2 SYNOPSIS

Name of Sponsor/Company	**Name of Finished Product**	**Name of Active Ingredient**
Helsinn Healthcare S.A.	Not applicable	Pracinostat

Study Number: PRAN-16-52

Title of Study: A Phase III, Double-Blind, Placebo-Controlled, Multicenter, Randomized Study of Pracinostat in Combination with Azacitidine in Patients ≥ 18 Years with Newly Diagnosed Acute Myeloid Leukemia (AML) Unfit for Standard Induction Chemotherapy

Investigators and Study Centers: Approximately 130 sites worldwide (planned), 116 sites where patients were randomized.

Publication (reference): None at the time of this report.

Study Period (years):	**Phase of Development:**
Date of First Patient Screened: 12 JUL 2017 Date of Last Patient Completed: 08 AUG 2020	III

Objectives: The primary objective of this study was to show superiority in terms of overall survival (OS) of treatment with pracinostat (Group A – experimental group) versus placebo (Group B – control group) in patients treated with azacitidine (AZA) as background therapy.

Secondary objectives were:

- To describe the efficacy of pracinostat by evaluating additional efficacy variables
- To assess the safety and tolerability
- To evaluate the pharmacokinetics (PK) of pracinostat and its main metabolites
- To assess the possible drug interaction of pracinostat on the PK of AZA
- To perform a health-economic evaluation of treatment and control group

Methodology: This was a Phase III, multicenter, with group sequential design double-blind, randomized study of pracinostat vs. placebo with AZA as background therapy in patients ≥ 18 years of age with newly diagnosed acute myeloid leukemia (AML), excluding acute promyelocytic leukemia and cytogenetic low-risk AML, who were unfit to receive intensive remission induction chemotherapy due to age ≥ 75 years or comorbidities.

Patients were randomized in a 1:1 ratio to receive either pracinostat plus AZA (Group A) or placebo plus AZA (Group B) whereby randomization was stratified by cytogenetic risk category (intermediate vs. unfavorable risk according to the Southwest Oncology Group [SWOG] Cytogenetic Risk Category Definitions) and the Eastern Cooperative Oncology Group (ECOG) performance status (PS) (0-1 vs. 2).

This study consisted of three phases: Screening, Treatment, and Long-term Follow-up. Treatment was administered based on 28-day cycles, with pracinostat/placebo administered orally once every other day, 3 times a week for 3 weeks, followed by one week of no treatment and AZA administered for 7 days of each cycle.

Study treatment continued until there was documented disease progression, relapse from complete remission (CR), or non-manageable toxicity. After discontinuation from study treatment, patients entered the long-term follow-up phase and were followed up for assessment of disease progression, if applicable, and survival every 3 months (±1 month) until death. Patients who received study treatment at the end of the study had the opportunity to continue to receive the study treatment for a maximum of 24 months (post-study observation period).

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Number of Patients (planned and analyzed): It was planned that 500 patients (250 per treatment group) at approximately 130 international investigative sites would be enrolled. A total of 725 patients were screened, of them 520 were enrolled (28 patients withdrew consent, 1 patient was lost to follow up, and 85 patients decided not to enter the study due to 'other' reasons), thus 406 were randomized at 116 investigative sites.

Diagnosis and Main Criteria for Inclusion:

Male or female patients ≥ 18 years of age with newly diagnosed, histologically or cytologically confirmed, AML including *de novo*, secondary to antecedent hematologic disorders, or treatment-related disease with intermediate or unfavorable risk cytogenetics, unable to receive intensive chemotherapy regimens at enrollment.

Test Product, Dose and Mode of Administration, Batch Number:

Group A (experimental): pracinostat + background therapy (AZA)

Pracinostat: one 60 mg capsule orally, once a day, 3 times a week (e.g., Monday, Wednesday, and Friday) for 3 weeks, followed by 1 week of rest during each 28-day cycle. Pracinostat oral administration was to be taken before injection of AZA.

AZA was administered as background therapy at a dose of 75 mg/m^2 by subcutaneous (SC) or intravenous (IV) injection daily for 7 days of each 28-day cycle.

Dose reduction was not allowed within each 28-day cycle, but only between cycles. One pracinostat dose reduction was allowed from 60 mg to 45 mg. Up to 2 AZA dose reductions were allowed: Dose level -1: 37.5 mg/m^{2,} dose level -2: 25 mg/m^2.

Batch numbers:

Pracinostat 45 mg	Pracinostat 60 mg	AZACITIDINE
39001047	39001049	8F085A
39001049	39001097	7A959A
XHWB	XHWD	6J932A
XHWD	XHWF	6F897A
ZWZN	ZVDB	6G896A
		6K945A
		7C979B
		9G214A
		9A148A
		8H905A
		7L036A
		9K250A
		9C169B
		6C865A
		6K939A
		7E994A
		5A754C
		7K027A
		9F201A
		7A952A
		9A146A
		7A952A

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Reference Therapy, Dose and Mode of Administration, Batch Number:

Group B (experimental): placebo + background therapy (AZA)

Placebo: one capsule orally, once a day, 3 times a week (e.g., Monday, Wednesday, and Friday) for 3 weeks, followed by 1 week of rest during each 28-day cycle. Placebo oral administration was to be taken before injection of AZA.

AZA was administered as background therapy at a dose of 75 mg/m^2 by SC or IV injection daily for 7 days of each 28-day cycle.

Dose reduction was not allowed within each 28-day cycle, but only between cycles. Up to 2 AZA dose reductions were allowed: Dose level -1: 37.5 mg/m^{2,} dose level -2: 25 mg/m^2.

Batch numbers:

Placebo	AZACITIDINE
39001051	8F085A
XHWC	7A959A
ZKFM	6J932A
	6F897A
	6G896A
	6K945A
	7C979B
	9G214A
	9A148A
	8H905A
	7L036A
	9K250A
	9C169B
	6C865A
	6K939A
	7E994A
	5A754C
	7K027A
	9F201A
	7A952A
	9A146A
	7A952A

Duration of Treatment: The study duration was dependent on reaching 390 events (deaths) for final survival analysis. It was assumed that recruitment would occur over a 30-months period with 18 additional months to reach 390 events.

The individual study duration for each patient included a screening period (up to 28 days before commencement of Cycle 1 Day 1), a treatment period (minimum of 6 cycles of 28 days as long as there was no evidence of disease progression or non-manageable toxicity), and a long-term follow-up period (until death). Patients still on treatment or in follow-up at the time of 390 events entered the 24-months post-study observation period.

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Endpoints for Evaluation:

Efficacy:

The primary efficacy endpoint was the OS, as measured from the time of randomization until death from any cause.

The secondary efficacy endpoints were:

- Morphologic CR rate
- Transfusion independence
- CR without minimal residual disease (CR_{MRD}-) rate
- Cytogenetic CR (CRc) rate.

The exploratory endpoints were:

- Composite CR (cCR) rate
- Relapse free survival (RFS)
- Progression free survival (PFS)
- Duration of morphologic CR
- Duration of cCR
- Time to CR
- Morphologic CR within 6 cycles rate
- Quality of Life (QoL).

Pharmacokinetics:

The PK endpoints planned for this study were:

- To characterize the PK of pracinostat and its main metabolites in AML patients by a population PK approach.
- To characterize demographic, physiopathological and therapeutic covariates that may influence pracinostat PK parameters and their interindividual variability.
- To characterize the pracinostat exposure-response relationship for safety and efficacy endpoints (PK/pharmacodynamic [PD]).
- To assess the possible drug interaction of pracinostat on the PK of AZA in AML patients by comparing the descriptive statistics of PK parameters of AZA in the two groups.

Safety:

The safety variables evaluated were physical examination, vital signs, 12-lead electrocardiogram (ECG), laboratory test (hematology, blood chemistry, and coagulation panel), and adverse events (AEs) assessments.

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Statistical Methods:

Analysis Sets:

The following analyses sets were defined:

- All randomized (intent-to-treat [ITT]) – This set comprised all randomized patients, regardless if the patient was administered study drug. Patients were assigned to treatment groups based on the randomized study drug assignment.

  A specific ITT set was also defined: ITT-2 – This set comprised patients in the ITT set with abnormal cytogenetics at enrollment. This was the primary set used for the analysis of the efficacy endpoint CRc rate.
- Safety – This set comprised all patients who received at least one dose of pracinostat/placebo. Patients were assigned to treatment groups based on the actual drug received. This was the primary set analyzed for safety and some baseline characteristics.
- Efficacy Evaluable 1 (EE-1) – This set included all patients in the ITT set who had a complete disease response assessment, defined as at least 1 post-baseline peripheral blood count determined and 1 post-baseline bone marrow assessment performed, with an Investigator response reported. This was the secondary set used for the analysis of the efficacy endpoints CR rate, CR_{MRD-} and cCR rate.
- Efficacy Evaluable 2 (EE-2) – This set included all patients in the ITT-2 who had a complete disease response assessment, defined as at least 1 post-baseline peripheral blood count determined and 1 post-baseline bone marrow assessment performed, with an Investigator response reported. This was the secondary set used for the analysis of the efficacy endpoint CRc rate.
- Per Protocol (PP) – This set comprised patients who met all eligibility criteria and received randomized study treatment (i.e., study drug and AZA) without substantial deviations or violations. This set was the secondary set analyzed for the efficacy endpoint OS. This was to be the secondary set for the efficacy endpoint OS.
- PK – At least 2 sets were planned to be defined for the PK analysis, the first set for analyzing the pracinostat data and the other set for analyzing the AZA data: this last set would be limited to the patients from selected sites included in the sub-study and who consented for the sampling for the PK of AZA.

Interim Analysis:

An interim analysis at 67% (2/3) of events (260 over 390 events [deaths], being the study event-driven) was to be performed for both futility and superiority. This interim analysis was already performed when 232 over 390 events (deaths) occurred per Independent Data Monitoring Committee (IDMC) request.

Primary Endpoint:

The primary efficacy endpoint of OS was analyzed using the ITT set. The primary OS analysis was based on the log-rank test stratified by ECOG PS and cytogenetic risk, both used for the randomization, comparing the 2 survival functions of the active treatment group and placebo at the overall one-sided $\alpha = 0.025$ level of significance (a group sequential design according to Gamma family spending function, adopting γ=-3.6 for superiority and γ=-5.5 for futility). Additionally, the duration of the follow-up was calculated using a reverse Kaplan Meier analysis, considering events patients who were alive and censoring patients at the date of death. The unadjusted analysis was performed as sensitivity analysis.

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Secondary Endpoints:

If the primary endpoint was statistically significant, then the first secondary endpoint was tested, and so on for the other secondary endpoints. All secondary efficacy endpoints were summarized descriptively and the proportions in the two treatment groups were compared using the Cochran-Mantel-Haenszel test stratified by cytogenetic risk and ECOG PS (values stated at randomization). In addition, the two-sided 95% confidence interval (CI) for the difference between the responder proportions in the two treatment groups was provided, using the unstratified Newcombe method, and an unstratified analysis was done for sensitivity purpose by means of likelihood ratio Chi-square test.

Exploratory Endpoints:

Time-to-event endpoints (RFS, PFS, duration of morphologic CR, duration of cCR, and time to morphologic CR) were summarized using Kaplan Meier estimates including median with 95% CI, number of events and number censored. cCR rate and morphologic CR within 6 cycles rate endpoints were summarized descriptively and the proportions in the two treatment groups were compared using the Cochran-Mantel-Haenszel test stratified for cytogenetic risk and ECOG PS (values stated at randomization). Best response and QoL endpoints were descriptively summarized.

Safety Analysis:

Safety analyses were performed on the safety set. Safety variables including treatment-emergent adverse events (TEAEs), laboratory tests, physical examination, vital signs, and ECGs, were summarized using appropriate descriptive statistics by treatment group. Pretreatment adverse events (AEs) and posttreatment AEs were only listed.

PK Analysis:

The sparse plasma concentration-time data collected for pracinostat and its metabolite was planned to be analyzed by non-linear mixed effect modelling according to a population PK data analysis approach. Dense plasma concentration time data for AZA from the sub-study was planned to be analyzed by non-compartmental analysis. However, no PK data analysis was performed due to the early study termination.

Summary of Results:

Based on request of the IDMC, the interim analysis was actually done on 30 JUN 2020 when 232/390 events occurred in the study. The study was stopped for futility. The analysis presented in this Clinical Study Report (CSR) includes also patients randomized in the time from the cut-off for the interim analysis and the decision to stop, and the additional data collected during that period and is based on 252 events.

Patient disposition:

- In the study, 725 patients were screened. Of these, 319 patients were considered screening failures, so a total of 406 patients were randomized to receive either pracinostat + AZA (203 patients) or placebo + AZA (203 patients), however, 4 patients were not treated with the study medication (2 patients in each treatment group), thus a total of 402 patients were treated with pracinostat + AZA or placebo + AZA during the study (201 patients in each treatment group).
- Due to the early termination of the study, all patients were discontinued from the study treatment. The most frequently reported reason for discontinuation from study treatment was ‘other’ (108 [26.6%] patients), followed by ‘progressive disease’ (106 [26.1] patients), and ‘death’ (72 [17.7%] patients).

Demographic and baseline characteristics:

- The overall mean age was 75.3 years. About 60% of the patients were male. Approximately 12% of the patients were 'Hispanic or Latino'. Overall mean height was 165.4 cm and mean weight was 73.4 kg. More than half of the patients had an intermediate cytogenetic risk at randomization (216 [53.2%] patients per central laboratory results, and 271 [66.7%] patients per local or central laboratory results used for randomization, of them 79 patients did not have the central assessment), and ECOG PS of Grade 0-1 (227 [55.9%] patients per ECOG PS used for randomization, and 224 [55.2%] patients per ECOG PS at Cycle 1 Day 1).
- Regarding AML characteristics, more than half of the patients had bone marrow blast count > 30% at diagnosis and at screening. The most frequently reported AML recurrent genetic abnormality type was 'AML with mutated NPM1' (17 [4.2%] patients). A total of 202 (49.8%) patients reported AML with myelodysplasia-related changes and overall 88 (21.7%) patients were reported to have a prior treatment for AML, being hydroxycarbamide the most frequently reported.

Efficacy Results:

Primary Efficacy Endpoint

- Median OS was identical in both treatment groups (303.0 days) with no statistically significant differences between treatment groups (p=0.8275). No statistically significant differences between treatment groups were observed either in the additional analysis performed (sensitivity analysis, unstratified analysis, patients with new AML interceding therapy, or subgroups). However, curves showed a shorter survival time in the pracinostat arm until median survival time but a longer survival thereafter.

Secondary Efficacy Endpoints

- The proportion of patients who achieved morphologic CR during the study was slightly higher in the placebo + AZA group (17.2%) when compared to the pracinostat + AZA group (11.8%), although no statistically significant differences between groups were observed (p=0.1244). Similar results were observed for the additional analysis performed.
- The number and proportion of patients with transfusion independence rate was comparable between treatment groups.
- No statistically significant differences between treatment groups were observed for the number and proportion of patients who achieved CR_{MRD-} during the study (p=0.1430).
- The number and proportion of patients who achieved CRc were comparable between treatment groups and no statistically significant differences were observed (p=0.9977).

Exploratory Efficacy Endpoints

- The number and proportion of patients who achieved cCR during the study was slightly higher in the pracinostat + AZA group (73 [36.0%] patients) when compared to the placebo + AZA group (64 [31.5%] patients) in the ITT set without reaching any statistically significant differences between treatment groups (p=0.3502). However, statistically significant differences were observed in favor or the pracinostat + AZA group when compared to the placebo + AZA group when this endpoint was analyzed for patients who had a complete disease response assessment (p=0.0102), defined as at least 1 post-baseline peripheral blood count determined and 1 post-baseline bone marrow assessment performed, with an Investigator response reported.
- Median overall time of RFS was slightly longer in the pracinostat + AZA group (291.0 days) when compared to the placebo + AZA group (190.0 days), although no statistically significant differences were observed between treatment groups (p=0.4656).
- Median overall time of PFS was comparable between treatment groups (p=0.7063).

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- Curves of duration of and time to morphologic CR rate did not reach 0.5 level of probability/incidence, so median value was not possible to be calculated for the pracinostat + AZA group, although no statistically significant differences were observed between treatment groups (p=0.0592 and p=0.3835, respectively). The trend was similar within each stratum and the sample size was limited. However, curves showed an advantage of pracinostat + AZA group when compared to placebo + AZA group.
- Although no statistically significant differences (p=0.0502) were observed between treatments for the duration of cCR, median duration of cCR was longer in the pracinostat + AZA group (576.0 days) when compared to the placebo + AZA group (319.0 days).
- The number and proportion of patients who achieved morphologic CR within 6 cycles did not show any statistically significant difference (p=0.7099).
- Results for best overall response were in general comparable between treatment groups. Overall response which included CR, partial remission, incomplete blood count recovery (CRi), or morphologic leukemia free state (MLFS) was achieved by 36.0% patients in the pracinostat + AZA group and by 31.5% patients in the placebo + AZA group.
- In general, no statistically significant differences were observed in favor of pracinostat + AZA group for the subgroups analyzed on the OS or morphologic CR by cytogenetic risk and ECOG PS.
- No statistically significant differences were observed for the endpoints analyzed by geographical area.
- In general, a slight worsening in all the parameters analyzed was observed for the change from baseline to the End of Treatment visit in the QoL quality of life scale.

Pharmacokinetics Results:

- Not applicable as no PK analysis was performed due to the early termination of the study.

Safety Results:

- There were 5241 TEAEs reported on study which were comparable across treatment groups.
- Across both treatment groups the frequently reported TEAEs by SOC were Gastrointestinal disorders (288 [71.6%] patients, 1029 events), Infections and infestations (269 [66.9%] patients, 614 events), Blood and lymphatic system disorders (257 [63.9%] patients, 874 events), and General disorders and administration site conditions (247 [61.4%] patients, 566 events. In general, the most frequently reported TEAEs by SOC were comparable between groups.
- The most frequently reported TEAEs by PT were nausea (164 [40.8%] patients, 226 events), febrile neutropenia (130 [32.3%] patients, 220 events), anemia (128 [31.8%] patients, 284 events), constipation (116 [28.9%] patients, 152 events), and vomiting (114 [28.4%] patients, 176 events). In general, the most frequently reported TEAEs by PT were also comparable between treatment groups.
- More than half of TEAEs reported were deemed to be of grade 1-2 NCI CTCAE with comparable results between treatment groups.

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- There were 1439 pracinostat/placebo related TEAEs reported in 252 (62.7%) patients. Higher frequencies in the pracinostat + AZA group (132 [65.7%] patients, 815 events) were observed when compared to the placebo + AZA group (120 [59.7%] patients, 624 events). In general, the most frequently reported pracinostat/placebo related TEAEs by SOC and PT were comparable between treatment groups. Regarding severity (TEAEs with NCI CTCAE grade ≥ 3) Blood and lymphatic system disorders (126 [31.3%] patients, 338 events), Infections and infestations (46 [11.4%] patients, 65 events), and Investigations (39 [9.7%] patients, 114 events) were the most frequently reported grade ≥ 3 TEAEs by SOC. By PT, the most frequently reported TEAEs were febrile neutropenia (59 [14.7%] patients, 93 events), anaemia (49 [12.2%] patients, 103 events), thrombocytopenia (38 [9.5%] patients, 63 events), and neutropenia (37 [9.2%] patients, 56 events). In general, results were comparable between treatment groups.
- A higher number (1680) of AZA related TEAEs compared to (1439) pracinostat/placebo related TEAEs were observed with comparable results between treatment groups. The same TEAEs by SOC and PT as for the pracinostat/placebo related grade ≥ 3 TEAEs were reported with comparable results between treatment groups.
- TEAEs leading to pracinostat/placebo and/or AZA dose reduction were low. Overall, 14 (3.5%) patients reported 16 TEAEs leading to pracinostat/placebo dose reduction and 25 (6.2%) patients reported 31 TEAEs leading to AZA dose reduction with comparable results between treatment groups, respectively. The most frequently reported TEAEs leading to pracinostat/placebo dose reduction by SOC was General disorders and administration site conditions (6 [1.5%] patients, 6 events) and leading to AZA dose reduction was Blood and lymphatic system disorders (9 [2.2%] patients, 9 events).
- A total of 103 [25.6%] patients reported 207 TEAEs leading to pracinostat/placebo temporary dose interruption. Slightly higher frequencies were reported in the pracinostat + AZA group (28.4%) when compared to the placebo + AZA group (22.9%). The most frequently reported TEAEs leading to pracinostat/placebo dose interruption by SOC were Infections and infestations (41 [10.2%] patients, 58 events), followed by Blood and lymphatic system disorders (30 [7.5%] patients, 48 events) and Investigations (18 [4.5%] patients, 25 events), and by PT were febrile neutropenia (13 [3.2%] patients, 15 events), neutropenia (11 [2.7%] patients, 22 events), and pneumonia (10 [2.5%] patients, 13 events) with comparable results between treatment groups.
- Overall, 93 (23.1%) patients reported 177 TEAEs leading to AZA dose interruption with comparable results between treatment groups. The most frequently reported TEAEs leading to AZA dose interruption by SOC was Infections and infestations (36 [9.0%] patients, 47 events), Blood and lymphatic system disorders (26 [6.5%] patients, 47 events), and General disorders and administration site conditions (17 [4.2%] patients, 21 events), and by PT pyrexia (13 [3.2%] patients, 15 events), neutropenia (12 [3.0%] patients, 23 events) and febrile neutropenia (12 [3.0] patients, 15 events).
- Overall, 52 (12.9%) patients discontinued the study due to TEAEs with comparable results between treatment groups. Most of TEAEs leading to permanent discontinuation were not reported in more than 1 patient.

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- Serious TEAEs were overall reported in 304 (75.6%) patients with comparable results between treatment groups. The most frequently reported serious TEAEs by PT were febrile neutropenia (113 [28.1%] patients, 184 events), pneumonia (56 [13.9%] patients, 64 events), and sepsis (33 [8.2%] patients, 37 events). No differences on the most frequently reported serious TEAEs by PT were observed between treatment groups.
- Pracinostat/placebo related serious TEAEs were overall reported in 119 (29.6%) patients and AZA related serious TEAEs in 127 (31.6%) patients with comparable results between treatment groups. The most frequently reported serious related TEAEs by SOC were Infections and infestations (178 (44.3%) patients, 264 events), followed by Blood and lymphatic tissue disorders (144 (35.8) patients, 255 events), and General disorders and administration site conditions (47 (11.7%) patients, 54 events); and by PT were febrile neutropenia (113 [28.1%] patients, 184 events), followed by pneumonia (56 [13.9%] patients, 64 events), and sepsis (33 [8.2%] patients, 37 events).
- TEAEs of special interest were overall reported in 310 (77.1%) patients with comparable results between treatment groups. The most frequently reported TEAEs of special interest were related to the SMQ 'grade ≥ 3 anemia, neutropenia, febrile neutropenia, and thrombocytopenia' (246 [61.2%] patients).
- A total of 249 (61.9%) patients died during the study with comparable results between treatment group. Overall, the primary cause of death was underlying disease progression. By treatment group, the cause of death was differently distributed between pracinostat + AZA group (AE) and placebo + AZA group (disease progression). A higher proportion of patients in the pracinostat + AZA group (25.6%) experienced mortality secondary to an AE compared to the placebo + AZA group (18.9%).
- All documented safety variables (clinical laboratory parameters, physical examination, vital signs, and ECG) showed no clinically relevant differences between treatment groups and did not indicate any unexpected safety issues.

Conclusions: This double-blind, placebo-controlled, with group sequential design, multicenter, randomized study did not demonstrate that the combined administration of pracinostat and AZA compared to AZA as a single agent could improve the OS in adult newly diagnosed AML patients who were unfit to receive intensive induction chemotherapy.

Date of the Report: CSR final version v1.0 14 APR 2021