Zentrum
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Leipzig

Summary of the Trial Report
[Synopsis according to ICH E3]

Treatment of MDS/AML patients with an impending Hematological relapse with Azacitidine alone or in combination with PEvonedistat - a randomized phase 2 trial

(Randomized, multi-centre, open-label, phase 2 trial)

SHAPE

Name of Finished Product/Name of Active Substance:

Pevonedistat in combination with azacitidine

Indication/Diagnosis:

MDS/AML with MRD and impending relapse after allogeneic stem cell transplantation and/or conventional chemotherapy

Phase of Development:
Phase II

EudraCT-Number:
2019-004536-37

Registration-Number:
Clinical Trials.gov identifier: NCT04712942

Date of report: 2023-08-30
Version: final 1.0

Trial start: 07.01.2021
End of Trial: 31.01.2023

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The signing authors approve the report presented here by their signature. The described clinical trial was conducted according to the Declaration of Helsinki, Good Clinical Practice (GCP) as well as the applicable statutory provisions.

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Table of contents

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2 Name of Finished Product	3 Name of active Ingredient
Pevonedistat (MLN4929)	Pevonedistat
VIDAZA®	Azacitidine

4 Individual study table

Not applicable.

5 Title of Study

Treatment of MDS/AML patients with an impending Hematological relapse with Azacitidine alone or in combination with Pevonedistat - a randomized phase 2 trial (SHAPE)

The final trial protocol was version final 4.0 as of November 11st, 2021, including the following amendments:

- Amendment 01; submitted in July 2021:
  - More detailed information on inclusion and exclusion criteria
  - An additional blood sample collection for the scientific accompanying project "Immunomonitoring".
  - IMP dose change: henceforth use of 4.4 ml instead of 5 ml vials
  - Addition of three new trial sites (Kiel, Hamburg, Frankfurt)
  - Few text corrections and changes were made in the patient information in accordance with the protocol.
  - Resulting in protocol version final 3.0 (07.07.2021)
- Amendment 02; submitted in November 2021:
  - Premature end of enrollment
  - New IB
  - Resulting in protocol version final 4.0 (11.11.2021)

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8 Publications

Not applicable.

9 Studied period (in years)

Date of first enrolment: 07.01.2021

Date of last completed: 31.01.2023

10 Premature stop of enrollment:

Takeda Pharmaceutical Company Limited, who was financing the SHAPE trial and providing the IMP (pevonedistat), announced in September 2021 that the Phase 3 PANTHER study (Pevonedistat-3001, EudraCT Number: 2017-000318-40) did not achieve its pre-defined statistical significance for the primary endpoint of event-free survival (EFS). The trial evaluated whether the combination of pevonedistat (PEV) plus azacitidine (AZA) as first-line treatment for patients with higher-risk myelodysplastic syndromes, chronic myelomonocytic leukemia and low-blast acute myeloid leukemia improved EFS versus azacitidine alone. EFS was defined as „time from randomization to the date of an EFS event (defined as death or transformation to AML in patients with MDS or CMML, whichever occurs first, and defined as death in patients with low-blast AML) “.

Due to this result, the IMP manufacturer decided to stop future drug development and production of pevonedistat. This decision had significant implications for the SHAPE trial.

Recruitment to the SHAPE trial needed to be ended prematurely, since it was not possible to ensure the continued combination-treatment of the patients without available IMP.

11 Objectives

The SHAPE trial was a Phase II trial using an unapproved pharmaceutical for the treatment of MDS/AML patients with an impending Hematological relapse in combination with approved azacitidine.

Primary objective:

To show that pevonedistat and azacitidine are more effective compared to azacitidine alone with regard to achievement of MRD negativity after 3 months of treatment (MRD status after 3 months of treatment).

Secondary objectives:

Cross-over from the control arm (azacytidine monotherapy) to the experimental arm (combination therapy of azacytidine and pevonedistat) was allowed in case of MRD positivity after 3 cycles or re-emergent MRD after cycle 4 to 9. That allowed to estimate the MRD negativity rate of 3 cycles of pevonedistat plus azacitidine in patients failing azacitidine alone.

To describe and compare outcome measures between two strategies: pevonedistat and azacitidine in combination versus azacitidine alone with cross over option:
Time to event endpoints:

- Overall Survival (OS): Time from randomization until death from any cause
- Relapse Free Survival (RFS): Time from randomization until hematological relapse or death from any cause (whichever comes first)

Time to event endpoints with competing risks:

- Cumulative incidence of documented MRD negativity with death, hematological relapse and transplant as competing events
- Cumulative incidence of hematological relapse with death and transplant as competing events
- Quality of life

Rate and severity of adverse events for patients treated with pevonedistat and azacitidine combination therapy and with azacitidine alone.

12 Methodology

This is a two armed, prospective, randomised, multi-centric, phase II trial.

Randomisation of patients between mono- and combination therapy was performed centrally via a secure web-based tool using a modified minimisation procedure with stochastic component according to Pocock (1983) in a 1:1 proportion.

Randomisation was balanced according to the following criteria:
• Disease entity (AML versus MDS)
• Prior allogeneic transplant (y/n)

The primary endpoint was assessed centrally, in a respective core lab, using standardized protocols: Central lab for MRD assessment (AgenDix GmbH, Fiedlerstr. 36, 01307 Dresden, Germany).

13 Number of patients (planned and analysed)

Planned number:	102 patients (51 patients per treatment group)
Registered/screened subjects:	19
Recruited subjects/randomized:	14
Analyzed patients:	14 (all patients included in final analysis)
Drop-outs:	2 patients dropped-out before the final visit

109 patients were pre-screened for MRD status.

For details see the CONSORT-flow diagram in appendix 21.1

14 Diagnosis and main criteria for inclusion

Inclusion criteria

- AML or MDS
- continuing first CR after conventional intensive chemotherapy OR continuing CR after alloSCT
- MRD positivity (assessed by local lab) as defined by:
    - NPM1mut status >1% in peripheral blood or bone marrow in NPM1 mutated patients at diagnosis or
    - Patients after allogeneic transplantation, who were NPM1 unmutated at diagnosis and have a blood or marrow CD34/CD117 chimerism <80%

Major exclusion criteria

- Patient does not accept bone marrow sampling during screening, primary end point visit and after the treatment.
- Patient does not accept several blood sampling during screening, treatment (up to bi-daily) and after the treatment.
- Inadequate organ function as defined in the list below:
    - White blood cell (WBC) count > 50 Gpt/L before administration of pevonedistat on Cycle 1 Day 1
    - Absolute neutrophil count (ANC) < 1.5 Gpt/L
    - Platelets < 100 Gpt/L
    - Albumin < 2.7 g/dL
    - Creatinine clearance < 30 mL/min (Cockcroft und Gault formula)
    - Total bilirubin > 1.5xupper limit of normal (ULN) except in patients with Gilbert's syndrome. Patients with Gilbert's syndrome may be enrolled if direct bilirubin > 1.5x ULN of the direct bilirubin.
    - Both Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) > 3.0 ULN
- ECOG performance status of ≥2
- Liver cirrhosis or severe pre-existing hepatic impairment
- Known severe cardiopulmonary disease
- Uncontrolled high blood pressure (i.e. systolic blood pressure > 180 mm Hg, diastolic blood pressure > 95 mm Hg)
- Known prolonged rate corrected QT interval ≥ 500 msec, calculated according to institutional guidelines

- Known left ventricular ejection fraction < 50% as assessed by echocardiogram or radionuclide angiography
- Known moderate to severe symptomatic chronic obstructive pulmonary disease, interstitial lung disease, or pulmonary fibrosis
- Active uncontrolled infection or severe infectious disease, such as severe pneumonia, meningitis, or septicemia
- Known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.
- Known Human Immunodeficiency Virus (HIV 1/2 antibodies)
- Known active Hepatitis B or Hepatitis C
- Major surgery within 14 days of randomization or a scheduled surgery during study period
- Known central nervous system (CNS) involvement
- Diagnosis or treatment for another malignancy within 2 years before randomization.
- Any evidence of residual disease of another malignancy
- Patients with uncontrolled coagulopathy or bleeding disorder
- History or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the subject's participation for the full duration of the trial, or is not in the best interest of the subject to participate, in the opinion of the treating investigator
- Prior HMA failure
- Prior HMA treatment without subsequent allogeneic transplantation
- Any ongoing therapy active against MDS or AML
- BCRP inhibitors (for exceptions, see section 5.7.5) are not permitted during the study and should be stopped 14 days before first dose of the study drug

15 Information on the Test Product

Pevonedistat was administered at 20 mg/m^2 body surface area (BSA) over 60 (±10) minutes as intravenous infusion additionally to azacytidine on days 1, 3, and 5 of each cycle for up to 12 months.

Dose: 20 mg/m^2 BSA

Mode of Administration: intravenous

Batch numbers: 202011005

16 Duration of Treatment

Treatment duration: maximum of 1 year

Follow-up duration (after EOT): one safety follow-up visit after three months

17 Reference Therapy

All Patients will receive azacitidine at 75 mg/m^2 BSA, IV or SC on days 1-7 on each treatment cycle (q4w) or on days 1-5, 8 and 9 to omit treatment during weekends.

Dose: 75 mg/m^2 BSA

Mode of Administration: intravenous or subcutaneous (on investigator's decision)

Batch numbers: n.a. (Commercially available, approved medication was used by the trial sites)

18 Criteria for Evaluation

18.1 Efficacy

The primary endpoint is the rate of documented MRD negativity after three cycles of treatment. Patients who do not receive three cycles for any reason (e.g. hematological relapse, toxicity), patients without valid MRD assessment after three cycles, as well as patients in whom the individually pertinent MRD criterion is positive after three cycles count as treatment failures.

Secondary End Points
Overall Survival (OS): Time from randomization until death from any cause.
Relapse Free Survival (RFS): Time from randomization until hematological relapse or death from any cause (whichever comes first).
Cumulative incidence of documented MRD negativity with death, hematological relapse and transplant as competing events.
Cumulative incidence of hematological relapse with death and transplant as competing events.
The rate of conversion to MRD negativity among patients crossing over from the control to the experimental arm after three crossed-over cycles.
Impact of treatment assessed by using the validated questionnaires EORTC QLQ-C30 and EQ-5D-5L.

18.2 Safety

Rate and CTC-toxicity graded severity of adverse events for patients treated with pevonedistat and azacitidine combination therapy and with azacitidine alone.

19 Statistical Methods/analysis procedures

The primary efficacy analysis was originally planned as a logistic regression adjusting for stratification factors AML vs. MDS and prior allogeneic transplant.
Comparative secondary efficiency endpoints were originally intended with similarly structured regression models: Time to event endpoints should be based on Cox regression, Time to event with competing risk endpoints should be based on Fine-Gray-Regression.
Because of the very low number of included patients all results are only described.

20 Summary/Conclusion

20.1 Efficacy results

Due to the limited number of patients, efficacy results are presented in form of a patient-wise listing (Table 1). 14 patients were randomised. Of the 14 randomised patients, seven have a documented MRD result at the primary endpoint visit after three cycles of therapy. Three of the seven patients with documented primary endpoint were MRD negative; two of three in the AZA-PEV arm and one of four in the AZA-mono arm. The remaining seven patients do not have a documented MRD result for the primary endpoint visit because the treatment was terminated prematurely. Five of these seven patients received fewer than three cycles of therapy. One of the other two patients has started, but did not complete cycle three. In a further patient in the AZA-PEV arm, the MRD assessment for the primary endpoint and cycle four visit was not performed; but the patient showed a negative MRD result already after the first cycle,

which was confirmed during the visits for cycles three, five and six. The other five of these seven patients remained MRD positive until the last documented cycle.
Overall survival in table 1 was estimated from date of randomisation until date of last information about the patient. Five of 14 patients were deceased at last information. One patient deceased in the AZA mono arm because of progressive disease. Four patients deceased in the AZA+PEV arm, one due to progressive disease, one by progressive disease and infection, one by infection and one by an unknown reason. Eight patients have a hematologic relapse four in the AZA mono arm and four in the AZA+PEV arm.
Three patients underwent a crossover from the AZA mono arm to the AZA+PEV arm after cycle three.
Further statistical analysis is not meaningful due to the low sample size.

Patient Nr.	Sex	Age [years]	Arm	AML/MDS-type	Crossover	max. cycle	MRD status after 3 cycles	Relapse free survival [months]	Overall survival [months]
1	male	68	AZA mono	MDS-MLD	yes	5	positive	5.2	9.1+
2	female	60	AZA mono	AML de novo	no	3	-	6.3+	6.3+
3	female	68	AZA mono	MDS-EB	no	3	positive	3.3	8.7+
4	female	52	AZA mono	AML de novo	yes	8	positive	10.2	13.0+
5	female	69	AZA mono	AML de novo	no	1	-	13.1+	13.1+
6	male	64	AZA mono	AML-MRC	no	2	-	1.9	6.5
7	male	62	AZA mono	AML-MRC	yes	6	negative	11.5+	11.5+
8	female	53	AZA mono	MDS-U	no	1	-	4.7+	4.7+
9	male	73	AZA+PEV	MDS-EB	-	12	negative	11.6+	15.8
10	male	56	AZA+PEV	AML-MRC	-	8	negative	8.4	10.8
11	male	59	AZA+PEV	AML-MRC	-	2	-	1.7	2.7
12	male	61	AZA+PEV	AML de novo	-	2	-	3.1	5.1
13	male	40	AZA+PEV	AML de novo	-	8	positive	7.1	11.2+
14	female	66	AZA+PEV	MDS-EB	-	6	-	9.9+	9.9+

Table 1: Listing of the efficacy results.

20.2 Safety results

In both arms the same number of adverse events (AEs) is documented. The documented AEs for the AZA mono arm are listed in table 2 and for the combination therapy arm in table 3. AEs are listed with their MedDRA-PT (PT-preferred term) coding together with their common toxicity criteria (CTC-toxicity grade).

AE (MedDRA-PT)	Ntotal	CTC1	CTC2	CTC3	CTC4	CTC5
Adjustment disorder with depressed mood	1	0	1	0	0	0
Bacterial infection	1	0	1	0	0	0
Blood immunoglobulin G decreased	1	0	1	0	0	0
Candida infection	1	0	1	0	0	0
Chronic graft versus host disease in eye	1	0	1	0	0	0
Coronavirus infection	1	0	1	0	0	0
COVID-19	1	1	0	0	0	0
Diarrhoea	4	4	0	0	0	0
Electrocardiogram QT prolonged	1	0	0	1	0	0
Enterocolitis	1	0	1	0	0	0
Fatigue	1	1	0	0	0	0
Graft versus host disease in skin	1	0	1	0	0	0
Hepatomegaly	1	1	0	0	0	0
Hypoalbuminaemia	1	0	1	0	0	0
Hypokalaemia	2	2	0	0	0	0
Hypomagnesaemia	1	1	0	0	0	0
Leukopenia	2	0	0	2	0	0
Lymphopenia	2	1	1	0	0	0
Muscular weakness	3	2	1	0	0	0
Nausea	3	2	1	0	0	0
Neutropenia	7	1	1	4	1	0
Neutrophil count decreased	3	0	0	1	2	0
Periarthritis	1	1	0	0	0	0
Peripheral swelling	1	1	0	0	0	0
Platelet count decreased	4	0	3	1	0	0
Respiratory tract infection viral	1	0	1	0	0	0
Splenomegaly	1	1	0	0	0	0
Thrombocytopenia	4	0	1	2	1	0
Tumour associated fever	1	0	0	1	0	0
Urinary tract infection	1	0	1	0	0	0
Vomiting	3	3	0	0	0	0

Table 2: Documented AEs with CTC toxicity grade for the AZA mono arm.

AE (MedDRA-PT)	Ntotal	CTC1	CTC2	CTC3	CTC4	CTC5
Abdominal pain upper	1	1	0	0	0	0
Acute myeloid leukaemia recurrent	1	0	0	1	0	0
Anaemia	2	0	1	1	0	0
Anisocoria	1	0	1	0	0	0
Arthralgia	1	1	0	0	0	0
Bone pain	1	0	1	0	0	0
Chronic graft versus host disease	1	0	1	0	0	0
Constipation	2	1	1	0	0	0
Cystitis	1	0	1	0	0	0
Decreased appetite	1	1	0	0	0	0
Diarrhoea	3	2	1	0	0	0
Discomfort	1	0	0	1	0	0
Disease progression	1	0	0	1	0	0
Dysgeusia	1	1	0	0	0	0
Dyspnoea	1	1	0	0	0	0
Fatigue	3	1	2	0	0	0
Febrile infection	1	0	1	0	0	0
Fungal infection	1	0	1	0	0	0
Haematoma	1	1	0	0	0	0
Haemoglobin decreased	1	0	0	1	0	0
Hepatic enzyme increased	2	2	0	0	0	0
Hepatic steatosis	1	1	0	0	0	0
Hyperaesthesia teeth	1	1	0	0	0	0
Hypokalaemia	1	1	0	0	0	0
Hypophosphataemia	1	1	0	0	0	0
Hypotension	1	0	1	0	0	0
Leukopenia	2	0	0	2	0	0
Muscle spasms	1	1	0	0	0	0
Myalgia	1	1	0	0	0	0
Nausea	1	1	0	0	0	0
Neutropenia	9	0	0	5	4	0
Neutrophil count decreased	1	0	0	1	0	0
Platelet count decreased	1	0	0	1	0	0
Pruritus	1	1	0	0	0	0
Serum ferritin increased	1	0	0	1	0	0
Skin infection	1	1	0	0	0	0
Syncope	1	0	0	1	0	0
Thrombocytopenia	4	0	1	3	0	0

Table 3: Documented AEs with CTC toxicity grade for the AZA+PEV combination arm.

Table 4 shows a summary of all listed AEs from the tables 2 and 3 above, divided by treatment arm. The AEs are further divided in severe adverse events SAEs. The CTC34 columns means patients or AEs with CTC3- or CTC4-toxicity grade.

Arm	AEs	Patients with AEs	AEs with CTC34	Patients with CTC34	SAEs	Patients with SAEs
AZA mono	57	8	16	5	3	2
AZA+PEV	57	6	23	6	1	1

Table 4: Adverse events (AEs) summary.

20.3 Conclusions

The study was terminated prematurely by company decision. There were no safety concerns. Since only 14 of the planned 102 patients were randomised, a detailed statistical analysis is pointless. Three of seven patients with documented primary endpoint were MRD negative; two of three in the AZA-PEV arm and one of four in the AZA-mono arm.

21 Appendix

21.1 CONSORT Flow chart

Figure 1 shows the patient flow in the study. Of the eight patients randomized to the AZA mono arm three patients undergo a crossover to the AZA+PEV combination arm.

Figure 1