An Investigator-Initiated Study To Evaluate Ara-C and Idarubicin in Combination with the Selective Inhibitor Of Nuclear Export (SINE) Selinexor (KPT-330) in Patients with Relapsed Or Refractory AML

Study code: SAIL

Phase II study

STATISTICAL ANALYSIS PLAN

Signatures:

Statistical Analysis Plan was prepared by:

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1 Abbreviations

AE	Adverse event
AML	Acute myeloid leukemia
ATC	Anatomical Therapeutic Chemical
CI	Confidence Interval
CR	Complete Response
CRi	Complete Response with incomplete blood recovery
CTCAE	Common Terminology Criteria for Adverse Events
ECOG	Eastern Cooperative Oncology Group
EFS	Event-free-survival
GFR	Glomerular filtration rate
ITT	Intent-to-treat
KM	Kaplan-Meier
OS	Overall Survival
RFS	Recurrence-free-survival
SAE	Serious adverse event
SCT	Stem Cell Transplant
PP	Per-protocol

2 Study objective(s)

The primary objective is to determine the efficacy of Selinexor in patients with relapsed/ refractory AML by complete response rate (CR or CRi), as defined by the revised recommendations of the International Working Group for diagnosis, standardization of response criteria in Acute Myeloid Leukemia for AML (Cheson et al 2003).

Secondary objectives of the study are 1) To determine the efficacy of Selinexor in combination with standard chemotherapy in patients with relapsed/ refractory AML by:

- Rate of partial remissions
- Percentage of patients being transplanted after induction therapy
- Early death rate
- Overall survival (OS)
- Event-free survival (Events are defined as Death, not achieving a CR or CRi, Relapse after CR or CRi) and

2) To evaluate overall safety and tolerability of Selinexor.

3 Design and type of the study

This is a phase II non-randomized, single-arm, open-label, multicentre study in patients with relapsed or refractory AML.

4 Study variables

The following variables will be evaluated.

The demographic and baseline variables:

Gender, age, race, details on leukemia diagnosis, prior therapy, medical history, current symptoms and residual toxicities form prior therapies, ECOG performance status, clinical neurological examination, cardiac evaluation, disease status, concomitant medication, prior transplantation, primary or secondary AML, early/late relapse from first therapy, mutation, karyotype risk category.

The primary efficacy variable:

The rate of complete responders according to the Cheson criteria.

The secondary efficacy variables:

Rate of partial remissions, percentage of patients being transplanted after induction therapy, early death rate, Overall survival (OS), Event-free survival (EFS), Recurrence-free-survival (RFS)

The safety variable:

Adverse events (AE), blood pressure, pulse, temperature, physical examination, urine analysis, hematology, clinical chemistry, coagulation tests.

5 Sample size considerations

The sample size calculation is based on the evaluation of response rates according to Fleming using the A'Hern extension (Sample size tables for exact single-stage phase II designs. Statist. Med.2001;20:859-866). In Fleming's procedure to response levels p0 and p1 are specified, where p0 is the largest proportion of responders, which would clearly imply that the treatment does not warrant further investigations and p1 the minimum required proportion of responders that would imply that the treatment warrant further investigations. The following characteristics were specified in the sample size calculation:

- $p0 = 0.30$
- $p1 = 0.60$
- $\alpha = 0.05$ (one-tailed) and
- $\beta = 0.10$

The sample size calculation ended up in 25 patients to be recruited to ensure a power of 90 % for the discrimination of p0 and p1. In addition, 15 additional patients were submitted to an adapted drug regimen (flat dose 60mg of Selinexor instead of 40 mg /m^2 of Selinexor). Using a similar approach, the power will be 80 % to discriminate a p0=30 % from a p1=65 %, with a one-tailed α of 0.05 %.

6 Statistical hypotheses

The purpose of this study is to evaluate efficacy of Selinexor in patients with relapsed/ refractory AML by complete response rate (CR or CRi). The null-hypothesis to be tested is

H_0 : The observed response rate is less or equal than 30 %

against the alternative hypothesis

H_1 : The observed response rate is over 30 %

7 Analysis sets

A detailed subject classification document will be prepared in a Data Review meeting prior database lock. The document will assign patients to the respective analysis sets depending on the observed protocol violations.

7.1 Intention-to-treat (ITT) set

The ITT set includes all subjects who have received study medication at least once and for whom efficacy data upon treatment are available.

7.2 Per protocol (PP) set

The PP set will consist of all randomized subjects who completed the treatment section (up to Visit 9) with no relevant protocol violations, detailed in the subject classification document.

7.3 Safety set

The Safety set will comprise all subjects who received at least one administration of the study medication at any dosage and who have a subsequent safety measurement available.

8 General statistical considerations

The aim of the study is to evaluate the effect of Selinexor in patients with relapsed / refractory AML by complete response rate (CR or CRi).

All background, primary and secondary efficacy variables, and safety variables will be summarized by visit and treatment group. In addition to absolute values, changes from baseline values will be summarized, if feasible.

Summary statistics will include at least the number of patients, mean, standard deviation, median, minimum and maximum for continuous variables, and frequencies and percentages for categorical variables. The results of statistical tests (including 95% CIs) will be included in the tables, when appropriate.

If the assumptions of the parametric statistical test are not met, the use of common transformations (e.g. logarithmic, square root) will be considered. Appropriate non-parametric methods will be used if normality assumptions are not met even after transformations.

In the statistical analyses a p-value less than 0.05 will be considered as statistically significant. If not stated otherwise, all tests will be performed as two-sided and two-sided 95% CIs will be produced for the treatment differences. No adjustments for the p-values will be made. Missing values will not be imputed in the analyses.

Subgroup analyses by dosing schedule (Selinexor / mm^2 vs. flat dose of Selinexor) will be conducted for all study data.

The table and figure plan is presented in Appendix 18.2.

9 Demographic and other baseline characteristics

All background and other baseline characteristics will be tabulated with descriptive statistics. Medical history and other medication will be summarized with frequency distributions. Tabulations will be conducted overall and by dosing schedule. No statistical tests will be carried out for any baseline measures between the dosing schedules.

10 Concomitant medication/treatment

Concomitant medication and treatments will be summarized overall and by dosing group using ATC classification.

11 Extent of exposure and compliance

The extent of exposure and treatment compliance will be summarized descriptively overall and by dosing schedule.

12 Analysis of efficacy

Descriptive statistics of all of the efficacy data will be presented overall and by dosing schedule and visit for the ITT and PP analysis sets.

12.1 Primary efficacy variables

The primary efficacy variable is the response rate based on the Cheson criteria. The response rate will be presented in percentages together with 95 % confidence interval (CI) calculated using the Wilson score method.

The analysis will be conducted both for the overall population and separately by the dosing schedule.

The response rate will also be presented in several subgroups, if feasible. Following subgroups will be investigated for the primary endpoint: primary vs. secondary AML, remission >12 Months vs. remission <12 months, relapse after SCT vs. no prior SCT, karyotypic risk group, FLT3 vs. NPM1 mutation.

12.2 Secondary efficacy variables

The secondary efficacy variables; rate of partial remissions, percentage of patients being transplanted after induction therapy and early death rate will be analysed using similar methods as with the primary analysis.

Overall survival, recurrence-free-survival and event-free survival will be analysed applying the Kaplan-Meier-method (KM). OS is calculated from the date of informed consent to the date of death, the patients still alive will be censored at the last date of follow-up. RFS is calculated from the date of informed consent to the date of recurrence or death, whichever occurs first, censoring patients who were alive without recurrence on the date of last follow-up visit. EFS is calculated from the date of CR/CRi until death or relapse, whichever occurs first. Patients are censored on the date of last follow-up visit if they are alive without relapse.

The survival curves will be displayed graphically for the overall population and by dosage schedule. In addition median survival and follow-up times (including interquartile range and 95 % CI if feasible) will be calculated.

12.3 Additional analyses

The survival analyses (OS, RFS, EFS) will be repeated using a different censoring approach than presented in 12.2. The calculation will be otherwise similar as previously presented, except for patients receiving a stem cell transplant (SCT). For these patients, the patient is censored at the time of the SCT.

13 Analysis of safety

All subjects who have participated in the study will be included in the safety analysis.

13.1 Adverse events

All adverse events occurring during the course of the trial and for up to 30 days after the last dose of study medication will be captured, documented and reported. The number of patients developing adverse experiences will be tabulated using [NCI CTCAE] Version 4.03. The CTC v4.03 will be the basis for grading the laboratory changes. Additionally, the subset of adverse experiences considered treatment-related will be summarized. Listings of adverse experiences leading to treatment discontinuation will be provided.

Clinical adverse events and laboratory adverse events will be reported in separate tables. The adverse events will be reported as a whole and additionally based on the severity grading (separate table for grade 3-5 AEs).

Adverse events classified as serious adverse events (SAEs) will be listed separately. Deaths together with the reason for death and the possible relation to study treatment will be summarized.

13.2 Laboratory safety variables

Descriptive statistics of laboratory safety variables (hematology, clinical chemistry, urine analysis, coagulation tests) will be computed, together with the changes from baseline values. The changes from baseline will be analyzed by ANOVA method if feasible.

13.3 Other safety variables

Vital signs (blood pressure, heart rate, temperature) will be summarized with descriptive statistics by visit and dosing group. In addition, the changes from baseline values will be given. The changes from baseline will be analyzed by ANOVA method if feasible. Physical examination, ECG and ECOG results will be summarized with frequency tables.

14 Completion and premature discontinuation

Completion and premature discontinuation will be listed. The reasons for premature discontinuation will be presented.

15 Deviations from the analyses planned in the study protocol

The primary hypothesis of the study was clarified in the Statistical Analysis Plan compared to the definition in the protocol.

16 Execution of statistical analyses

Statistical analyses will be performed by 4Pharma Ltd.

17 Hardware and software

Statistical analysis, tables and patient data listings will be performed with SAS® version 9.3 for Windows (SAS Institute Inc., Cary, NC, USA).

18 References

Clinical Study Protocol, Final Protocol, Version 2 (25.08.2015)

19 Appendices

19.1 Schedule of assessments

Assessments by visit	Screening	Baseline	Induction cycle(s)		Consolidation	Maintenance	End of treatment	Follow-up
Time window	Within 14 days prior registration	Before Day 1 of induction	During treatment, twice weekly	End of cycles	Weekly (D2,8, 15,21 ± 2 days)	Twice per cycle (D1,15 ± 2 days)	30 days after last dose/prior to SCT	Every 3 months ± 28 days
Informed consent[1]	X							
Inclusion/exclusion criteria	X							
Demographics	X							
Medical History[2]	X							
Pregnancy test[3]	X							
Physical examination and ECOG[4]	X		X	X	X	X	X	
Body height and weight[5]	X			X	X	X	X	
BSA	X							
Vital signs[6]	X		X	X	X	X	X	
Standard clinical neurological examination	X							
12-lead ECG	X			X	X	X		
Cardiac ultrasound[7]	X			X			X	
Hematology[8]	X		X	X	X	X	X	X
Calculation of GFR[9]	X			X	X		X	

Clinical chemistry[10]	X			X	X	X	X	
Assessments by visit	**Screening**	**Baseline**	**Induction cycle(s)**		**Consolidation**	**Maintenance**	**End of treatment**	**Follow-up**
Urine analysis[11]	X			X	X	X		
Coagulation test[12]	X		X	X	X	X		
HIV testing[13]	X							
Assessment of signs and symptoms, AE	X		X	X	X		X	
CTCAE v 4.03 scale toxicity			X	X	X	X	X	
Concomitant medication	X		X	X	X	X	X	
Bone Marrow Aspirate[14]	X			X	X	X		X
Survival								X
Selinexor baseline dose[15]		X						
Bone marrow aspirates for translational research[16] (optional)		X						
Blood draws for translational research[17] (optional)			X		X			
Blood draws for Pharmcokinetics[18] (optional)			X					
Opthalmological examination[20]	X							

Notes

1 Prior to the first study-specific measures

2 Medical history includes baseline symptoms as well as a detailed history of prior cancer therapies including start and stop dates, disease progression during or after therapy, as well as discontinuations due to intolerability or any other serious illness.

[3] Applicable for women of childbearing potential. Serum β-HCG test within 7 days before the first dose of study drug. To be repeated by urine test, if date of first result exceeds the 7-day window
[4] Full physical examination for baseline and end of study visit. Physical examinations during the study should be symptom directed.
[5] Body height will be measured at screening only.
[6] Vital signs: blood pressure, pulse and temperature
[7] Echocardiography of left ventricular ejection fraction (LVEF) to observe cardiac toxic city of idarubicin**.** at baseline, before a second facultative induction course and before first consolidation therapy. Maybe repeated if clinically indicated.
[8] Hematology: hemoglobin,red blood cell (RBC) count, platelets, white blood cell (WBC) count and WBC differential (neutrophils, lymphocytes), leukemic blasts.
[9] Calculated GFR according to the formula of Cockroft and Gault.
[10] Clinical chemistry: Sodium, Potassium, Calcium, Creatinine, Total Bilirubin, Alkaline Phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), Total Protein, Albumin, LDH
[11] Urine analysis will include urine bilirubin, glucose, hemoglobin, ketones, pH, protein (once per cycle in consolidation/maintenance)
[12] Coagulation test include prothrombin time (PT) and activated partial thromboplastin time (aPTT) (once per cycle in consolidation/maintenance)
[13] If not performed within the last 6 months
[14] Including cytogenetic, flow cytometry and molecular analysis (FLT3 ITD or TKD mutation or NPM-1 mutation, FLT3 ITD at baseline only) at baseline, end of each induction and consolidation cycle. In maintenance and FU after SCT if blood count is suspicious for progression of disease/relapse.
[15] Baseline Selinexor dosing: single dose given after registration but before beginning of first induction cycle.
[16] Bone marrow aspirates for translational research will be taken prior to baseline Selinexor dose and 24 hour post-baseline dose. 2 ml of each aspirate will be used to isolate viable cells for mouse studies; 2 ml of each aspirate will be processed to isolate RNA for stem cell expression array analysis.
[17] Blood draws for translational research (exploratory pharmacodynamic analysis): (2 x 2.5 ml for XPO1 inhibition in leukocytes, 2 ml for cytokines) will be collected on day of first in-clinic dose of Selinexor during each induction and consolidation cycle. 2 x 2.5 ml, plus 2 ml blood will be collected pre-dose and 2 x 2.5 ml will be collected 4 hr post-dose.
[18]Blood draws (2 ml) for PK analysis will be performed during first induction cycle on day of first in-clinic dose of Selinexor: pre-dose, 2 hr and 4 hr post-dose.
[19] Follow-up is to include all patients, including those having undergone SCT
[20] required at screening and if clinically indicated during the treatment phase. Ophthalmologic examination includes:

- prior to dilation: best corrected visual acuity and slit lamp examination including tonometry
- following dilation: fundoscopy and a slit lamp exam to document lens clarity.

19.2 Table and figure plan

14.1 Demographic data

Table 14.1.1 Number of randomized patients per center

Table 14.1.2 Disposition of patients

Table 14.1.3 Analysis datasets

Table 14.1.4 Descriptive statistics of demographics variables

Table 14.1.5 Details on leukemia diagnosis

Table 14.1.6 Details of prior therapy

Table 14.1.7 Current symptoms and / or residual toxicities from prior therapies

Table 14.1.8 Summary of other medical history

Table 14.1.9 Results of HIV and pregnancy tests

Table 14.1.10 Summary of concomitant medication

14.2 Efficacy data

Figure 14.2.1 Kaplan-Meier curves for Overall survival (ITT)

Figure 14.2.2 Kaplan-Meier curves for Recurrence-free survival (ITT)

Figure 14.2.3 Kaplan-Meier curves for Event-free survival (ITT)

Figure 14.2.4 Kaplan-Meier curves for Overall survival (censoring at time of SCT) (ITT)

Figure 14.2.5 Kaplan-Meier curves for Recurrence-free survival (censoring at time of SCT) (ITT)

Figure 14.2.6 Kaplan-Meier curves for Event-free survival (censoring at time of SCT) (ITT)

14.2.1 Analysis of treatment Response

Table 14.2.1.1 Frequency table for best treatment response overall and by dosing schedule (ITT)

Table 14.2.1.2 Frequency table for best treatment response overall and by dosing schedule (PP)

Table 14.2.1.3 Response rates (CR/CRi) overall and by dosing schedule (ITT)

Table 14.2.1.4 Response rates (CR/CRi) overall and by dosing schedule (PP)

14.2.2 Secondary efficacy analysis

Table 14.2.2.1 Rate of partial remission overall and by dosing schedule (ITT)

Table 14.2.2.2 Rate of partial remission overall and by dosing schedule (PP)

Table 14.2.2.3 Percentage of patients being transplanted after induction therapy (ITT)

Table 14.2.2.4 Percentage of patients being transplanted after induction therapy (PP)

Table 14.2.2.5 Early death rate (ITT)

Table 14.2.2.6 Early death rate (PP)

Table 14.2.2.7 Summary statistics for overall survival endpoint (ITT)

14.3.4 Other safety variables

Addendum to Statistical Analysis Plan dated 2017Aug25

Date and version of the addendum: **Version 1, 2018Apr04**

Sponsor: **GSO Global Clinical Research B.V.**

Principal Investigator: **Prof. Dr. Walter Fiedler, Hamburg**

The addendum to the Statistical Analysis Plan was approved by:

10 Apr 2018
Date

Signature ~~Dr. Anne L. Kranich, CEO~~ GSO Global Clinical Research B.V.
Stefanie Amberg
Medical Writer
SA 10 Apr 2018

9.4.18
Date

Signature Prof. Dr. Walter Fiedler,
University Hospital Hamburg-Eppendorf

1. Purpose of the addendum to SAP

The purpose of this addendum to the Statistical Analysis Plan (SAP) dated 2017Aug25 is to clarify the analysis of the primary endpoint and to add an analysis of the difference between the subgroups.

2. Analysis of the primary endpoint

The primary objective of the clinical trial is to determine the efficacy of Selinexor in combination with standard chemotherapy in patients with relapsed/refractory acute myeloid leukemia (AML) by determination of rate of complete remission (CR) or morphologic complete remission with incomplete blood count recovery (CRi), as defined by the recommendations on diagnosis and management of AML in adults from an international expert panel, on behalf of the European LeukemiaNet.

The primary endpoint is defined as the percentage of patients achieving a CR or CRi. Patients with morphologic leukemia free-state (MLFS) shall be included into the group of responders.

To determine to efficacy of Selinexor in combination with standard chemotherapy, the best response after Selinexor treatment shall be analysed, thus the best response after the induction cycle(s).

A response achieved after stem cell transplantation or in the follow-up period after the patient has received another treatment cannot be used to determine the efficacy of Selinexor in combination with standard chemotherapy as the response may be attributable to the stem cell transplantation or a subsequent therapy.

3. Subsequent updates of the analysis

For the initial analysis of the clinical trial, the best response of each patient throughout the whole study period was used, not the best response obtained after the induction cycle(s).

Therefore, the following tables are required to be updated:

- Frequency tables for best response after Selinexor treatment
- Response rates after Selinexor treatment
- Summary statistics and Kaplan-Meier curves for relapse-free and event-free survival
- Subgroup analyses: Response rates by
    - Primary vs. secondary AML
    - Length of remission: remission < 12 months vs. remission > 12 months
    - Prior SCT: yes vs. no
    - Karyotypic risk group: favourable/intermediate vs. unfavourable vs. unknown karyotypic group

- FTL3 mutation: mutation vs. wildtype
- NPM1 mutation: mutation vs. wildtype

For the updated analysis, the table in attachment 1 shall be used. This table includes

- response data after the induction cycle, updated,
- updated survival data,
- updated data on relapse in the follow-up, and
- updated data on length of remission prior to the SAIL study (for subgroup analysis "length of remission").

Overall survival shall be re-calculated by the current data on survival.

4. Subgroup analysis: Addition of analysis of the difference between the subgroups

Subgroup analysis has currently been conducted separately by subgroup. Additionally, a p-value for the difference between the groups (e.g. patients with early vs. late relapse) shall be provided.

Attachment 1: SAIL Data table response_survival_relapse_length of remission dated 2018Mar27