SYNOPSIS CLINICAL STUDY REPORT

according to ICH E3 guideline

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A RANDOMIZED PLACEBO-CONTROLLED PHASE 2 STUDY OF DECITABINE/AZACITIDINE WITH OR WITHOUT ELTROMBOPAG IN AML PATIENTS ≥65 YEARS OF AGE NOT ELIGIBLE FOR INTENSIVE CHEMOTHERAPY

DELTA

Trial Protocol version 5.0 F, 24.06.2016

including protocol version 4.0, 30.07.2015, protocol version version 3.0, 19.12.2014

Sponsor	**Technische Universität Dresden** 01062 Dresden
Principal Coordinating Investigator	**Prof. Dr. med. Uwe Platzbecker** Medizinische Fakultät der TU Dresden Medizinische Klinik und Poliklinik I, Universitätsklinikum Dresden Fetscherstraße 74, 01307 Dresden
Sponsor Code:	TUD-DELTA1-063
EudraCT-Number:	2014-003150-13
ClinicalTrials.gov Identifier:	NCT02446145
Name of Finished Product and Active Substance	Finished Product: Eltrombopag / Placebo Active Substance: Eltrombopagdi(olamin)

TABLE OF CONTENTS

1 SUMMARY OF TRIAL INFORMATION

Sponsor	**Technische Universität Dresden** 01062 Dresden
Principal Coordinating Investigator	Prof. Dr. med. Uwe Platzbecker Medizinische Klinik und Poliklinik I, Universitätsklinikum Fetscherstr. 74, 01307 Dresden
Full Title	A randomized placebo-controlled phase 2 study of decitabine / azacitidine with or without eltrombopag in AML patients ≥65 years of age not eligible for intensive chemotherapy
Short Title	DELTA
Trial Protocol	Trial Protocol version 5.0 F, 24.06.2016 including Trial Protocol version 4.0, 30.07.2015 and Trial Protocol version 3.0, 19.12.2014
Indication	Newly diagnosed or secondary acute myeloid leukemia in adult thrombopenic patients ≥65 years of age ineligible for intensive chemotherapy
Phase of development	Phase II
Study design	Two-arm, double-blind, multicenter randomized-controlled phase-II trial
Objective(s) of the clinical trial	Trial objective(s): To assess whether the addition of eltrombopag improves efficacy and tolerability of the standard treatment with hypomethylating agents in thrombocytopenic AML patients who are ≥65 years of age and nonfit for intensive chemotherapy
Endpoints of the clinical trial	Primary Endpoint(s): Treatment change-free survival (TCFS) Secondary Endpoints: Efficacy • Overall survival (OS) in the presence of competing risk treatment change • Overall response rate (CR, PR, SD) • Relapse-free survival (RFS) • Number of platelet transfusions during cycles 1-4 Safety and tolerability of treatment with EPAG / placebo, including • Incidence of bleeding events • Number of bone marrow blasts from baseline and after 5, 9 and 12 months
Number of patients	planned sample size: n = 238; exclusive 19 patients recruited within protocol version 4-0 patients screened: 139 patients enrolled: 132 patients analysed: 105 (FAS) / 124 (SES)

Studied period	• First patient in: 18.06.2015 • Recruitment stop: 12.05.2016 – 21.09.2016 reason: supply shortage of IMP • Recruitment stop: 18.04.2019 – 15.05.2019 reason: disagreement with the patient insurance company with regard on extension of duration of patient insurance • Premature end of recruitment: 30.06.2020 reason: insufficient recruitment due to new treatment options shown to be superior to study treatment • Last patient in: 02.06.2020 • Last patient last visit: 26.12.2020
Inclusion criteria	• Newly diagnosed AML (including therapy-related AML or with antecedent MDS) other than acute promyelocytic leukemia (APL) according to WHO criteria, i.e. bone marrow aspirate / biopsy or peripheral blood must contain ≥20% blasts • In AML defined by cytogenetic aberrations according to WHO the proportion of blasts may be <20% • Age ≥ 65 years • ECOG performance status 0-3 • Patients not eligible for intensive induction therapy (according to investigator's decision) • Planned therapy with DAC or AZA • Platelet count <75 Gpt/L taken within 4 weeks prior to randomisation • Adequate liver function as assessed by the following laboratory requirements during screening (within 4 weeks prior to study inclusion): o Total bilirubin ≤ 3 times the upper limit of normal (except for Gilbert's Syndrome) o ALT and AST ≤ 3 times upper limit of normal • Signed Informed Consent
Exclusion criteria	• Acute promyelocytic leukemia (APL) • Previous treatment of higher-risk MDS or AML with TPO-R agonists, hypomethylating agents or intensive chemotherapy • Substance abuse, medical, psychological or social conditions that may interfere with the patient's participation in the study or evaluation of the study results • Treatment with an investigational drug within 30 days or 5 half-lives (whichever was longer) preceding to first dose of study mediation • Uncontrolled active infection • NYHA stage ≥ 2 due to heart insufficiency • Positive Human Immunodeficiency Virus (HIV) or Hepatitis B / C serology • Patients unable to swallow medication • Known immediate or delayed hypersensitivity reaction or idiosyncrasy to drugs chemically related to EPAG, DAC, AZA or excipients that contraindicates their participation
Test product(s)	Eltrombopag (Verum)

	Dose of administration: 0-400mg daily dose Mode of administration: oral Batch number(s): Bulk batch numbers: R586951 (122367781); (packed batch number: 122367790, 100mg tabs R647666 (132375545); (packed batch number: 142385723), 100mg tabs R586940 (122367780); (packed batch number: 122367791), 50mg tabs R635655 (132374135); (packed batch number: 132375754), 50mg tabs R758803 (162395905); (packed lot number: 162395765), 50mg tabs R795981, 50mg tabs 162395905, 50mg tabs
Reference therapy	Placebo (Comparator) Dose of administration: 0-400mg daily dose (corresponding dose to Verum) Mode of administration: oral Batch number(s): Bulk batch numbers: R576843 (121364336) (packed batch number: 122365476) R628071 (132371977) (packed batch number: 132374540) R760438 (162397906)
Duration of treatment	Treatment arm “Verum” Product: Eltrombopag Dose: Starting dose 200 mg/d p.o.; escalation up to 300 mg/d p.o *East Asian patients:* *Starting dose 100 mg/d p.o.; escalation up to 150 mg/d p.o* Duration: cycle days 12-25 q4w (max. 12 cycles) Treatment arm “Control” Product: Placebo Dose: number of tablets according to Verum arm Duration: cycle days 12-25 q4w (max. 12 cycles) Concomitant medication (both treatment arms): Treatment with standard-dose DAC Decitabine 20 mg/m² i.v. d 1-5 q4w or Treatment with standard-dose AZA Azacitidine 75 mg/m2 s.c. d 1-7 q4w

2 INDIVIDUAL STUDY TABLE

Not applicable

3 INVESTIGATORS AND TRIAL SITES

No. of Trial Site	Trial Site	Investigator(s)
068	Universitätsklinikum Aachen der RWTH	Dr. med. Martina Margit Crysandt
012	Sozialstiftung Bamberg	PD Dr.med. Ruth Seggewiß-Bernhardt
045	Klinikum Bayreuth GmbH	Prof. Dr. Alexander Kiani
046	Universitätsmed. Charite CBF	Dr.med. Kathrin Rieger
411	MVZ Onkologischer Schwerpunkt	PD Dr. Philipp Kiewe
014	Klinikum Chemnitz gGmbH	PD Dr.med. Mathias Hänel
303	BAG Freiberg-Richter, Jacobasch, Illmer, Wolf, Dresden	PD Dr. Thomas Illmer
030	Universitätsklinikum Dresden	Dr.med. Anke Mütherig
671	Marien Hospital Düsseldorf	Prof. Dr. Aristoteles Giagounidis
054	Universitätsklinikum Essen	Dr. med. Karl Richard Maria Noppeney
066	Universitätsklinikum Halle (Saale)	Dr.med. Maxi Wass
777	St. Barbara-Klinik Hamm	Dr. Dr. Heinz Albert Dürk
032	St. Bernward Krankenhaus	Prof. Dr. Ulrich Kaiser
067	Universitätsklinikum Jena	Prof. Dr. Sebastian Scholl
002	Westpfalz-Klinikum GmbH	Prof. Dr. med. Gerhard Held
227	Gemeinschaftsklinikum Mittelrhein gGmbH	Dr.med. Dirk Niemann
077	Universitätsklinikum Leipzig	Prof. Dr. med. Uwe Platzbecker
084	Klinikum rechts der Isar der TU München	Prof. Dr. med. Katharina Götze
745	Hämato-Onkologische	Dr.med. Burkhard Schmidt
003	Klinikum Nürnberg Nord	Dr.med. Kerstin Schäfer-Eckart
409	MVZ für Blut- und Krebserkrankungen	Dr.med. Hartmut Linde
410	Wissenschaftskontor Nord GmbH & Co KG	Dr.med. Andreas Lück
018	Diakonie-Krankenhaus	Dr.med. Thomas Geer
184	Klinikum Sindelfingen-Böblingen	PD Dr.med. Markus Ritter
008	Robert-Bosch-Krankenhaus	Dr. med. Martin Kaufmann
117	Rems-Murr-Klinikum Winnenden	Dr.med. Alexander Reichart

4 METHODOLOGY

This trial was conducted as a prospective, double-blind, randomized multicenter phase II trial. Aim of this trial was to investigate the efficacy and tolerability of eltrombopag (EPAG) versus placebo in addition to the standard treatment with hypomethylating agents in elderly thrombocytopenic AML patients.

4.1 BACKGROUND

Acute myeloid leukemia (AML) is a disease with a poor prognosis including a 5-year overall survival (OS) of approximately 20% for the entire population.[3;4] In particular, the outcome of elderly patients with AML is dismal and the majority of patients die within the first year after diagnosis. This is also because treatment options for elderly patients with AML significantly differ from patients of younger age. In fact, comorbid conditions, such as heart disease, renal insufficiency and vascular disease are common among the elderly thus influencing the ability to withstand intensive therapy. Elderly patients are also more likely than younger patients to develop severe, life threatening infections during the course of treatment. In addition to infectious complications, hemorrhages due to severe thrombocytopenia are responsible for morbidity and mortality in a considerable amount of patients.

Compared with younger AML patients, elderly individuals with AML display a higher incidence of poor-prognosis karyotypes, of a preceding myelodysplastic syndrome (MDS) and greater expression of proteins involved in intrinsic resistance to chemotherapeutic agents. As a result conventional anthracycline-based chemotherapy is only infrequently used in patients above the age of 65 years. Based on a randomized trial[1] epigenetic therapy with decitabine (DAC) has become one of the first-line standard of care treatments in most European countries including Germany.

A few years later azacitidine (AZA) - another hypomethylating agent - has been approved as an important treatment option for older patients with newly diagnosed AML. It has been shown that AZA prolongs OS compared with conventional care regimens in the subset of older patients with at least 20% bone marrow (BM) blasts.[2;5] Nevertheless, even with either DAC or AZA–based treatment the 1-year OS is still dismal and seems comparable between both agents.[6]

Thrombocytopenia is one of the main side effects of both hypomethylating therapies and can prevent adequate continuation of treatment, which, however, would be crucial for treatment success. Supportive care with platelet transfusions is usually effective for limited periods of time only and often require hospitalisation, leading to impaired quality of life of these patients in their palliative situation. Therefore, patients could benefit from an approach aiming at an increase of platelet counts through combined use of DAC or AZA with an oral thrombopoietin receptor agonist, such as eltrombopag (EPAG). This could allow for a better adherence to the primary AML therapy by preventing dose delays due to prolonged thrombocytopenia.

Additionally, the potential antileukemic effect of EPAG (as described in the next section) could also be beneficial for these AML patients.

4.2 RISK BENEFIT ASSESSMENT

Hypomethylating therapy with DAC has been the standard of care as first line treatment in elderly AML patients in Europe. Compared to the initial version of the study protocol (3.0) treatment options for AML have expanded in 2015 with the availability of AZA additionally to DAC.[2] Both agents have a comparable efficacy and toxicity profile including prolonged thrombocytopenia in many cases.[8]

EPAG is an orally bioavailable small molecule TPO-R agonist stimulating platelet production by a mechanism similar but not identical to endogenous TPO. It is indicated for the treatment of thrombocytopenia in patients with chronic immune (idiopathic) thrombocytopenic purpura (ITP) who have had an insufficient response to corticosteroids, immunoglobulins or splenectomy. Additionally, EPAG is also licensed for the treatment of Hepatitis C Virus (HCV) infection related thrombocytopenia.

There is a theoretical concern that stimulation of the TPO-R on the surface of hematopoietic cells may also increase the risk for developing or accelerating hematologic malignancies. As such, extensive preclinical research to ascertain any potential relationship between treatment with EPAG and proliferation of malignant cells has been performed. In contrast to the stimulating effects of EPAG on megakaryocytes, EPAG decreased the growth of 16 different leukemia and lymphoma cell lines in vitro.[9] The decrease in proliferation was due to death of the cells by a mechanism other than apoptosis. There was no significant effect on the differentiation of the leukemic cell lines. While recombinant TPO caused a small increase in the proliferation of leukemic cells, EPAG did not induce a similar increase, but rather inhibited proliferation, even in the presence of TPO. While G-CSF increased the proliferation of leukemic cells (OCI AML2), EPAG decreased it. The anti-proliferative effect on hematologic malignancies was investigated further in several additional experiments using samples from patients with AML or MDS.[10] A decrease in malignant cell numbers was seen in the majority of the experiments. There was no significantly decreased apoptosis, no increased immature cells or blasts, nor any evidence of increased long-term self-renewal of AML or MDS cells in any of the samples. To test anti-proliferative effects of EPAG in animals, BM cells from patients with AML were transplanted into cohorts of sub-lethally irradiated NOD mice. Successfully transplanted mice were treated with or without EPAG. Confirming the results from the in vitro assays, treatment with EPAG did not enhance the in vivo engraftment of human AML cells in this xenotransplantation model.[10] However, EPAG prolonged survival in murine models of leukemia. Recently, the same group has published that EPAG, at equivalent concentrations used in the MDS/AML clinical program, inhibits proliferation and induces differentiation of leukemic cells through reduction of intracellular iron levels, independently of the TPO-R.[7] The authors showed that in contrast

to EPAG, recombinant human TPO and another TPO-R agonist, romiplostim, did not modulate intracellular iron levels. Based on this research, there is no evidence in vitro or in vivo that EPAG stimulates malignant growth. In fact, at higher yet clinically achievable concentrations of EPAG the proliferation of leukemic cells is inhibited. In several independently conducted experiments[7;9-12] it has been consistently demonstrated that EPAG, at concentrations achievable with ≥100mg daily dosing, can inhibit the proliferation of leukemic cells. Interestingly, the anti-proliferative effect of DAC on leukemic cell lines was enhanced by co-incubation with EPAG. Most importantly, this drug has been safely explored in advanced MDS and AML patients as single agent and with other chemotherapeutic agents. This randomized phase I/II trial evaluated the safety and tolerability of EPAG in 98 patients with advanced MDS or AML. Patients were relapsed/refractory or ineligible for standard treatments, had platelet counts <30,000/µL or were platelet transfusion dependent. Patients were randomized (2:1) to EPAG (n=64) or matching placebo (n=34). Once-daily treatment was dose-adjusted within each patient (starting dose: 50 mg; maximum: 300 mg). No significant differences in bone marrow or peripheral blasts were observed. The most common adverse events (AEs) were pyrexia, nausea, diarrhea, fatigue, decreased appetite, and pneumonia. Drug-related AEs (Grade ≥3) were reported in 56% (9%) and 35% (12%) of the EPAG and placebo groups, respectively. Grade ≥3 hemorrhage occurred in 16% of EPAG and 26% of placebo patients. Median overall survival was 27.0 and 15.7 weeks with EPAG and placebo, respectively. Platelet transfusion independence (for ≥8 weeks) was reported in 38% and 21% of EPAG and placebo patients, respectively, and in 20% and 6%, respectively, for red blood cells. As a result of this important study[13] EPAG at a dose of up to 300 mg daily was safe in patients with advanced MDS/AML while the observed effects on bleeding and transfusions warrant further studies. Furthermore, our group has shown that single agent EPAG can even induce a complete remission in refractory AML disease.[14]

Therefore, patients could benefit from a combined approach with DAC or AZA and EPAG aiming at an increase of platelet counts and thus less bleeding and a better adherence to the scheduled DAC or AZA cycles. Furthermore, the potential anti-leukemic effect of EPAG could also enhance overall response rates and survival. As a result, the combination of EPAG and AZA was investigated in a phase I clinical trial in higher-risk MDS patients.[15] EPAG up to a dose of 200 mg combined with AZA was feasible and well tolerated.

An independent Data safety monitoring board (DSMB) was set in order to oversee the safety of the trial subjects by periodic safety assessments of the trial therapy .

4.3 RATIONALE FOR SUBSTANTIAL AMENDMENT (PROTOCOL VERSION 5.0)

During the trial, a significant protocol amendment took place in May 2016 for the following reasons. Despite positive results from a phase 1 trial indicating the viability and tolerance of

the EPAG and AZA combination in high-risk MDS[15], the subsequent placebo-controlled multicenter trial (SUPPORT trial, NCT02158936) evaluating EPAG in MDS patients with IPSS int-1/int-2/high-risk and thrombocytopenia was prematurely terminated in January 2016. This decision was based on an interim data analysis reported in March 2016, which revealed the following:

a. The primary reason for prematurely stopping the SUPPORT trial was based on results in relation to the primary endpoint (i.e. number of patients achieving platelet transfusion independence during C1-4). These results indicated that the futility criterion had been met. A total of 27 patients (meaning 40% of the patients) in the Placebo + AZA arm achieved platelet transfusion independence during C1-4; in comparison with 13 out of 79 patients (16% patients) in the Eltrombopag + AZA arm. The p-value was 1.0, which is greater than the required value of 0.9 for meeting the futility criterion.

b. With regards to the key secondary end point, overall survival (OS), there was no difference in overall mortality potentially indicating increased harm in one arm over the other – it was 12% in the placebo arm compared to 13% in the EPAG arm.

c. With regards to progression to AML, the data initially reviewed by the DSMB were based on local assessments and clearly unfavorable for EPAG: 2 patients progressed to AML in the placebo arm compared to 11 patients in the EPAG arm. A further analysis regarding progression was based on data supported and evaluated by a central review committee. The results of this second analysis of the progression data demonstrated that the aforementioned trend in favor of placebo persisted - although with less pronounced difference: based on the evaluation by central review, 2 patients progressed to AML in the placebo arm compared to 5 patients in EPAG arm.

Given the data above, we cannot exclude that these results have a direct implications for the DELTA study. Although the interim results of the SUPPORT trial are not completely transferable to the DELTA study (use of AZA, inclusion of lower-risk MDS patients) we believed that the data was strong enough to support an amendment of the DELTA study, which had recruited only a limited number of 19 patients at the time of submission. Within the SUPPORT trial, EPAG was given concomitantly to AZA therapy which might, at least partly, explain the presented results. In fact, TPO specifically activates Erk and NF-κB pathway that directly affects the double-strand break repair machinery through increased DNA-protein kinase phosphorylation and nonhomologous end-joining repair efficiency and fidelity.[16;17] As a matter of fact, EPAG, when given at the same time, might alleviate the desired effects of an HMA-based therapy. Therefore, the DELTA trial was amended in two ways.

1. We changed the concomitant EPAG administration to a sequential approach with no overlap in order to omit interactions between both agents.
2. Additionally, meanwhile AZA has become available as a treatment option for elderly AML patients comparable to DAC. Therefore, the use of AZA (or DAC) was allowed within the study as well.

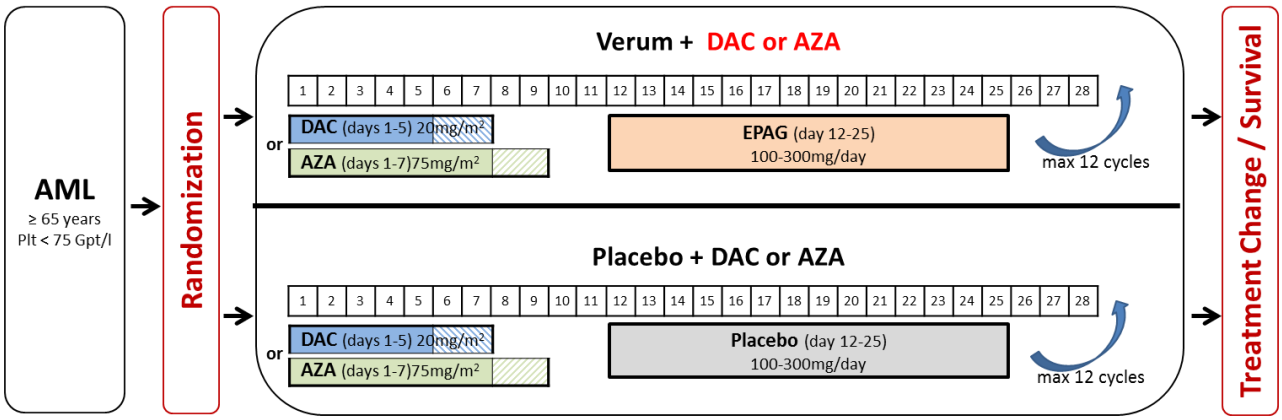
As a consequence of the amendment, the sample size was increased by 19 patients to account for the patients which have had enroled already.

During the preparation and approval of the amendment, the recruitment was paused due to shortage in IMP supply. Nevertheless, all active patients continued their therapy as per protocol. Patients who were still on therapy on day the new protocol came into effect, the therapy regimen switched to the sequential approach. This applied for three pateints only.

4.4 STUDY DESIGN

The DELTA trial was designed as a two-arm, double-blind, multicenter randomized-controlled phase-II study of EPAG or placebo in combination with standard-dose DAC or AZA treatment. Consequently, individuals aged 65 years or older with AML who were ineligible for intensive chemotherapy and intended to undergo therapy with DAC or AZA had to be enrolled.The purpose of this study was to explore the anti-proliferative and the platelet supportive effects of EPAG versus placebo in combination with DAC or AZA, the current standard of care for the treatment with low-intensity chemotherapy in the EU at that timepoint. To assess this objective, the treatment change-free survival (TCFS) of subjects receiving EPAG plus HMA needs to be compared with those treated with placebo plus HMA.

The DELTA trial was designed as a two-armed, double-blinded study. Patients will be randomized 1:1 into the experimental study arm and the control study arm (see figure 1). The randomisation was stratified by baseline karyotype (high risk vs. non-high risk) and platelet transfusion history (having received at least 2 platelet transfusions within 4 weeks prior to randomisation). The treatment was blinded for the research subjects and all study personnel. Treatment blinding was maintained by using matching placebo medication.



Option 1: DAC or AZA therapy may pause during weekend; restart as soon as possible but finish at the latest on day 7 (DAC) or day 9 (AZA)
Option 2: Administration of DAC or AZA at the beginning of a new cycle may be postponed for up to 14 days or should be skipped completely
Option 3: If DAC or AZA treatment is postponed, EPAG administrations starts with a minimum of a 48h pause after HMA with a fixed duration of 14 days, but has to end at least two days before a new cycle starts

Figure 1: Final flow chart of the DELTA study. The regimen was changed with amendment_2 in June 2016 according to 1.3 allowing for either DAC or AZA based AML therapy (weekend rest is allowed; see protocol chapter 5.5) and a sequential (not concomitant) treatment with EPAG.

4.5 CHOICE OF PRIMARY ENDPOINT

The most relevant endpoint for this trial was overall survival (OS) according to the scientific guideline on clinical trials in cancer from the EMA.[18] Unfortunately the unbiased estimation of OS is hardly possible due to the intervening event of 'change of disease modifying treatment' (TC). In elderly and frail patients with palliative treatment intention, progression free survival (PFS) is an appropriate endpoint according to the aforementioned guideline. However, there is no existing consensus definition of PFS or progressive disease (PD). Consensus outcome measures for AML are OS, relapse-free survival (RFS), event-free-survival (EFS) and cumulative incidence of relapse (CIR).[19]

Within the pivotal DACO016 trial[1] Kantarjian et al. reported that only 40 of 242 patients in the DAC-arm were still under study treatment after 3-years. About 50% of these patients died under study treatment, 45% had PD and 5% discontinued treatment because of adverse events (AE). About 40% of the PD patients received subsequent therapy. Due to the expected reduction of bleeding AEs and a potential antileukemic effect of the experimental treatment we expect an imbalance of discontinued patients in both arms. Bias on OS could be introduced by better/worse efficacy of subsequent treatments if it was ignored. Also censoring is no option, because censoring at PD, AE or TC would be informative.

EFS is also not appropriate for the trial, because for EFS the definition of treatment failure for the study population has to be based on PD. RFS cannot be used because the proportion of patients reaching complete remission (CR) will be limited and the majority of patients would have to be excluded from primary analysis.

According to the data of the DACO016 trial[1] most of the patients who discontinued study treatment suffered from PD. PD is an indicator for the lack of efficacy of a treatment. However, PD is not well defined for AML. Patients with PD and no subsequent treatment are likely to die within a short period of time. For patients with subsequent treatment and TC after PD, TC should serve as a valid surrogate parameter for PD. A small proportion of patients will discontinue study treatment because of AE. Some of these patients are also likely to die without subsequent treatment and will therefore experience TC. In these cases, TC will serve as surrogate parameter for lack of benefit compared to the risk for the patient. In some cases patients might respond in such a good way that further therapy can be administered with curative intent. In these cases, TC paradoxically would be a surrogate for effective treatment. In case of more efficient experimental treatment it would decrease the size of the desired effect and introduce bias towards the control treatment. In case of more efficient control treatment it would decrease the undesired effect and introduce bias towards experimental treatment. It is expected that this happens in a very small proportion of patients only. In our opinion the ease of determination of TC and death in comparison to a determination of PD weighs out this disadvantage. Intent and regimen of subsequent treatments will be recorded to allow detailed analyses of TC and conclusions regarding validity of TC as part of the composite endpoint. Due to blinding we expect no effect of study treatment on decisions regarding subsequent treatment.

As a result we have chosen ‘treatment change free survival’ (TCFS) defined as time from randomisation until day one of the new disease modifying treatment (all chemotherapeutic and disease modifying agents except hydrea including when given within subsequent clinical trials) or death as the primary endpoint of this study. Time until death will be recorded for all patients, including patients undergoing treatment change. This will also allow analysis of OS in presence of the competing risk of treatment change. For a patient who was not known to have died or changed disease modifying treatment by the end of observational period (Treatment period + follow-up period), observation of TCFS will be censored on the date the patient was last known to be alive. Change of disease modifying treatment will be defined as switching to other AML specific treatments with palliative (exception was hydrea) or curative intent (like induction chemotherapy), inclusion into another clinical trial with investigational AML drugs or addition of other disease modifying treatments.

4.6 RANDOMISATION / STRATIFICATION

All patients were randomly assigned to one of the treatment arms, using a stratified randomisation scheme. The possibility to receive either EPAG or placebo was 50%. The central randomisation process will ensure allocation concealment. A random allocation sequence was generated by the data management unit of the SAL study office using a R program for both arms and each stratum. To ensure balance at any point of time the

randomisation sequence was divided into blocks of variable length. The program code and random seeds were kept confidential both from access by investigators as well as other sponsor representatives or other units of the SAL study office. Based on the random allocation sequence, randomisation lists were generated for each stratum. Eligible study patients were randomized by consecutive entry into the randomisation list. Randomisation was stratified according to platelet transfusion history (patient has received or not received at least 2 platelet units within 4 weeks prior to randomisation) and adverse cytogenetic risk according to ELN 2017 defined by the presence of one or more of the following criteria (but absence of any low risk aberration (inv(16); t(8;21); t(16;16)):

- inv(3)(q21q26.2) or t(3;3)(q21;q26.2); RPN1-EVI1
- t(6;9)(p23;q34); DEK-NUP214
- t(v;11)(v;q23); MLL rearranged
- -5 or del(5q); -7; abnl(17p); complex karyotype (Three or more chromosome abnormalities in the absence of one of the WHO designated recurring translocations or inversions, that is t(15;17), t(8;21), inv(16) or t(16;16), t(9;11), t(v;11)(v;q23), t(6;9), inv(3) or t(3;3)).

In case the cytogenetic risk classification was not known at date of randomization, the patient was put in the non-high risk stratum. The same applied for patients with normal caryotype.

Treatment assignment was blinded.

4.7 ENROLMENT AND STUDY TREATMENT

Potential patients were identified at participating centers based on referrals for suspected AML. The screening tests outlined in the protocol are standard practice and could be conducted before obtaining consent. Patients who fulfilled the eligibility criteria for trial participation were provided with the approved patient information sheet by the investigator, allowing them to make an informed decision regarding their participation. If informed consent was given, the investigator carried out comprehensive screening evaluations to ensure the patient met all inclusion and exclusion criteria. Subsequently, the patient was registered and randomized using a web-based database. Neither the treating investigator nor the sponsor designee was aware of the randomization result.

Any containers of the trial mediacation – Verum/placebo – were labled with a unique medication number. The assignment of the correct trial medication to be handed out to a specific patient was done by use of the above mentioned web-based database. Any clinical data was captured in a separate web-based eCRF.

Initially, all trial subjects (N=19) started with continuous EPAG/placebo administration. Concomittantly, all patients received dectitabine (DAC) according to approval as backbone AML therapy. Following approval of the substantial amendment in submitted July 2016, treatment of EPAG/placebo switched to a sequential approach (for rationale for change in

regimen refer to section 4.3). Thus, out of 19 patients who started with continuous treatment, three patients switched to the new treatment approach after approval of the protocol amendment. Furthermore, due to the approval extension of azacitidine AZA (another hypomethylating agent (HMA) homologous to decitabine), it was allowed to be used as backbone AML therapy instead of decitabine. As a consequence, the primary AML treatment consisted of standard-dose DAC or AZA, whereas the choice remained investigator decision considering all relevant factors and medical reports. In any case, EPAG treatment should start on day 12 of the first cycle with an initial dose of 200 mg EPAG (100 mg for East Asian patients). The treatment period of EPAG should be 14 days in each cycle. Thus, EPAG administration should end on day 25 of each cycle. Dose escalation was possible from start of cycle 2 and should not exceed 300 mg EPAG per day (150 mg/d for East Asian patients).

Ideally, one treatment cycle repeated every 28 days. Each cycle started with a DAC/AZA administration. Thus, day 29 should have been the first day of the next cycle (= day 1). DAC was given in standard dosage on days 1-5 and AZA on days 1-7 of each cycle. In order to adhere to clinical routine, it was allowed to pause the DAC/AZA treatment over the weekend. Therapy should have been resumed as soon as possible but at the latest on day 7 (DAC) or day 9 (AZA). Once one of the two available HMAs (DAC or AZA) was chosen for a given patient, it was not allowed to switch between DAC and AZA administration during the trial. Change of HMA administration met the definition of treatment change (primary endpoint), thereupon patients reached the end of study visit followed by further observation during survival follow up period. If indicated (e.g. based on insufficient blood cell recovery or any safety reasons) the administration of DAC or AZA at the beginning of a new cycle could have been postponed for up to 14 days or should have been skipped completely. Dose reductions for DAC or AZA should have been made according to the SmPC. Following dose modifications, the cycle duration should have been returned to 28 days starting DAC or AZA administration on day 1.

EPAG/placebo treatment lasted from day 12 to 25 of each DAC or AZA cycle, respectively. If DAC or AZA treatment was postponed, EPAG administration started with a minimum of a 48h pause after HMA with a fixed duration of 14 days, but had to end at least two days before start of a new cycle. If one cycle of DAC or AZA need to be skipped completely, EPAG/placebo should have been started on day 12 counting from the hypothetical start of the cycle. EPAG or placebo had to be administered depending on the absence of toxicity grade or excessive platelet response and as long as the subject received DAC or AZA but for a maximum amount of 12 cycles. It was recommended that patients should be treated with DAC or AZA for a minimum of 4 cycles; however, a complete or partial remission may take longer than 4 cycles to be achieved. Treatment may have been continued as long as the patient showed response, continued to benefit or exhibited stable disease, i.e., in the absence of overt progression. Patients who discontinued treatment with EPAG/placebo and/or DAC/AZA permanently

completed the end of study visit and entered the survival follow up for observation of treatment change and survival. Subjects had to be observed (treatment period + follow-up period) until 12 months after randomisation of the last patient or until death (whichever occured first).

4.8 DOSE ADJUSTMENT OF EPAG / PLACEBO

Dose adjustments primarily relied on changes in platelet counts, with adjustments being made in increments of 100 mg (50 mg steps for East Asian patients). A platelet count below 100 Gpt/l resulted in a dose increase. Maximum permissible dose of EPAG or placebo should not exceed 300 mg/d (150 mg/d for East Asian patients). A platelet count between 100 Gpt/l and 450 Gpt/l did not require any change in the dosage of EPAG/placebo. In patients with a platelet count above 450 Gpt/l, treatment with the investigational product (but not DAC/AZA) should have been interrupted until platelets were below 100 Gpt/l. Then treatment should have been resumed at the next lower dose level. There was no time limit for resuming treatment of EPAG/placebo when discontinued due to high platelet counts. After any dose adjustment, platelets counts should have been monitored at least weekly for 2 weeks. The investigator may also have been made dose adjustments based on safety assessments.

4.9 CONCOMITANT MEDICATION AND SUPPORTIVE CARE

Disease specific (e.g. hydrea, G-CSF) concomitant medications as well as NSAIDs and anticoagulants like Marcumar, Warfarin, Heparin or any other anticoagulants taken during the study will be recorded in the eCRF. Patients may receive supportive care (treatments to manage disease symptoms and related problems; i.e. blood transfusions, growth factors) anytime during the study. Pre-medication for the prevention of nausea and vomiting is not routinely recommended but may be administered if required.

Since cycle 1-4 platelet transfusion independence was one of the secondary endpoints for this study, the ASCO guidelines counted for platelet transfusions. In this study, platelet transfusions were required if a subject’s platelet count was below 10 Gpt/L. Subjects with platelet counts greater than or equal to 10 Gpt/L should not be transfused with platelets unless the subject had fever, septicemia or bleeding.

Red blood cell transfusions were recommended according to institutional guidelines but, in general, at a Hb of less than 8 g/dl (5 mmol/l).

Oral mineral supplements (such as calcium, magnesium, aluminum, zinc, selenium or iron) as well as dairy products (such as milk, yogurt and cheese) were permitted during the study. To avoid significant reduction in EPAG absorption due to food or drug interactions, the investigational product should have been taken on an empty stomach.

G-CSF or GM-CSF was allowed during the study for subjects with severe neutropenia and recurrent infections and may have been used according to local standards.

Subjects were be permitted to use HMG-CoA reductase (3-hydroxy-3-methyl-glutaryl-CoA) inhibitors during the study, but these drugs should have been used with caution. A 50% dose reduction of the HMG-CoA reductase inhibitor was recommended, with close monitoring for safety, such as liver chemistry and signs and symptoms of myolysis, and efficacy, such as cholesterol and triglycerides (refer to individual product information for monitoring recommendations).

Preclinical data showed that EPAG is an inhibitor of the transporters OATP1B1 and BCRP. Concomitant administration of EPAG and other OATP1B1 or BCRP substrates should be used with caution.

The following medications were prohibited during the study treatment period:

- Any other TPO-R agonists, without exception
- Disease Modifying Agents: hypomethylating agents (other than DAC or AZA), chemotherapy, induction therapy, and other investigational therapy incl. lenalidomide. Hydrea was allowed to control leukemic proliferation during the first 2 cycles of study treatment.

Drugs that affect platelet function (including, but not limited to, aspirin, clopidogrel and/or NSAIDs) and anticoagulants (e.g. warfarin, heparin) may affect the results of the bleeding assessments during the study and wer permitted with restricted use if their use was clinically indicated.

Subjects must have had discontinued hormone replacement therapy prior to study enrolment due to the potential for inhibition of Cytochrome P450 (CYP) enzymes that metabolize estrogens and progestins.

4.10 END OF TRIAL AND FURTHER TREATMENT OF THE PARTICIPANTS

Every patient was observed (including treatment period and follow-up period) for a minimum of 1 year (for the last patient) starting on day of randomisation up to a maximum of 60 months (for the first patient) or until death (whichever occured first). The end of study was defined as the last assessment and documentation of survival status and treatment change 12 months after randomisation of the last patient. After premature discontinuation of EPAG/placebo and/or DAC/AZA treatment (if treatment must have been stopped due to treatment related toxicity and couldn’t be resumed within 60 days after discontinuation) or completion of the maximum number of cycles, patients had undergone the end of study visit (EOS) and has further been observed in defined visits during survival follow-up.

4.11 ASSESSMENT OF SAFETY

During the trial all adverse events CTCAE ≥ grade 3 have been documented in the eCRF. AEs needed to be documented from the date of randomisation until 28 days after the date of study termination. All bleeding events were to be assessed according to Rodeghiero et al. 2013 [16] and had to be documented in the eCRF as well. Any cytopenia as sign of hematotoxicity/myelosuppression are intended and expected events due to antileukemic activity of DAC / AZA during treatment of AML or are directly caused by the underlying disease. Therefore, they did not fulfill the criteria of adverse events and did not need to be documented as AE or SAE (leukopenia, thrombocytopenia, anemia). Worsening of the underlying disease or other pre-existing conditions have been recorded as an AE. Death of any cause including death from AML progression or relapse constituted an SAE in this trial and must have been reported immediately to the sponsor. SAEs from any severity grade have been reported according regulations until 28 days after the date of study termination.

An independent DSMB committee has overseen the safety data of the study regularly.

5 STATISTICAL METHODS

5.1 ANALYSIS POPULATION

The **full analysis set (FAS)** consists of all patients randomized into the study, treated under study protocol version 5.0, and included in the treatment phase with EPAG or placebo. This population was defined also as intention-to-treat population.

The **safty evaluation set (SES)** consists of all patients who received at least one dose of placebo or EPAG. Including patients randomized before introduction of the sequential treatment approach (protocol version 5.0).

5.2 RANDOMIZATION AND STRATIFICATION

The randomization was stratified according to baseline karyotype and history of platelet transfusions. Defined as having received at least 2 platelet transfusions within 4 weeks prior to randomization. The stratification groups are as follows:

- high-risk karyotype without platetlet transfusion history (HRnoPL)
- high-risk karyotype with platetlet transfusion history (HRPL)
- non-high-risk karyotype without platetlet transfusion history (noHRnoPL)
- non-high-risk karyotype with platetlet transfusion history (noHRPL)

5.3 PLANNED INTERIMS ANALYSIS

No planned interims analysis was conducted.

The statistical analysis conducted for the DSMB did not reveal any statistically significant differences between the groups in terms of survival and safety. Based on this finding, the DSMB decided to proceed with the study.

5.4 HANDLING OF MISSING DATA AND DROP-OUTS

Missing data were not imputed. Patients registered for participation in the trial, who were not randomized or patients wrongly diagnosed as AML, are defined as screening failures. For randomized patients, if consent for study participation or further survival follow up was withdrawn, time-to-event endpoints are censored on the date of withdrawal.

5.5 HANDLING OF MULTIPLE COMPARISON AND MULTIPLE PRIMARY VARIABLES

Not applicable.

5.6 EVALUATION OF PRIMARY VARIABLES

The primary endpoint was evaluated as Kaplan-Meier-Estimates of the median time to treatment change/death and two sided 95%-confidence intervals from the FAS. A log-rank test

was conducted to test the null hypothesis of equally distributed treatment change free survival times between the study arms. The significance level for the primary hypothesis was 5%. No adjustment of the alpha error rate for multiple testing was applied. Furthermore, survival rates and two sided 95%-cofidence intervals for 1-year, 2-year, and 3-year survivers were estimated according to Kaplan-Meier. Univariable and multivariable Cox models were fitted with covariate adjustment including randomized treatment arm, age, ECOG and transfusion history to calculate the hazard ratio.

5.7 EVALUATION OF SECONDARY VARIABLES

Secondary endpoints were analysed in the FAS population. Comparison of OS was conducted with a log-rank test. Furthermore, survival rates and two sided 95%-cofidence intervals for 1-year, 2-year, and 3-year survivers were estimated according to Kaplan-Meier. Number of bone marror blasts (baseline, 5 month, 9 month), incidence of bleeding events, and number of platelet transfusion cycles were analysed by ANOVA.

5.8 EVALUATION OF SAFETY VARIABLES

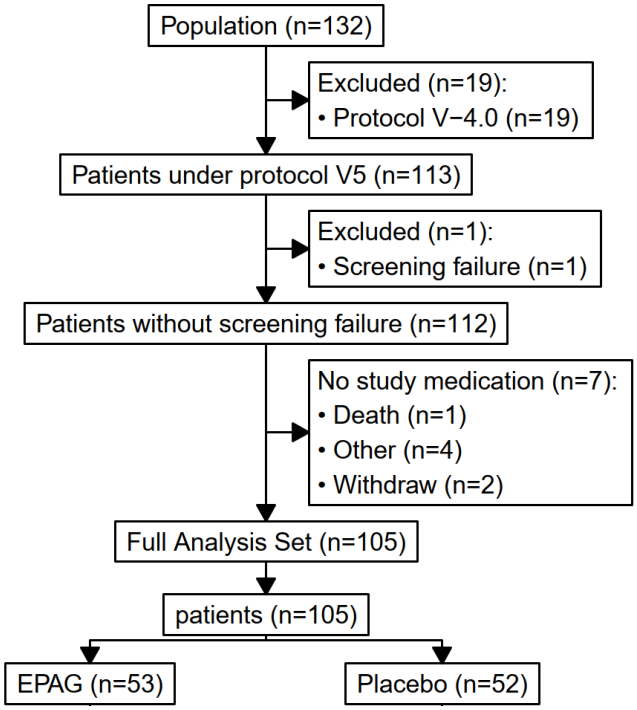
Descriptive statistics were calculated in the SES. Incidences of AEs and SAEs were summarized by intensity in tables. Absolute number and frequencys are presented. For SAEs related to deaths, the SAEs are listed for MedDRA system organ class and preferd term by treatment arm. Adverse events and SAEs were coded using MedDRA 25.0.

6 RESULTS

The study was terminated prematurely in June 2020 due to the EMA approval of HMA and venetoclax as new treatment standard for 1st line therapy in elderly AML patients, resulting in ethical conflicts concerning the trial therapy with HMA monotherapy.

Due to the premature termination of the study, the planned number of trial participants (n=238) could not be achieved, and the desired statistical power was not attained. Nevertheless, the primary hypothesis test was still conducted as the sole confirmatory analysis of the study.

Consort Flow Diagram



6.1 ANALYSIS POPULATIONS

In total 132 patients were enrolled between 2015 and 2020, but 27 patients had to be excluded from the analysis. Exclusions included patients enrolled before protocol version 5.0 (N=19), withdrawal of consent before the first administration of study medication (N=2), patient death before the first administration of study medication (N=1), no administration of study medication or placebo (N=4), and one patient whose diagnosis was changed from AML to MDS after randomization (N=1). 105 patients were randomized (1:1) to HMA+EPAG (n=53) or HMA+placebo (n=52).

6.2 BASELINE CHARACTERISTICS

Patient Characteristics of the FAS Population at Baseline

	EPAG (N=53)	Placebo (N=52)	Total (N=105)	p value
Age				0.724[1]
Median	77.0	78.0	78.0	
Range	65.0 - 87.0	66.0 - 88.0	65.0 - 88.0	
Q1, Q3	75.0, 81.0	75.8, 80.0	75.0, 81.0	
Sex				0.939[2]
female	20 (37.7%)	20 (38.5%)	40 (38.1%)	
male	33 (62.3%)	32 (61.5%)	65 (61.9%)	
Ethnicity				0.310[2]
Caucasian	53 (100.0%)	51 (98.1%)	104 (99.0%)	
Other	0 (0.0%)	1 (1.9%)	1 (1.0%)	
AML type				0.081[2]
De novo AML	29 (54.7%)	37 (71.2%)	66 (62.9%)	
Secondary AML	24 (45.3%)	15 (28.8%)	39 (37.1%)	
ELNRisk 2017				0.522[2]
N-Miss	29	34	63	
adv	8 (33.3%)	6 (33.3%)	14 (33.3%)	
fav	4 (16.7%)	1 (5.6%)	5 (11.9%)	
int	12 (50.0%)	11 (61.1%)	23 (54.8%)	
History of malignancy				0.053[2]
no	28 (52.8%)	37 (71.2%)	65 (61.9%)	
yes	25 (47.2%)	15 (28.8%)	40 (38.1%)	
Chemotherapy in anamnesis				0.300[2]
N-Miss	20	28	48	
no	22 (66.7%)	19 (79.2%)	41 (71.9%)	
yes	11 (33.3%)	5 (20.8%)	16 (28.1%)	
Height				0.890[1]
Median	169.0	170.0	170.0	
Range	152.0 - 186.0	148.0 - 190.0	148.0 - 190.0	
Q1, Q3	165.0, 175.0	164.0, 177.2	165.0, 175.0	
Weight				0.263[1]
Median	75.0	78.0	76.4	
Range	47.0 - 115.0	50.3 - 130.0	47.0 - 130.0	
Q1, Q3	67.6, 82.0	70.0, 87.0	69.0, 85.4	
ECOG				0.043[2]
0	2 (3.8%)	10 (19.2%)	12 (11.4%)	
1	33 (62.3%)	26 (50.0%)	59 (56.2%)	
>=2	18 (34.0%)	16 (30.8%)	34 (32.4%)	
Transfusion				0.890[2]

	EPAG (N=53)	Placebo (N=52)	Total (N=105)	p value
noPL	35 (66.0%)	35 (67.3%)	70 (66.7%)	
PL	18 (34.0%)	17 (32.7%)	35 (33.3%)	
Stratum				0.565[2]
HRnoPL	9 (17.0%)	13 (25.0%)	22 (21.0%)	
HRPL	7 (13.2%)	4 (7.7%)	11 (10.5%)	
noHRnoPL	26 (49.1%)	22 (42.3%)	48 (45.7%)	
noHRPL	11 (20.8%)	13 (25.0%)	24 (22.9%)	
NPM1				0.254[2]
N-Miss	14	14	28	
negative	32 (82.1%)	27 (71.1%)	59 (76.6%)	
positive	7 (17.9%)	11 (28.9%)	18 (23.4%)	
PML_RARalpha				0.306[2]
N-Miss	20	18	38	
negative	32 (97.0%)	34 (100.0%)	66 (98.5%)	
positive	1 (3.0%)	0 (0.0%)	1 (1.5%)	
Abl1				0.554[2]
N-Miss	22	21	43	
negative	30 (96.8%)	29 (93.5%)	59 (95.2%)	
positive	1 (3.2%)	2 (6.5%)	3 (4.8%)	
RUNX1				0.686[2]
N-Miss	12	13	25	
negative	38 (92.7%)	37 (94.9%)	75 (93.8%)	
positive	3 (7.3%)	2 (5.1%)	5 (6.2%)	
CBFbMYH11				0.314[2]
N-Miss	18	17	35	
negative	34 (97.1%)	35 (100.0%)	69 (98.6%)	
positive	1 (2.9%)	0 (0.0%)	1 (1.4%)	
CEBPA				0.321[2]
N-Miss	15	15	30	
negative	37 (97.4%)	37 (100.0%)	74 (98.7%)	
positive	1 (2.6%)	0 (0.0%)	1 (1.3%)	
FLT3ITD				0.052[2]
N-Miss	15	18	33	
negative	34 (89.5%)	34 (100.0%)	68 (94.4%)	
positive	4 (10.5%)	0 (0.0%)	4 (5.6%)	
Karyotype				0.776[2]
N-Miss	4 (7.5%)	3 (5.8%)	7 (6.7%)	
abnormal	29 (54.7%)	26 (50.0%)	55 (52.4%)	
normal	20 (37.7%)	23 (44.2%)	43 (41.0%)	

1. Linear Model ANOVA
2. Pearson's Chi-squared test
3. Chi-squared test for given probabilities

6.3 STUDY TREATMENT AND COMPLIANCE

Both arms, EPAG and Placebo have been monitored during the trial for each patient. Eight patients did not receive any study treatment (shown in consort diagram). These patients were excluded from the FAS.

6.4 UNBLINDING DURING STUDY

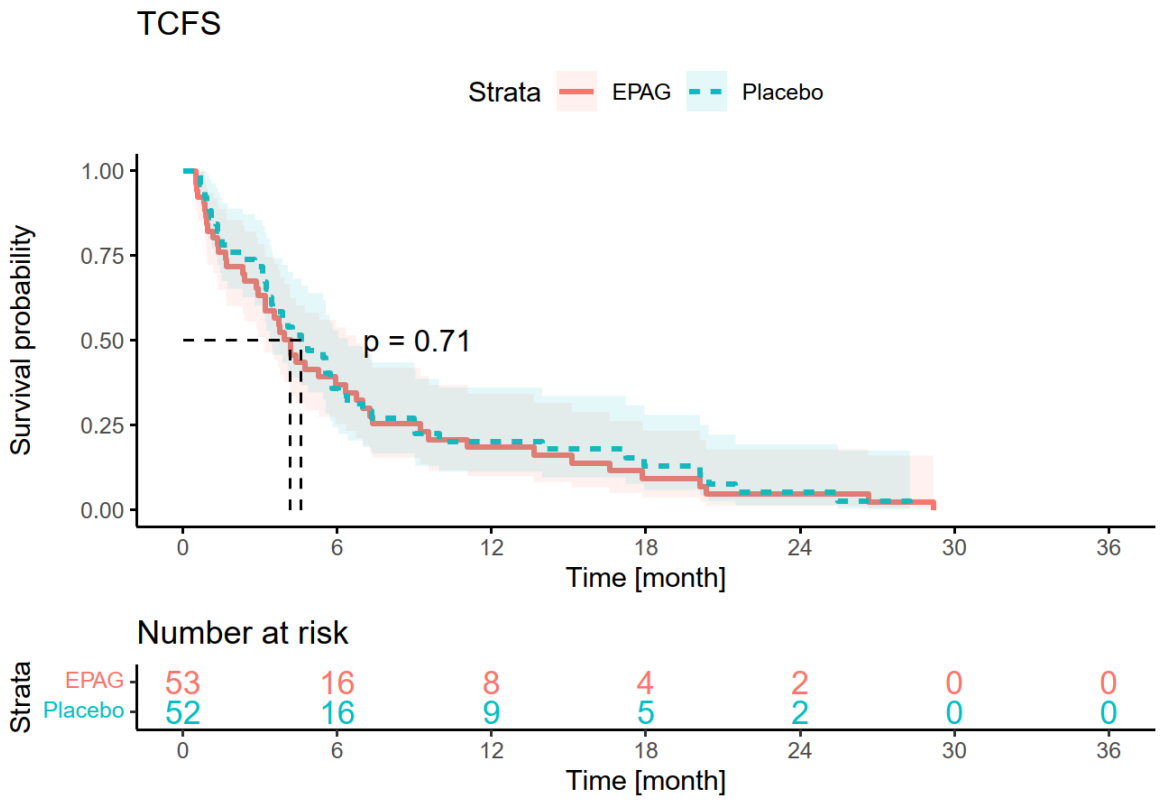
Seven patients were unblinded during the study.

Patient ID	Result of unblinding	Description of reason for unblinding
030-012	Placebo	unblinded after disease progression on request of investigator for decision making of further treatment and eligibility for participation in subsequent clinical trial
030-106	Verum	unblinded due to SAE (acute myocardial infarction) on request by the marketing authorization holder for assessment of reportability by company
068-060	EPAG	unblinded by investigator after disease progression for decision making of further treatment and eligibility for participation in subsequent clinical trial
068-123	Placebo	unblinded after end of study due to SAE (musculoskeletal disorder) on request by the marketing authorization holder for assessment of reportability by company
409-107	Placebo	unblinded by sponsor due to fatal SAE (ventricular fibrillation) for assessment of SUSAR reportability by sponsor
045-122	Placebo	unblinded by sponsor due to SAE (unknown cause of death) for assessment of SUSAR reportability by sponsor
008-043	Placebo	unblinded by sponsor due to SAE (bone marrow reticulin fibrosis) for assessment of SUSAR reportability by sponsor

6.5 PRIMARY ENDPOINT

Result of primary efficacy analysis in the FAS.

The null hypothesis for the primary endpoint of equal TCFS between both study armes can not be rejected, based on a log-rank test (p-value = 0.71).



Median-, one-, two-, and three-year TCFS times in the FAS.

Characteristic	Median TCFS time [month] (95% CI)
EPAG	4.2 (3.2, 6.7)
Placebo	4.6 (3.5, 6.4)

Characteristic	1-year TCFS (95% CI)
EPAG	18% (10%, 34%)
Placebo	20% (11%, 36%)

Characteristic	2-year TCFS (95% CI)
EPAG	4.6% (1.2%, 18%)
Placebo	5.1% (1.4%, 19%)

Characteristic	3-year TCFS (95% CI)
EPAG	— (—, —)
Placebo	— (—, —)

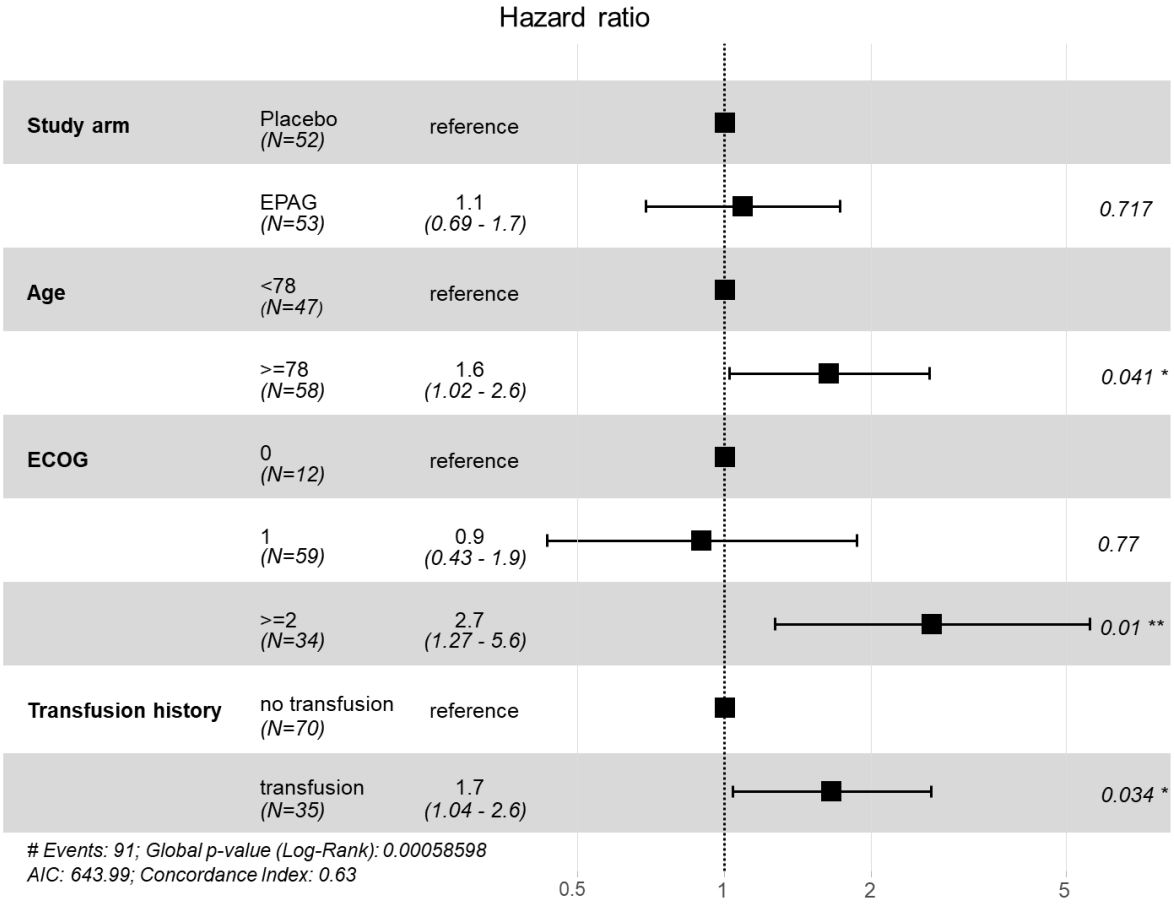
Hazard Ratio calculated with a cox regression model on TCFS in the FAS.

Characteristic	Hazard Ratio (95% CI)	Global p-value (Log-Rank)
EPAG	1.1 (0.72, 1.6)	0.71
Placebo (reference)	1 (—, —)	

There were no significant differences in TCFS time between EPAG+HMA and placebo+HMA within each stratum, as revealed by subgroup analyses

Multivariate analysis for Primary endpoint TCFS:
Increasing age (≥78 years), ECOG ≥ 2 and transfusion dependency are independent risk factors in terms of treatment change free survival. The adjusted HR for the EPAG arm was not significant different from placebo and confirms the results of the primary analysis.

Cox proportional hazard model for TCFS (HR > 1 indicates an increased risk for treatment change or death):



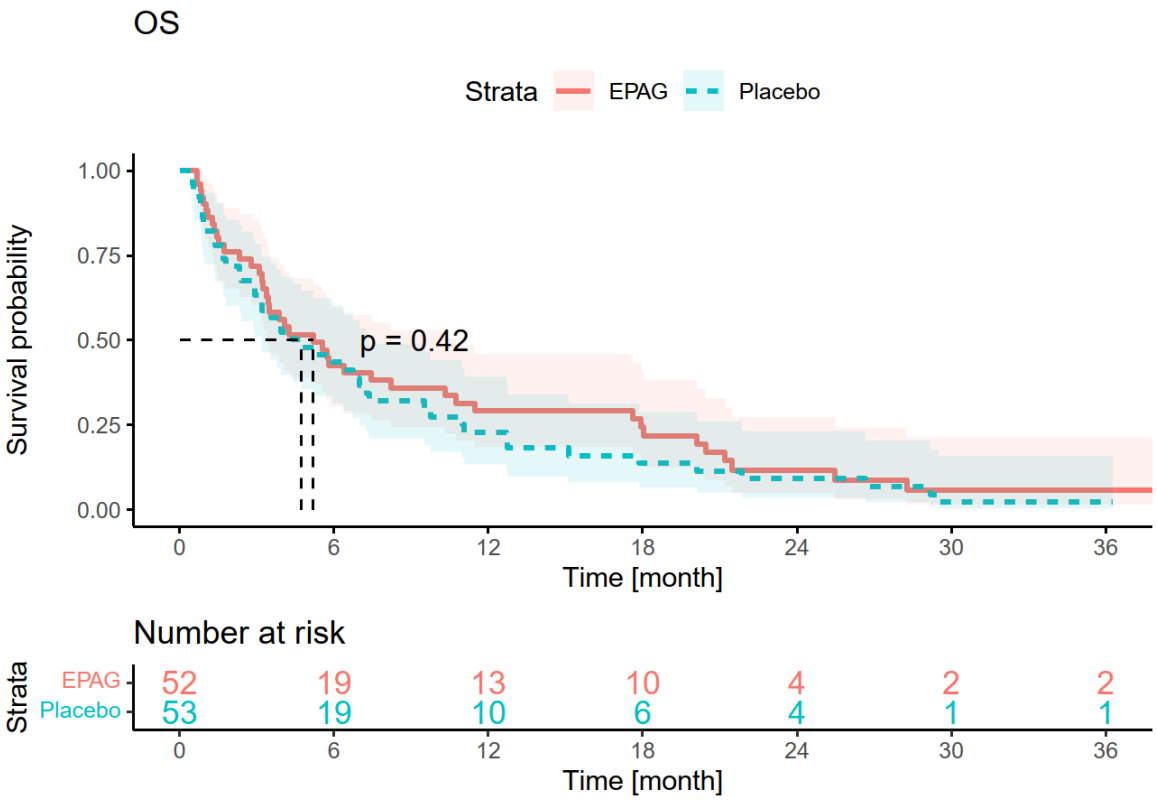
6.6 SECONDARY ENDPOINTS OF EFFICACY

6.6.1 OVERALL SURVIVAL (OS)

For the secondary endpoint OS no differences between both study armes were observed, based on a log-rank test (p-value = 0.42).

Median overall survival was 4.7 months in HMA+EPAG compared to 5.2 months in t

HMA+placebo group (HR 1.2, 95%-CI, 0.78- 1.8; p=0.432).



Characteristic	Median OS time [month] (95% CI)
Placebo	5.2 (3.5, 11)
EPAG	4.7 (3.2, 7.4)

Characteristic	1-year OS (95% CI)
Placebo	29% (19%, 46%)
EPAG	23% (13%, 39%)

Characteristic	2-year OS (95% CI)
Placebo	12% (5.0%, 27%)
EPAG	9.2% (3.6%, 23%)

Characteristic	3-year OS (95% CI)
Placebo	5.8% (1.6%, 21%)
EPAG	2.3% (0.3%, 16%)

Hazard Ratio calculated with a cox regression model on OS in the FAS.

Characteristic	Hazard Ratio (95% CI)	Global p-value (Log-Rank)
EPAG	1.2 (0.78, 1.8)	0.42
Placebo (reference)	1 (—, —)	

6.6.2 NUMBER OF BONE MARROW BLASTS (FAS)

There were no difference observed between the groups in terms of bone marrow blast counts over time, as indicated below:

	EPAG (N=53)	Placebo (N=52)	Total (N=105)	p value
baseline				0.338[1]
N	50	46	96	
Median	42%	54%	52%	
5 month				0.247[1]
N	16	11	27	
Median	10%	6.0%	6.0%	
9 month				0.860[1]
N	6	4	10	
Median	14%	9%	14%	

1. Linear Model ANOVA

6.6.3 BEST RESPONSE WITHIN STUDY (FAS)

Best overall response rates (complete or partial response, stable disease) were 30% in the HMA+EPAG group and 30 % for the HMA+placebo group (p=0.607).

	EPAG (N=53)	Placebo (N=52)	Total (N=105)	p value
BestResponse				0.607[1]
CR/CRi	7	7	14	
PR	7	5	12	
SD	2	4	6	

1. Pearson's Chi-squared test

6.6.4 INCIDENCE OF BLEEDING EVENTS (FAS)

There were no significant differences in the overall incidence of severe bleeding events (≥grade 3) between the groups (12% versus 16%, p=0.52), nor in the rates of platelet transfusion (see 6.65; p=0.39)

	EPAG (N=53)	Placebo (N=52)	Total (N=105)	p value
Number of events				0.963[1]
Patients	25	30	55	
Median number of bleedings	2.0	2.0	2.0	
Number of severe events (≥ grade 3)				0.525[1]
Patients	8	9	17	

	EPAG (N=53)	Placebo (N=52)	Total (N=105)	p value
Sum of events	12.0	16.0	28.0	

1. Linear Model ANOVA

6.6.5 NUMBER OF PLATELET TRANSFUSIONS BETWEEN CYCLE 1-4 (FAS)

Only patients were included who completed 4 treatment cycles :

	EPAG (N=25)	Placebo (N=25)	Total (N=50)	p value
Number of transfusions				0.399[1]
Patients with transfusions	17	21	38	
Median number of transfusions per patient	4.0	3.0	3.0	

1. Linear Model ANOVA

6.7 SECONDARY ENDPOINTS OF SAFETY

Re-evaluation of total bleeding events and severe bleeding events in the safety evaluation set (SES) yielded no significant differences.

6.7.1 BLEEDING EVENTS (SES)

	EPAG (N=63)	Placebo (N=61)	Total (N=124)	p value
Number of events	30	32	62	0.705[1]
Number of severe events (≥ grade 3)	8	9	17	0.525[1]

6.7.2 ADVERSE EVENTS (SES)

Reports of all adverse events of grade ≥ 3 showed no significant difference between both treatment arms.

The most common adverse events (AEs) classified by MedDRA system organ class were infections and infestations (37 % in the HMA+EPAG group and 37% in the HMA+Placebo group), neoplasms (13% HMA+EPAG and 8% HMA + Placebo) and, general disorders and administration site conditions (12% HMA+EPAG and 9% HMA Placebo), blood and lymphatic system disorders (9% HMA+EPAG and 10% HMA+Placebo).

There was no significant difference in the occurrence of serious adverse events (SAE) between both treatment groups. Although the incidence of SAE grade 5 was slightly higher in the EPAG+HMA group compared to the Placebo+HMA group, this difference did not reach statistical significance.

Number of adverse events and number of patients with adverse events.

	Number of AEs		Number of Patients with Event		
	EPAG	**Placebo**	**EPAG**	**Placebo**	**p value**
Any AE	153	145	55	54	0.643
Any AE ≥ 3	118	122	54	50	0.162
Any SAE	99	86	50	50	0.337
Any SAE ≥ 3	65	63	48	44	0.384
Any SAE = 5	37	30	36	29	0.470

Listing of deaths related to SAE by preferred term.

System Organ Class	**Preferred Term**	**EPAG**	**Placebo**
Blood and lymphatic system disorders	Bone marrow reticulin fibrosis	0	1
Cardiac disorders	Ventricular fibrillation	0	1
Gastrointestinal disorders	Mechanical ileus	0	1
General disorders and administration site conditions	Death	1	1
	Multiple organ dysfunction syndrome	0	1
	General physical health deterioration	1	0
	Sudden cardiac death	0	1
Infections and infestations	Atypical pneumonia	1	0
	Cellulitis	1	0
	Diverticulitis intestinal perforated	1	0
	Infection in an immunocompromised host	1	0
	Influenza	1	0
	Intervertebral discitis	1	0
	Neutropenic infection	0	1
	Pneumonia	0	1
	Pulmonary sepsis	1	4
	Sepsis	4	2
	Staphylococcal infection	0	1
	Urosepsis	1	0
Neoplasms benign, malignant and unspecified	Acute myeloid leukaemia	11	10

	Non-small cell lung cancer	0	1
Renal and urinary disorders	Acute kidney injury	1	0
	Renal failure	1	0
Respiratory, thoracic and mediastinal disorders	Respiratory failure	1	0
Vascular disorders	Subarachnoid haemorrhage	0	1
	Subdural haematoma	1	0

6.7.3 DSMB

Regular safety assessments were conducted to ensure that patients were exposed to minimal or no study-related risks. The safety of trial subjects was overseen by an independent Data Safety Monitoring Board (DSMB), consisting of two physicians who were not involved in the study and independent of the sponsor. The DSMB followed specific guidelines outlined in the DSMB charter. While the DSMB members had access to unblinded study data, the sponsor remained blinded throughout the trial. Three DSMB meetings were conducted during the course of the trial.

The first meeting was conducted in June 2016 after enrolment of 19 patients. Of them, nine patients have been observed for at least 6 months. In conclusion, neither the medical experts, the statistician nor the sponsor have any safety or ethical concerns which would force a premature termination of the study. The DSMB members requested to meet again prematurely after enrolment of approximal 20 patients treated within the new treatment scheme according to protocol version 5.0.

The second meeting was conducted in November 2017 after enrolment of further 41 patients who have been treated according to protocol version 5.0. Of them, 24 patients have been observed for at least 6 months. The DSMB informed the sponsor that the committee concordantly decided that there was no safety concern. The trial could further proceed as planned.

The third meeting took place in June 2020 after enrolment of 131 patients. Except of five patients, all patients have been observed for at least 6 months or have been died before. The DSMB committee was told that the enrolment will be stopped prematurely by 30th June 2020 upon the sponsors' decision. In advance to that meeting, the DSMB received substantial patient baseline data as well as information on the primary endpoint for external analysis blinded to the sponsor. According to the DSMB charta the committee discussed early mortality rate, critical toxicities between the two treatment arms, and premature study discontinuation. Furthermore, the DSMB committee wanted to analyze the primary endpoint. In addition, early death in DAC/AZA patients has also been identified as an issue which needs to be discussed. The DSMB informed the sponsor that the committee concordantly decided that there is no

safety concern. The trial can further proceed as planned. The DSMB committee strongly recommended analyzing the effect of the concomitant AML treatment (DAC or AZA) on the primary endpoint and early death within the final analysis.

7 CONCLUSION

Our study investigating the addition of eltrombopag to standard hypomethylating therapy in newly diagnosed elderly AML patients with thrombocytopenia ineligible for intensive treatment, did not reach the intended primary endpoint of prolonged treatment change-free survival. Although adding eltrombopag to HMA therapy was feasible and safe, it did not impact treatment change free survival (TCFS) in this study.

Similarly, no significant differences were observed in the secondary trial endpoints such as overall survival and best overall response rate between both treatment arms. Additionally, there were no significant differences in the incidence of clinically significant bleeding events (12.69% in the HMA+EPAG group versus 14.75% in the HMA+placebo group, p=0.52) or platelet transfusion rates between both groups (p=0.39).

Given that the median overall survival in the group receiving HMA+EPAG was 4.4 months and in the group receiving HMA+placebo was 5.6 months, which was considerably lower compared to the classical historical HMA mono therapy[1,2], we can infer that the participants in this study belonged to a "high risk" population. For instance, the median age in our study was 77-78 years and a significant proportion of our patients had secondary AML (45% in the EPA+HMA group compared to 28% in the Placebo+HMA group). Additionally more than one-third of the patients had an ECOG performance scale of 2 or higher and the median baseline blasts in the bone marrow were approximately 45%. These patient characteristics may help explain the poorer overall survival observed in our study.

Notably, no new safety concerns regarding AML progression were noted in the EPAG containing combination arm. There were no differences observed between both groups in terms of bone marrow blast counts over time.

In summary, the addition of eltrombopag to standard HMA therapy was safe , but did not result in improved outcomes for AML treatment in elderly AML patients.

8 PUBLICATIONS

P554 RESULTS OF A RANDOMIZED PLACEBO-CONTROLLED PHASE 2 STUDY OF HYPOMETHYLATING AGENTS WITH OR WITHOUT ELTROMBOPAG IN ELDERLY AML PATIENTS (DELTA). K.Sockel, A.Mütherig, M.Crysandt, M.Hänel, R.Noppeney, K.Schäfer-Eckardt, M.Kaufmann, C.Röllig, J.Schetelig, S.Zukunft, F.Fiebig , A.Giagounides, S.Scholl, A.Lück, K. Rieger, K.Götze, T.Geer P.Kiewe, C.Müller-Tidow H.Serve , CD.Baldus, U.Kaiser, S.Mahlmann, B.Schmidt S.Parmentier , T.Illmer, R. Seggewiss-Bernhardt, A.Kiani , H.Linde, H. Dürk, M.Kramer, D.Kunadt K.Schmidt-Brücken, J.Hase, S.Helas, JM. Middeke, M.Bonin, U.Oelschlaegel, G.Ehninger , C.Thiede, M.Bornhäuser, U.Platzbecker.

Presented at the EHA annual meeting on 9th June 2023 in Frankfurt am Mai

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10 SIGNATURES

The signing persons 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 legal regulations.

Sponsor

Prof. Dr. med. Uwe Platzbecker	25.6.23	
Name in block letters	Place, Date	Signature

Biostatistics

Dr. Sven Zukunft		
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11 LIST OF ABBREVIATIONS

AE	adverse event
AESI	adverse event of special interest
ALAT	Alaninaminotransferase
AMG	Arzneimittelgesetz
ANC	Absolute Neutrophil Count
AP	Alkaline phosphatase
APL	Acute Promyelocytic Leukemia
ASAT	Asparataminotransferase
ASCO	American Society of Clinical Oncology
ANC	Absolute Neutrophil Count
AR	adverse reaction
AUC	Area under the Curve
AZA	Azacitidine
BCRP	Breast Cancer Resistance Protein
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte
Bili	Bilirubin
BM	Bone Marrow
CBC	Complete Blood Count
CRA	Clinical Research Associate
Crea	Creatinine
$CR_{(i)(m)(c)}$	Complete Remission (incomplete recovery)(molecular)(cytogenetic)
CRF	Case Report Form
CRO	Clinical Research Organisation
CTCAE	Common Terminology Criteria for Adverse Events
DAC	Decitabine
DSMB	Data Safety Monitoring Board
eCRF	Electronic Case Report Form
ECG	Echocardiography
ECOG	Eastern Cooperative Oncology Group
EDTA	Ethylenediaminetetraacetic acid
EFS	Event Free Survival
EPAG	Eltrombopag
EudraCT	European Union Drug Regulating Authorities Clinical Trials
FAS	Full analysis set
Fib	Fibrinogen
FISH	Fluorescence in-situ Hybridization
FPFV	First Patient First Visit
GCP	Good Clinical Practice
GI	Gastrointestinal

gGT	Gamma-Glutamyl-Transpeptidase
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HMA	Hypomethylating Agent
IADL	Instrumental Activities of Daily Living
IEC	Independent Ethics Committee
INR	International Normalized Ratio (blood test)
IPSS	International Prognostic Scoring System
ITT	Intent-To-Treat Population
i.v.	Intravenous
ICH	International Conference on Harmonization
ICMJE	International Committee of Medical Journal Editors
ISF	Investigator Site File
ITP	Immune Thrombocytopenia
ITT	Intent-To-Treat Population
KKS	Koordinierungszentrum für Klinische Studien
KPS	Karnofsky Performance Status
LKP	Leiterin/Leiter der klinischen Prüfung (Coordinating Investigator)
LPLV	Last patient last visit
LVEF	Left Ventricular Ejection Fraction
MDS	Myelodysplastic Syndrome
MRD	Minimal Residual Disease
NA	not applicable
ND	not done
NSAID	Non-steroidal anti-inflammatory drug
NYHA	New York Heart Association (NYHA) Functional Classification
OATP1B1	Organic Anion Transporter Polypeptide 1B1
OS	Overall Survival
ORR	Overall Hematologic Remission Rate
PEI	Paul-Ehrlich-Institut
PPA	Per Protocol Analysis
PPS	Per protocol set
PFS	Progression Free Survival
p.o.	Per os
PT	Prothrombin Time
PTT	Partial Thromboplastin Time
PUH	Pharmacy of the University Hospital
RCT	Randomized-Controlled Trial
RFS	Relapse-Free Survival
q4w	every 4 weeks
SAE	Serious Adverse Event

SAL	Study Alliance Leukemia
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SAS	Safety Analysis Set
SD	Stable Disease
SDV	Source Data Verification
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SPSS	Statistical Package for the Social Sciences
SUSAR	Suspected Unexpected Serious Adverse Reaction
TCFS	Treatment Change Free Survival
TEE	Thromboembolic Events
TMF	Trial Master File
TPO-R	Thrombopoietin receptor
TRALI	Transfusion Related Acute Lung Injury
UAR	Unexpected Adverse Reaction
ULN	Upper Limit Normal

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