is normal [≤ULN]; >20.0 x baseline if baseline is abnormal [> ULN]
ALP increased (IU/L)	>ULN – 2.5 x ULN if baseline is normal [≤ULN]; 2.0 x baseline – 2.5 x baseline if baseline is abnormal [> ULN]	>2.5 x ULN – 5.0 x ULN if baseline is normal [≤ULN]; 2.5 x baseline – 5.0 x baseline if baseline is abnormal [> ULN]	>5.0 x ULN – 20.0 x ULN if baseline is normal [≤ULN]; >5.0 x baseline – 20.0 x baseline if baseline is abnormal [> ULN]	>20.0 x ULN if baseline is normal [≤ULN]; >20.0 x baseline if baseline is abnormal [> ULN]
AST increased (IU/L)	>ULN – 3.0 x ULN if baseline is normal [≤ULN]; 1.5 x baseline – 3.0 x baseline if baseline is abnormal [> ULN]	>3.0 x ULN – 5.0 x ULN if baseline is normal [≤ULN]l; >3.0 x baseline – 5.0 x baseline if baseline is abnormal [> ULN]	>5.0 x ULN – 20.0 x ULN if baseline is normal [≤ULN]; >5.0 x baseline – 20.0 x baseline if baseline is abnormal [> ULN]	>20.0 x ULN if baseline is normal [≤ULN]; >20.0 x baseline if baseline is abnormal [> ULN]
GGT increased (IU/L)	>ULN – 2.5 x ULN if baseline is normal[≤ULN]; 2.0 x baseline – 2.5 x baseline if baseline is abnormal [> ULN]	>2.5 x ULN – 5.0 x ULN if baseline is normal [≤ULN]; >2.5 x baseline – 5.0 x baseline if baseline is abnormal [> ULN]	>5.0 x ULN – 20.0 x ULN if baseline is normal [≤ULN]; >5.0 x baseline – 20.0 x baseline if baseline is abnormal [> ULN]	>20.0 x ULN if baseline is normal [≤ULN]; >20.0 x baseline if baseline is abnormal [> ULN]

Any grade corresponds to a laboratory value with NCI-CTCAE version 5.0 grade 0, 1, 2, 3 or 4.

A grade 0 corresponds to a laboratory value within limit or reference range.

The LOWEST value for a patient is defined as the lowest absolute laboratory value during the treatment period.

A lowest value for a cycle is defined as the lowest laboratory value in that cycle.

The time to lowest value is defined from the date of the first IMP intake to the sampling date of the lowest value.

The time to lowest value in a cycle is defined from the first date of IMP intake in that cycle to the sampling date of the lowest value.

The HIGHEST value for a patient is defined as the highest laboratory value during the treatment period.

A highest value for a cycle is defined as the highest laboratory value in that cycle.

The time to highest value is defined from the date of the first IMP intake to the sampling date of the highest value.

Urinary results

The category positive includes results '+', '++' '+++', and '++++'.

The category negative corresponds to 'Absent' class.

Creatinine clearance

Creatinine clearance will be approximated by MDRD_GFR. This will be calculate as:

MDRD_GFR (mL/min/1.73m^2) = 175 x (serum creatinine in mg/dL)$^{-1\ 154}$ x age$^{-0\ 203}$ x 0.742 (if female) x 1.212 (if black race).

Serum creatinine conversion:

Serum creatinine (mg/mL) = Serum creatinine (µmol/L)/88.4.

MDRD_GFR will be categorised in 4 categories:
- Normal renal function (MDRD_GFR >90 mL/min/1.73m^2).
- Mild renal impairment (MDRD_GFR 60-90 mL/min/1.73m^2).
- Moderate renal impairment (MDRD_GFR 30-59 mL/min/1.73m^2).
- Severe (MDRD_GFR <30mL/mn/1.73m^2).

Worst value

Worst value will be analysed as follow:

- For the urinalysis parameters, the worst class will correspond to 'Positive' class, then 'Trace' and finally 'Negative' will be considered as normal class.
- For creatinine clearance, the worst class will correspond to "severe" category, then "moderate", then "mild" and finally "normal".
- Baseline and post baseline worst grade for High and Low:
  - Low: If the result is below lower normal range limit, low =grade (for gradable parameter) or result (for non-gradable parameter), Else low=0.
  - High: If the result is above upper normal range limit, high =grade (for gradable parameter) or result (for non-gradable parameter), Else high =0.

4.2.3.5. Vital signs, clinical examination and other observations related to safety

4.2.3.5.1. Vital signs and clinical examination

Worst value

For ECOG, SBP, DBP and HR, the worst (highest) value will be derived.

For Weight, SBP, DBP and HR, the worst (lowest) value will be derived.

ECOG performance status

GRADE	*STATUS* ECOG - ZUBROD / WHO
0	Normal unrestricted activity
1	Arduous physical activity restricted, but patient able to walk unaided and perform light work
2	Able to walk unaided and independent but unable to work more than half-time
3	Much less independent. Spends more than half his / her time in bed or seated.
4	Incapable of looking after him / herself. Completely confined to bed or to a chair

4.2.3.5.2. Electrocardiogram

Multiple samples

For the analysis of QT criteria per measurement time, only values at each scheduled post-baseline visits are analysed. All data obtained from triplicate ECGs are taken into account in the analysis. For these schedule ECGs, for each measurement time, the mean of available values is calculated and taken into account in the analyses.

The measurement times of QT criteria will be those fulfilled in the database and transferred by Banook Group.

QT corrected

QTcF: QT corrected using Fredericia's formula is calculated as follows:

$$\boldsymbol{QTcF\ (msec)} = \left(\frac{\boldsymbol{QT(msec)}}{\left(\boldsymbol{60/\left(HR(bpm)\right)}\right)^{\boldsymbol{1/3}}} \right).$$

For all other analyses, all analysable values are taken into account, whether at planned visit or not, initial sample or additional sample.

ECG abnormality:

ECG abnormality corresponds to ECG for which the conclusion is ABNORMAL, NOT CLINICALLY SIGNIFICANT or ABNORMAL, CLINICALLY SIGNIFICANT.

Clinically significant ECG abnormality:

Clinically significant ECG abnormality corresponds to ECG for which the conclusion is ABNORMAL, CLINICALLY SIGNIFICANT.

Emergent ECG abnormality / Emergent clinically significant ECG abnormality:

Occurrence of emergent ECG abnormality / emergent clinically significant ECG abnormality after the first study treatment administration date (included) are defined as follows:

Triplicates Baseline		**Record on treatment**	**Emergence Abnormality ECG**	**Emergence Significant Abnormality ECG**
All ECG within normal limit	and	Abnormality no significant	Yes	No
All ECG within normal limit	and	Abnormality significant	Yes	Yes
At least one line “Abnormality no significant “ and no line “Abnormality significant”	and	Abnormality significant	No	Yes
No baseline	or	No post baseline	Missing	Missing
If triplicate baseline is not missing and records on treatment are not missing and the combination is not covered by the previous cases.			No	No

Maximum absolute prolongation during treatment period = max (Absolute prolongation during treatment period).

Maximum change from baseline = Maximum absolute prolongation - Absolute prolongation at baseline.

4.2.3.5.3. LVEF

For this parameter, the worst value will correspond to the *lowest* measure.

Analysis by grade according NCI-CTCAE version 5.0:

Grade 0: other cases.
Grade 2: LVEF [40 – 50%] or Change [-20; -10%].
Grade 3: LVEF [20 – 40%[or Change < -20%].
Grade 4: LVEF < 20%.

4.2.4. Biomarkers

N/A.

5. REFERENCES

Guidelines

CTCAE (Common Terminology Criteria for Adverse Events) v5.0

Guideline on Missing Data in Confirmatory Clinical Trials – Adopted by CHMP, June 2010, issued as EMA/CPMP/EWP/1776/99 Rev. 1.

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ICH E14 – The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic drugs – Adopted by CHMP, May 2005, issued as CHMP/ICH/2/04.

ICH E3 Q&A - Structure and Content of Clinical Study Reports - Questions & Answers (R1) - July 2012, issued as EMA/CHMP/ICH/435606/2012.

ICH E3 - Structure and Content of Clinical Study Reports – Adopted by CPMP, December 1995, issued as CPMP/ICH/137/95/step 5.

ICH E9: Statistical Principles for Clinical Trials Final version – March 1998.

Points to consider

Points to Consider on Adjustment for Baseline Covariates – Adopted by CPMP, May 2003, issued as CPMP/EWP/2863/99.

Points to Consider on Multiplicity Issues in Clinical Trials – Adopted by CPMP, September 2002, issued as CPMP/EWP/908/99.

Bibliography

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