

CLINICAL TRIAL PROTOCOL



ALIDHE phase 3b study design: ivosidenib + azacitidine in adults with newly diagnosed *IDH1* mutant acute myeloid leukemia

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ABSTRACT

Introduction: Ivosidenib is an inhibitor of mutant isocitrate dehydrogenase 1 (mIDH1) that is approved alone or in combination with azacitidine in patients with mIDH1 acute myeloid leukemia (AML) that are ineligible to receive intensive chemotherapy.

Aims: Here we describe the design of ALIDHE, an international, multicenter, single-arm, open-label Phase 3b study of ivosidenib + azacitidine for treatment of newly diagnosed mIDH1 AML in usual clinical practice.

Methods: The primary endpoints are adverse events (AEs), clinical laboratory anomalies assessed as AEs, patients requiring transfusion and number of units transfused, and infection rate. The impact of ivosidenib + azacitidine treatment on health-related quality of life, healthcare resource utilization and measurable residual disease will also be assessed.

Clinical trial registration number: NCT05907057 (ClinicalTrials.gov)

ARTICLE HISTORY

Received 31 March 2025
Accepted 25 September 2025

KEYWORDS

Acute myeloid leukemia; mutant isocitrate dehydrogenase 1; ivosidenib; azacitidine; quality of life; healthcare utilization

1. Introduction

Acute myeloid leukemia (AML) is the most common acute leukemia in adults, with more than 20,000 and 22,000 new cases diagnosed in Europe and America each year, respectively [1,2]. Somatic mutations in isocitrate dehydrogenase 1 (*IDH1*) are found in approximately 2.2–10% of patients with AML [3–5], and in up to 16.0% of patients with *de novo* cytogenetically normal AML [5,6]. *IDH1* mutations are frequently found in AML patients presenting with diploid or other intermediate-risk cytogenetics, like trisomy 8, and a maintained platelet count [7]. *IDH1* mutations lead to the accumulation of D-2-hydroxyglutarate (2-HG), an oncometabolite that competitively inhibits enzymes that regulate the epigenome. This ultimately leads to delayed and impaired hemopoietic differentiation [7]. Studies have shown that mutant *IDH1* (mIDH1) AML is more common in older patients and is associated with a poorer prognosis, particularly in cytogenetically normal AML [6,8,9].

The treatment for medically fit patients with AML is intensive chemotherapy (IC), usually an anthracycline with cytarabine [10]. However, most patients with AML are ineligible for IC and are typically treated with less intensive, non-curative treatments, which have poorer outcomes than IC [11,12]. There remains an unmet need for treatment options for patients that are medically unfit for IC.

Ivosidenib is an oral mIDH1-specific inhibitor that lowers 2-HG levels. Ivosidenib is currently approved in Europe and the USA in combination with azacitidine for the treatment of patients with newly diagnosed mIDH1 AML ineligible for IC [13]. This approval was based on the results of a Phase 3, multicenter, double-blind, randomized, placebo-controlled clinical study (AGILE, NCT03173248) [14], and long-term follow-up in this trial showed median overall survival (OS) was longer in patients treated with ivosidenib + azacitidine compared to those treated with placebo + azacitidine (29.3 and 7.9 months, respectively) [15]. During the study, grade 3 or higher hematological adverse events (AEs) occurred at a higher frequency in the ivosidenib + azacitidine group compared to the placebo + azacitidine group (70% and 64%, respectively) [14]. Whereas infection rates were lower in patients receiving ivosidenib + azacitidine than patients receiving placebo + azacitidine (21% and 30%, respectively) [14]. Additionally, differentiation syndrome and QT prolongation were AEs of special interest (AESI) that occurred more frequently among patients treated with ivosidenib + azacitidine (14.1% and 9.9%, respectively) compared with placebo + azacitidine (8.2% and 4.1%, respectively) [14]. Despite occurring in 10 patients or fewer in either group [14], these AESIs along with potential pharmacological interactions of the

Article highlights

- The phase 3 AGILE study previously showed improved survival in patients with acute myeloid leukemia treated with ivosidenib + azacitidine versus placebo + azacitidine.
- ALIDHE is an international, multicenter, single-arm, open-label phase 3b study investigating the safety, tolerability, and efficacy of ivosidenib + azacitidine for the treatment of patients with newly diagnosed acute myeloid leukemia.
- This study has been designed in collaboration with patient representatives from the Acute Leukemia Advocates Network to reduce the burden of participation for patients and their families.
- The aim of this study is to bridge the gap between the pivotal results of AGILE and the use of ivosidenib in routine clinical practice, once it is commercially available.
- The primary objective of this study is to assess the safety and tolerability of treatment with ivosidenib + azacitidine using endpoints such as adverse events, laboratory anomalies, transfusion requirements, and infection rates.
- Secondary endpoints include the efficacy of treatment and the impact on health-related quality of life.
- The study will aim to enroll approximately 245 patients with acute myeloid leukemia across 100 centers in 13 countries. Results of ALIDHE are estimated in 2027.

ivosidenib + azacitidine combination with other treatments warrant additional characterization [14].

Despite the proven clinical benefit of ivosidenib + azacitidine in AGILE, data from the real-world, including patients' lived experiences, are increasingly recognized as important to supplement clinical trial data. Consistent with the efficacy demonstrated in the AGILE study, real-world evidence from a retrospective United States-wide cohort study of patients with AML ineligible for IC reported higher response rates and longer event-free survival with ivosidenib + hypomethylating agent (HMA) than venetoclax + HMA [16], but studies of ivosidenib + azacitidine in the real-world setting are lacking. Therefore, ALIDHE, an ongoing, single-arm, open-label Phase 3b study, was initiated to obtain safety, tolerability and efficacy data on ivosidenib + azacitidine in routine practice. Other objectives of ALIDHE are to assess the impact of treatment on health-related quality of life (QoL), healthcare resource utilization (HCRU) and measurable residual disease.

One distinctive feature of ALIDHE is the active participation of the patient group Acute Leukemia Advocates Network (ALAN) in the development of the study, which is described in further detail elsewhere [17]. Here we describe the study protocol, which includes a summary of the patient input into the study concept.

2. Methods

2.1. Study design

ALIDHE is an international, multicenter, single-arm, open-label Phase 3b study to evaluate the safety, tolerability and efficacy of ivosidenib + azacitidine for the treatment of *mIDH1* AML in newly diagnosed adult patients ineligible for IC. The expected study duration is approximately 3.5 years, and at time of publication ALIDHE is open to enrollment (Figures 1 and 2). The participating countries include Austria, Belgium, Canada, France, Greece, Hungary, Ireland, Italy, The Netherlands, Portugal, Romania, Spain, and the United Kingdom.

ALAN is an independent global network of patient organizations (56 member organizations from 52 countries) that aims to strengthen patient advocacy and change patient outcomes within the acute leukemia research environment. The ALIDHE study was designed collaboratively with ALAN, commencing with workshops to gather insights into patient's lived experiences with AML.

2.2. Eligibility criteria

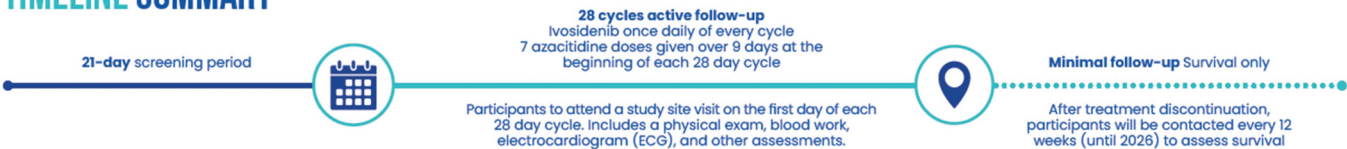
The study aims to enroll approximately 245 patients across 100 centers in 13 countries. Specialists routinely involved in the treatment of patients with AML will be included. Criteria for center selection includes the ability to obtain genomic analyses to confirm *mIDH1*, and to purchase and administer azacitidine, in accordance with the 2022 ELN Guidelines [18]. Selection criteria and basic site information will be collected via a site qualification survey.

All patients presenting during the enrollment period will be assessed for eligibility according to the defined selection criteria (Table 1) and all eligible patients will be consecutively proposed to be enrolled in the study. Adult (≥ 18 years of age) patients enrolled into this study are newly diagnosed with *mIDH1* AML and deemed ineligible for treatment with IC. Patients that have received prior treatment for AML are not eligible for this study, with the exception of hydroxyurea or leukapheresis for white blood count control. All inclusion and exclusion criteria are summarized in Table 1.

2.3. Interventions

Daily study treatment will begin on Cycle 1, Day 1 and treatment cycles are 28 days long (± 2 days). Ivosidenib will be administered orally once daily at a dose of 500 mg provided

TIMELINE SUMMARY



If at any point ivosidenib is made available as a medical prescription at the patient's site, the patient will switch to commercial product and will continue to be followed according to the protocol.

Figure 1. Summary of timeline for participating patients.

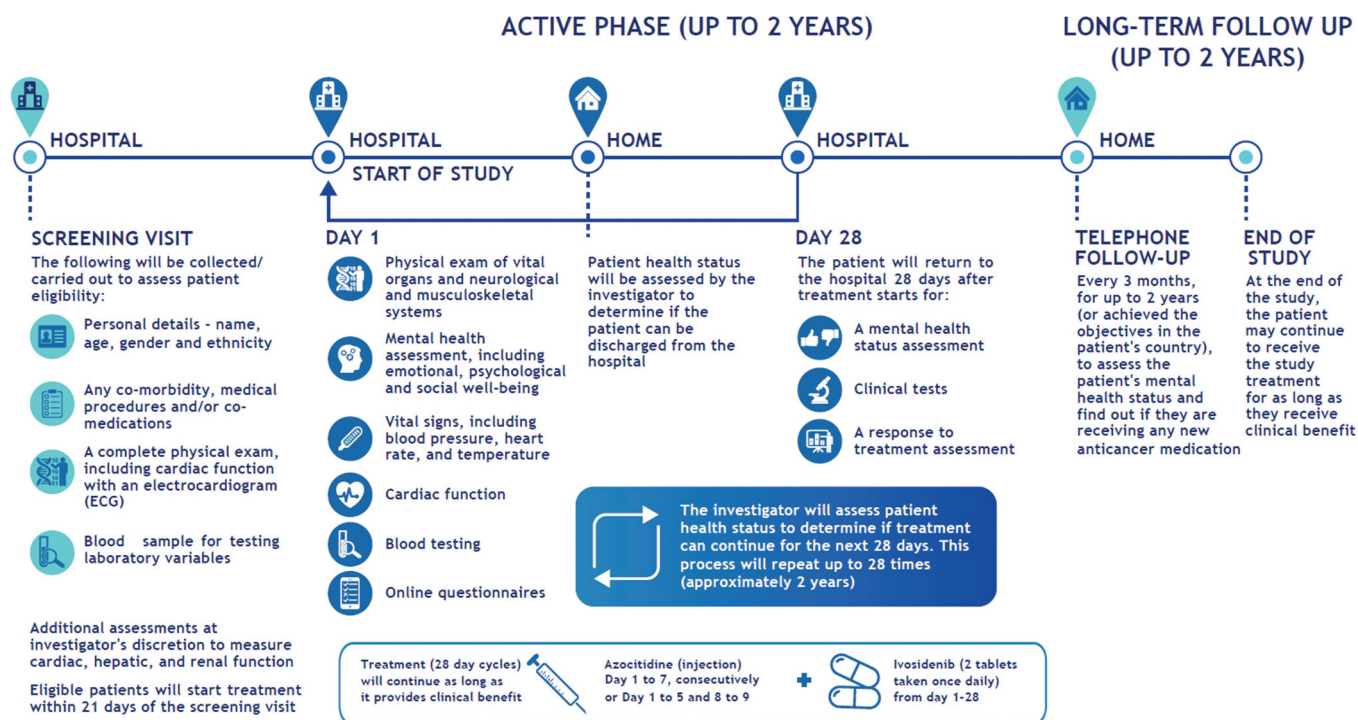


Figure 2. ALIDHE study overview for participating patients.

as 250 mg tablets. Azacitidine will be administered subcutaneously or intravenously according to local product information at a dose of 75 mg/m²/day for 7 days (on Days 1–7, or Days 1–5 and 8–9) in every 28-day cycle, starting on Day 1. Patients receiving ivosidenib + azacitidine will be assessed prospectively every 28 days for a maximum of 112 weeks (28 cycles; Figure 1), and then every 12 weeks for OS until death, withdrawal of informed consent, or until the end of the study. Ivosidenib will be provided by Servier throughout the trial. Once ivosidenib is approved and commercially available in each country, enrollment may then continue with newly enrolled patients receiving commercial ivosidenib, whereas patients that are already enrolled in ALIDHE will switch to commercial ivosidenib and continue to be followed according to the protocol. This will allow for continuous data collection in this study to bridge the gap between the pivotal AGILE trial and routine clinical practice [14].

Investigators may decide to delay or modify the dose of ivosidenib for any AE, based on clinical judgment. Dose delays are discouraged, except as needed for the management of AEs, dose holds during palliative radiotherapy, and washout from palliative radiotherapy. Dose delays of up to 28 days will be permitted at the discretion of investigators for the management of AEs and for mitigating circumstances (e.g., planned procedures).

Patients that discontinue treatment with ivosidenib + azacitidine at any point will receive subsequent therapy according to local clinical practice and will be followed-up every 12 weeks for OS until death, withdrawal of informed consent, or until the end of the study. Patients are assessed according to the schedule summarized in Table 2. Through collaboration with ALAN, a priority during the study design was to focus on

ease of administration, and to use a simplified recruitment and reporting process for the patient and clinician.

Treatment adherence of ivosidenib will be based on return of unused drug and will be collected in the electronic case report form (eCRF) based on information in the patient's medical record. Once ivosidenib is commercially available, adherence with ivosidenib will not be monitored.

Treatment adherence of azacitidine throughout the entire study period will be recorded in the eCRF. All relevant medications and other treatments taken by the patient during the study, including those treatments initiated before the start of the study, will be recorded on the eCRF. The eCRF will be used to collect indication, product names, dose, route of administration and duration of treatment for all concomitant therapies. The COVID-19 vaccines will be recorded as a concomitant medication with no interaction with ivosidenib.

2.4. Outcomes

2.4.1. Primary endpoints

The primary objective of ALIDHE is to assess the safety and tolerability of treatment with ivosidenib + azacitidine using the endpoints of AEs, clinical laboratory anomalies assessed as AEs, patients requiring transfusion and number of units transfused, and rate of infections.

AEs are graded by Common Terminology Criteria for Adverse Events (CTCAE) v5.0 [19]. The incidence of treatment emergent AEs (TEAEs; events with onset dates during the on-treatment period or worsening from baseline) will be included. Events with missing onset dates will be included as treatment emergent. Multiple occurrences of the same AE are counted once at the greatest severity and strongest relationship with

Table 1. Patient and family/carer eligibility criteria for ALIDHE study.

Inclusion criteria	Exclusion criteria
Patient	
<ul style="list-style-type: none"> • Previously untreated AML, defined according to the 2022 ELN Recommendations for AML or the International Consensus Classification of myeloid neoplasms and acute leukemia [18] • ≥ 18 years of age at time of consent • At least one of the following criteria defining ineligibility for intensive chemotherapy: <ul style="list-style-type: none"> ◦ ≥ 75 years old ◦ ECOG PS = 2 ◦ Any comorbidity deemed to be incompatible with intensive chemotherapy by an investigator, including: <ul style="list-style-type: none"> • Severe cardiac disorder • Severe pulmonary disorder • Creatinine clearance < 45 ml/minute • Bilirubin > 1.5 times upper limit of normal • Any other co-morbidity judged to be incompatible with intensive chemotherapy by an investigator, as documented before study treatment • Documented R132 <i>mIDH1</i> based on local biomolecular profiling method • ECOG ≤ 2 • Adequate hepatic function, as evidenced by Child-Pugh class A or B • Adequate renal function, as evidenced by creatinine-based (eGFR_{Cr}) > 30 ml/min/1.73 m^2 • Willing to voluntarily provide written, signed, and dated informed consent • Females with reproductive potential, must have a negative serum pregnancy prior to the start of study therapy • Females with reproductive potential, as well as fertile males with female partners of reproductive potential, must use effective contraception during treatment 	<ul style="list-style-type: none"> • Prior treatment for AML with the exception of hydroxyurea or leukapheresis for white blood cell count control • Extramedullary disease alone • Previous treatment for an antecedent hematological disorder, including investigational agents, unless a washout period of ≥ 5 half-lives of the investigational or standard of care agent has elapsed since the last dose of that agent • Received prior treatment with an IDH1 inhibitor • Known hypersensitivity to any of the components of ivosidenib or azacitidine • Female patients who are pregnant or breastfeeding • Patients taking known strong cytochrome P450 (CYP) 3A4 inducers, inhibitors or sensitive CYP3A4 substrate medications with a narrow therapeutic window were not eligible, unless they can be transferred to other medications within ≥ 5 half-lives prior to dosing, or the patient can be monitored during the study • Patients taking known sensitive CYP3A4, CYP2B6, CYP2C8, CYP2C9 or CYP2C19 substrates with a narrow therapeutic window, unless they can be transferred to other medications within ≥ 5 half-lives prior to dosing, or the patient can be monitored during the study • Patients taking P-glycoprotein transporter-sensitive substrate medications or inhibitors, unless they can be transferred to other medications (transfer is allowed if a washout time of ≥ 5 half-lives prior to first study treatment can be adhered to), or unless the patient can be properly monitored during the study. The use of Dabigatran is strictly contraindicated • Active, uncontrolled, systemic fungal, bacterial or viral infection without improvement despite appropriate antibiotics, antiviral therapy, and/or other treatment • Prior history of malignancy other than myelodysplastic syndrome or myeloproliferative disorder under active treatment. However, a patient with the following history/concurrent conditions are allowed to participate in the study: <ul style="list-style-type: none"> ◦ Basal or squamous cell carcinoma of the skin ◦ Carcinoma <i>in situ</i> of the cervix ◦ Carcinoma <i>in situ</i> of the breast ◦ Incidental histological finding of prostate cancer • Significant active cardiac disease within 6 months prior to the start of study treatment, including New York Heart Association Class III or IV congestive heart failure, myocardial infarction, unstable angina, and/or stroke • Heart rate-corrected QT interval using Fridericia's method (QTcF) ≥ 450 msec or any other factor that increases the risk of QT prolongation or arrhythmic events. Patients with prolonged QTcF interval in the setting of bundle branch block may participate in the study • Taking medications that are known to prolong the QT interval unless the patient can be transferred to other medications within ≥ 5 half-lives prior to dosing, or unless the patient can be properly monitored during the study • Dysphagia, short-gut syndrome, gastroparesis, or any other condition that limits the ingestion or gastrointestinal absorption of orally administered drugs • Uncontrolled hypertension (systolic blood pressure > 180 mmHg or diastolic blood pressure > 100 mm Hg) • Clinical symptoms suggestive of active central nervous system (CNS) leukemia or known CNS leukemia. Evaluation of cerebrospinal fluid during screening is only required if there is a clinical suspicion of CNS involvement by leukemia during screening • Immediate, life-threatening, severe complications of leukemia, such as uncontrolled bleeding, pneumonia with hypoxia or sepsis, organ failure and/or disseminated intravascular coagulation • Other medical or physiological condition deemed by an investigator to likely interfere with the patient's ability to give informed consent or participate in the study • Patient's or carers who are unable to understand the language of the informed consent form or questionnaires
Family/carer	
<ul style="list-style-type: none"> • Willing to voluntarily participate in the electronic clinical outcome assessment (eCOA) portion of the study and provide consent according to local regulations 	

the study drug. All AEs will be listed by patient, along with information regarding onset, duration, severity, relationship to study drug, action taken with study drug, treatment of the event, and the outcome.

Serious adverse events (SAEs) are defined as any AE that is life-threatening, medically significant, a congenital anomaly/birth defect, requires inpatient hospitalization or prolongation of existing hospitalization, or results in persistent or significant

Table 2. ALIDHE trial assessment schedule.

Study Day	Screening/ Inclusion	Treatment period		Treatment discontinuation visit ¹	Overall survival follow-up
		Cycle 1 (±2 days)	Cycle × (28 ± 2 days)		
	Up to 21 days	C1D1	CxD1	14–28 days after ivosidenib treatment (if applicable) ¹	Until study closure
Informed consent	X				
Review eligibility criteria	X	X			
Demographics	X				
Disease history (including mIDH1 diagnostic pathway) ²	X				
Medical and surgical history	X				
Medication history	X				
Complete physical exam	X			X	
Limited physical exam ³		X	X		
Height ⁴ and weight	X			X	
Blood sample for mIDH1 allele subtype ⁵	X				
Mental health status ⁶	X	X	X	X	
ECOG PS	X	X	X	X	
Vital signs ⁷	X	X	X	X	
12-lead ECG ⁸	X	X ⁸	X ⁸	X	
Child-Pugh score	X				
Safety laboratory assessments ⁹	X	X	X	X	
ECHO or other methods according to institutional practice for LVEF, if clinically indicated ¹⁰	X	X	X	X	
Liver function tests (SGOT, SGPT)	X	X	X		
Kidney function tests (eGFR, serum creatinine and serum bicarbonate) ¹¹	X	X	X		
Pregnancy test ¹²	X	X	X	X	
Study treatments administration ^{13,14}		X	X		
Adherence assessment ¹⁵			X	X	
Response assessments					
Evaluate extent of disease ¹⁶	X		X	X	
Response to treatment ^{16,17}			X	X	
Other clinical assessments					
Quality of life assessments (HM-PRO, FROM-16) ¹⁸		X	X	X	
HCRU assessments (EQ-5D-5 L, ¹⁷ relevant concomitant medications ¹⁹ and procedures, transfusions [platelet and RBC], length of hospital stay, days at home)	X	X	X	X	
Blood and/or bone marrow sample: exploratory biomarkers ²⁰ (optional)	X		X	X	
Bone marrow sample: MRD status ^{20,21} (optional)	X		X	X	
AEs (including laboratory results assessed as AEs and infections) ^{9, 22}	X	X	X	X	
Survival status (including date and cause of death) and New Anticancer Therapy Check ^{23,24}					X

Abbreviations: AE, adverse event. AML, acute myeloid leukemia. ANC, absolute neutrophil count. C, cycle. D, day. ECG, electrocardiogram. ECHO, echocardiogram. ECOG, Eastern Cooperative Oncology Group. eCRF, electronic case report form. eGFRcr, creatinine-based estimated glomerular filtration rate. EQ-5D-5 L, 5-level EuroQol 5-dimensions. HCRU, healthcare resource utilization. HM-PRO, hematological malignancy – patient-reported outcome. mIDH1, mutant isocitrate dehydrogenase 1. LVEF, left ventricular ejection fraction. MRD, measurable residual disease. OS, overall survival. PS, Performance Status. RBC, red blood cell. SAE, serious adverse event. SGOT, serum glutamic-oxaloacetic transaminase. SGPT, serum glutamic pyruvic transaminase. WBC, white blood cell.

All cycles are 28 days (±2 days) in duration, there are no planned rest periods between cycles. On treatment days, all assessments should be conducted pre-dose.

¹If a patient discontinues both ivosidenib + azacitidine treatment during the 26-month active phase, a discontinuation visit will be performed 14 to 28 days after the last dose of ivosidenib.

²R132 mIDH1 testing based on local biomolecular profiling method must be performed prior to the screening visit; however, results may become available during the 21 day screening period.

³Collected per standard practice.

⁴Height is to be obtained only at the screening assessment.

⁵Blood sample will be collected to further retrospectively characterize IDH1 mutation subtype (R132C, R132G, R132H, R132L, or R132S allele substitution) by central assessment.

⁶Mental health status will be assessed by the investigator.

⁷Systolic and diastolic blood pressure, heart rate, respiratory rate, and temperature. Assessments will be conducted while the patient is seated or supine.

⁸All ECGs should be obtained following 5 minutes of recumbency or semi-recumbency. 12-lead ECGs are to be obtained weekly during the first 3 weeks of the first cycle (Cycle 1 Day 1, Day 8 and Day 15 [4–6 hours post-dose]) and monthly thereafter, i.e., on Day 1 (any moment) of every other cycle.

⁹Laboratory assessments should be monitored periodically according to institutional standards of care and any abnormalities managed promptly. Only clinically significant safety laboratory results (hematology, chemistry, coagulation, urinalysis) that are assessed as AEs will be collected for this study.

¹⁰Assessment of LVEF should be performed during the study only if clinically indicated. Methods should be per institutional practice and the same method should be used for any subsequent examinations for the individual patient.

¹¹Sites should follow their local standards for the calculation of eGFR.

¹²A serum pregnancy test (female patients of childbearing potential only) will be performed at screening and a urine pregnancy test will be conducted less than 72 hours before inclusion on C1D1 and confirmed negative prior to dosing, on Day 1 of all subsequent cycles, and at the treatment discontinuation visit.

¹³Ivosidenib orally at a dose of 500 mg once daily (QD). Daily study treatment will begin on Cycle 1, Day 1 (C1D1). Treatment cycles are 28 days (±2 days) in duration and dosing is continuous for ivosidenib, azacitidine will be administered SC or IV (according to local product information) at a dose of 75 mg/m²/day for 7 days (on Days 1–7, or Days 1–5 and 8–9) every 28 days until the end of the study (unless they are discontinued from treatment), starting on Day 1 (±2 days). In the event that 2 or fewer doses of azacitidine are missed during the 7-day dosing period, dosing should continue so that the patient receives the full 7 days of therapy. If 3 or more doses of azacitidine are missed during the 7-day dosing period, the Investigator should contact the Medical Monitor and a decision on dosing will be made on an individual case basis. A full 7 days of azacitidine are required, but as per institutional practice, a schedule of 5 days of daily dosing, followed by no

disability/incapacity, or death. AEs are defined as any AE (serious or non-serious) which is of medical interest or concern to investigators, including differentiation syndrome grade ≥ 2 and QT prolongation assessed as grade ≥ 3 .

The incidence of AEs leading to ivosidenib + azacitidine discontinuation, interruption or dose reduction, and AEs leading to death will be reported. Clinical laboratory anomalies will be assessed as AEs. Mental health status will be assessed by investigators at each visit during the treatment period (Table 2) according to individual center practices and will be defined as an AE. The number of patients requiring transfusion (platelet and red blood cell), and number of units transfused, will be reported. Rate of infections, based on clinical diagnosis by physicians, will also be recorded.

2.4.2. Secondary endpoints

The secondary objectives of ALIDHE are to assess:

- the efficacy of ivosidenib + azacitidine according to local clinical practice
- the impact of treatment on health-related QoL
- the impact of treatment on HCRU and costs
- the *mIDH1* diagnostic pathway

2.4.3. Clinical and biomedical assessments

Efficacy endpoints, including event-free survival (EFS), complete response (CR; defined as presence of $< 5\%$ bone marrow blasts, absence of circulating blasts, blasts with Auer rods and extramedullary disease, absolute neutrophil count [ANC] $\geq 1.0 \times 10^9/\text{L}$, platelet count $\geq 100 \times 10^9/\text{L}$) [18], CR with partial hematologic recovery (CR_h; defined as ANC $\geq 0.5 \times 10^9/\text{L}$ and platelet count $\geq 50 \times 10^9/\text{L}$, with all other CR criteria met) [18], CR with incomplete hematological

recovery (CR_i; all CR criteria met except for residual neutropenia [$< 1.0 \times 10^9/\text{L}$] or thrombocytopenia [$< 100 \times 10^9/\text{L}$] [18], duration of response (DOR; overall and by response type), time to response (TTR) and OS.

2.4.4. Subjective assessments

QoL of patients is measured by Hematological Malignancy Patient-Reported Outcome (HM-PRO) and 5-level EuroQoL 5-Dimensions (EQ-5D-5 L), and of family/carers by Family-Reported Outcome Measure (FROM-16) [20–22]. The HM-PRO consists of two scales, one to measure the impact of the malignancy on a patient's health-related QoL and one to capture the severity of disease- or treatment-related symptoms. The FROM-16 consists of 16 scored items to assess the impact on the QoL of an adult family member or partner of a patient with any health condition or disease. The questionnaires will be given to patients for self-administration at each scheduled visit during the treatment period and will be completed electronically on site on provided tablets.

HCRU, measured by length of hospital stay, number of outpatient and emergency room (ER) visits, and proportion of days patients are at home, will be reported. Molecular profiling method for *mIDH1* diagnosis, time to results, allele subtypes, and co-mutation profiles will also be recorded.

The exploratory endpoints of the study include genetic, epigenetic, and global gene expression profiles in bone marrow and/or peripheral blood samples for evaluation of measurable residual disease and characterization of biomarkers that may correlate with clinical outcomes.

2.5. Patient involvement in study design

The study design of ALIDHE was informed by input from a patient steering committee that includes patients and

dose received on the weekend and 2 daily doses given again at the start of the next week, is allowed. The same schedule should be used for a given patient throughout the duration of treatment, when possible. On days when both ivosidenib and azacitidine are given, ivosidenib will be given prior to azacitidine.

¹⁴Patients will receive ivosidenib from Servier throughout the whole study. As soon as ivosidenib becomes commercially available for prescription at their site and reimbursed by the health insurance (or otherwise), patients will switch to the commercial product without any stop on the therapy and will continue to be followed according to the protocol. The prescribed and administered treatment regimen will be determined by the physician treating the patient in accordance with the terms of the marketing authorization, and data elements as outlined in this protocol will continue to be collected as performed per standard of care.

¹⁵Treatment adherence of ivosidenib is to be assessed based on return of unused drug. Once the patient switches to the commercial product, there will be no monitoring of treatment adherence based on return of unused drug. Adherence of the commercially approved product and of azacitidine will be entered by the site in the eCRF.

¹⁶Hematology assessments (including hemoglobin, RBC count, WBC count with differential, ANC, platelet count, and peripheral blast count) will be used to assess response to treatment. Response evaluation will be based on modified IWG Response Criteria for AML to determine patient status and continuation on study treatment. Timing of response assessments will be based on general practices and standard of care of the site.

¹⁷Response to treatment is to be assessed at the treatment discontinuation visit if the patient discontinues ivosidenib treatment for the following reasons: consent withdrawal, adverse event, or disease progression without clinical benefit as per the Investigator discretion.

¹⁸PROs (including HM-PRO, FROM-16, and EQ-5D-5 L) will be assessed starting at baseline on Day 1 (± 2 days) of the first 6 cycles of the study and will then subsequently be assessed every 3 cycles of the study and at the end of the study.

¹⁹Relevant concomitant medications include anticancer medication, anti-infectious medications, growth factors and transfusions, and any procedures performed during the study, including those used to treat AEs.

²⁰For patients providing separate consent, a blood and bone marrow sample will be collected at the Screening visit, 24 weeks (Cycle 6), 48 weeks (Cycle 12), 60 weeks (Cycle 18), and at the treatment discontinuation visit within ± 7 days of each timepoint. The bone marrow sample will be used for MRD analysis. The left over of the bone marrow sample and the blood sample will be stored, in a central biobank, for later evaluation of *mIDH1* and other genes and exploratory biomarkers.

²¹Bone marrow samples collected for MRD and biomarkers analyses, together with blood sample for biomarkers analysis, will be shipped to the vendor immediately after collection and within a maximum of 24 hours.

²²Adverse events (AEs) will be graded according to the CTCAE v5.0. After informed consent has been obtained, all AEs and SAEs regardless of attribution will be collected. Any SAEs that are assessed as related to study treatment that occur > 28 days post-treatment are also to be reported.

²³After 112 weeks (28 cycles) of active phase, patients who have not withdrawn consent will be followed up for OS via telephone every 12 weeks until study closure, or until the patient has died or lost to follow-up (whichever occurs first). Patients may continue ivosidenib treatment during this phase if the Investigator assesses a clinical benefit. Only OS will be assessed during this phase, and patients will have varying durations of follow-up.

²⁴In addition to the regular survival status contacts, patients will be contacted for survival status in the 7 calendar days following the data cutoff date (i.e., survival sweep).

patient advocates from ALAN and has been reported in more detail [17]. Feedback from ALAN was used to guide protocol adjustments to reduce burden of participation for patients, such as minimizing additional clinical visits, optimizing study duration, and adapting study documents for comprehension.

2.6. Data collection, management and analysis

All data will be collected from the information routinely recorded in patient medical records or will be prospectively recorded by the investigator for the purposes of this study. Relevant data time points for the study are summarized in Table 2. All data will be collected and entered directly into the electronic data capture (EDC) system. All participating centers will have access to data regarding patients enrolled from their individual site. All sites will be trained on the use of the online EDC system and will be responsible for entering extracted patient data into a secure internet-based EDC registry database via the eCRF. Investigators should review, electronically sign, and date each eCRF, and investigators and site personnel will be able to access their account with a username and password.

Site monitoring will be performed by IQVIA clinical research associates (IQVIA Holdings Inc, North Carolina, USA) to examine adherence with the protocol and adherence to data collection procedures. Monitoring will include source data verification by review of original patient records and will close out at each site after the last patient's follow-up assessment is completed. Audits by the Servier's monitoring team and competent regulatory authorities may be carried out at any time during or after the study and will include inspection of all study-related documents.

Sample size was not driven by hypothesis testing due to the study design and descriptive nature of the analysis. Instead, sample size was chosen to ensure robustness of related AESIs. The estimated sample size assumed, based on data from AGILE [14], an incidence of 9.9% for QT prolongation Grade 3 or higher and 14.1% for differentiation syndrome grade 2 or higher, both with a dropout rate of 10%. The sample size of 245 ensures a 95% confidence interval with a width of 0.04 for QT prolongation and 0.046 for differentiation syndrome. Sample size calculations were performed using R version 3.6.1. Strategies to achieve target sample size included newsletters and for-cause monitoring visits. The full analysis set (FAS) will include all patients who are enrolled in the study. The safety analysis set will include all patients who received at least one dose of the study treatment. The safety analysis set will be the primary analysis for all safety analyses, unless otherwise specified.

Statistical evaluation will be performed using Statistical Analysis System (SAS)[®] software version 9.4 or higher (SAS Institute, Cary, NC). Categorical data will be summarized by frequency distributions (numbers and percentages of patients), and continuous data will be summarized by descriptive statistics (mean, standard deviation [SD], median, minimum, and maximum). Time-to-event endpoints will be estimated using the Kaplan-Meier methods, and where appropriate, point estimates and 95% confidence intervals will be provided.

Interim and final analyses are planned for this study and will include all endpoints (including EFS and OS). The duration

of the active phase and OS follow-up may be reevaluated based on the results of the interim analysis.

3. Ethics and dissemination

An institutional review board/independent ethics committee and Competent Authority approved the protocol and informed consent form before study enrollment began. This study will be conducted in accordance with the approved protocol and all applicable laws and regulations, including Good Clinical Practice (GCP), Good Pharmacovigilance Practices, the ethical principles that have their origins in the Declaration of Helsinki, and applicable privacy laws.

Changes to the protocol will be documented in written protocol amendments. Major amendments will be submitted to relevant institutional review board/independent ethics committees and Competent Authorities for approval. Minor protocol amendments will be filed by each participating site and will be submitted to relevant institutional review board/independent ethics committees and Competent Authorities, where required by applicable regulations.

Before any data collection occurs, patients must sign and date the approved informed consent form. Investigators must inform patients of the objectives, risks, benefits and requirements imposed by the study prior to gaining informed consent. Data protection and privacy regulations will be strictly observed in the capturing, processing and storing of patient data. General Data Protection Regulation (GDPR) will be followed to ensure patient confidentiality. Patient data will be housed and maintained by IQVIA and will not be shared with patients, insurance companies, employers, family members, general physicians or any other third party, unless required to do so by law. Each patient will be assigned a unique patient identifier upon enrollment and precautions will be taken to prevent genetic data being linked to the identity of a patient.

Datasets, summary results and a lay summary will be available upon request from www.clinicaltrials.servier.com and will be submitted for publication in scientific literature within 18 months of the end of the study.

4. Conclusion

This international, multicenter, single-arm, open-label Phase 3b study will evaluate the safety, tolerability and efficacy of ivosidenib + azacitidine, to supplement data obtained from the Phase 3 AGILE study and bridge the gap between these pivotal trial results and the use of ivosidenib in routine clinical practice, when it is commercially available. This study will collect safety data from a broad population of patients receiving ivosidenib + azacitidine that may be receiving concomitant therapies and have co-morbidities. The ALIDHE trial will also provide data on the impact of treatment on patient/carer QoL, HCRU and measurable residual disease. The descriptive nature of the study, the lack of comparator, and the potential for selection bias due to omission of objective tools for assessment of ineligibility for intensive chemotherapy, should be taken into consideration when extrapolating the findings of ALIDHE, which will be discussed further when presenting the study results.

An important aspect of the study design is the collaboration with ALAN to ensure that patient needs are met throughout the study and to minimize the burden of participation for patients and their family/carers [17]. Patient involvement in the design of ALIDHE, along with data on the use of ivosidenib + azacitidine in routine clinical practice, will allow balanced evaluation of the safety, tolerability and efficacy of ivosidenib + azacitidine in local practice and the impact of the treatment on patient and family/carer QoL.

Acknowledgments

The authors thank Nicola Lloyd-Wood of ESP Medical Communications Ltd, Crowthorne, UK, for providing editorial support, which was funded by Servier, Suresnes, France, in accordance with Good Publication Practice (GPP, 2022) guidelines (<https://www.ismpp.org/gpp-2022>).

Composition of groups overseeing the trial

The steering committee will oversee the conduct of the study and in some cases review the data periodically. This study will also be overseen by Servier onco-hematology team (evidence generation lead and medical director). The steering committee and Acute Leukemia Advocates Network, as part of the patient steering committee for ALIDHE, have reviewed the protocol, as well as any protocol amendments.

This study will be performed by IQVIA with guidance, input, review and approval of Servier Medical Affairs, including development of materials, recruitment, training and management of sites, electronic data capture, data management and analysis.

Author contributions

Paresh Vyas: Data curation, methodology, review/editing of the manuscript drafts and approval of the final version.

Sam Salek: Methodology, supervision, review/editing of the manuscript drafts and approval of the final version.

Susana Vives: Investigation, methodology, review/editing of the manuscript drafts and approval of the final version.

Christian Récher: Data curation, methodology, review/editing of the manuscript drafts and approval of the final version.

Hartmut Döhner: Data curation, methodology, review/editing of the manuscript drafts and approval of the final version.

Adriano Venditti: Data curation, methodology, review/editing of the manuscript drafts and approval of the final version.

Hélène Derrien, Stéphanie Chatin and Anne-Marie De La Bigne: Project administration and review/editing of the manuscript drafts and approval of the final version.

Jana Pelouchova, Ralph Hills and Samantha Nier: Conceptualization, methodology, review/editing of the manuscript drafts and approval of the final version.

All authors have agreed on the journal to which the article was submitted and agreed to take responsibility and be accountable for the contents of the article and to share responsibility to resolve any questions raised about the accuracy or integrity of the published work.

Funding

This study was sponsored by Servier Affaires Médicales, France. Servier Affaires Médicales Servier Affaires Médicales 35 rue de Verdun 92284 Suresnes CEDEX. Role of trial sponsor: responsible for the design of the study; collection, management, analysis, and interpretation of data; the decision to submit this report for publication. The sponsor had ultimate authority over these activities.

Disclosure statement

Paresh Vyas: Consultancy with honoraria from Charm Therapeutics, IMU, Astellas, AbbVie, Janssen, Pfizer, Servier, Stemline, Syndax; clinical research funding to institution from Bristol Myers Squibb; travel and accommodations from Servier. Scientific advisory board for Auron Therapeutics. Co-founder and on the board of Yellowstone Biosciences.

Sam Salek: Unrestricted educational grant from Glaxo SmithKline; research funding to Institution from Center for Innovation in Regulatory Science, Bristol Myers Squibb, Novartis, Sanofi. Consulting or advisory role with Servier, Advessa and Otsuka.

Susana Vives: Travel, accommodations, expenses from Astellas Pharma, Pfizer, Servier, AbbVie and Jazz Pharmaceuticals; research funding from Astellas Pharma; consulting or advisory role (without honoraria) for Astellas Pharma, Pfizer, Servier, AbbVie and Jazz Pharmaceuticals.

Christian Récher: consulting or advisory role with AbbVie, Astellas, BMS, Boehringer, Daiichi-Sankyo, Jazz Pharmaceuticals, J&J as well as Servier, received research funding from AbbVie, Astellas, BMS, Daiichi-Sankyo, IQVIA and Jazz Pharmaceuticals, and support for attending meetings and/or travel from AbbVie, Novartis and Servier.

Hartmut Döhner: Consultancy with honoraria: AbbVie, AstraZeneca, Gilead, Janssen, Jazz, Pfizer, Servier, Stemline, Syndax; Clinical Research Funding to Institution: AbbVie, Astellas, Bristol Myers Squibb, Celgene, Jazz Pharmaceuticals, Kronos Bio, Servier: Travel, accommodations: AbbVie, Servier.

Adriano Venditti: research funding from Jazz Pharmaceuticals; consultancy for Amgen, Servier, AstraZeneca, Pfizer, Kyte-Gilead, AbbVie, Janssen, Astellas, Astex, Otsuka, Stemline Menarini, BMS, Glycostem, Novartis, Delbert.

Hélène Derrien, Stéphanie Chatin and Anne-Marie De La Bigne: Employees of Servier.

Jana Pelouchova, Ralph Hills and Samantha Nier: No financial or non-financial interest to declare in relation to this manuscript.

The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Reviewer disclosure

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose

Writing disclosure

Medical writing support was provided by Nicola Lloyd-Wood of ESP Medical Communications Ltd and was funded by Servier.

Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval and/or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

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References

Papers of special note have been highlighted as either of interest (*) or of considerable interest (**) to readers.

- Heuser M, Ofra Y, Boissel N, et al. Acute myeloid leukaemia in adult patients: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2020;31(6):697–712. doi: 10.1016/j.annonc.2020.02.018
- National Cancer Institute. Cancer stat facts: leukemia — acute myeloid leukemia (AML). 2025 [cited 2025 Aug 15]. Available from: <https://seer.cancer.gov/statfacts/html/amyl.html>
- Molenaar RJ, Maciejewski JP, Wilmsink JW, et al. Wild-type and mutated IDH1/2 enzymes and therapy responses. *Oncogene*. 2018;37(15):1949–1960. doi: 10.1038/s41388-017-0077-z
- Mardis ER, Ding L, Dooling DJ, et al. Recurring mutations found by sequencing an acute myeloid leukemia genome. *N Engl J Med*. 2009;361(11):1058–1066. doi: 10.1056/NEJMoa0903840
- Xu Q, Li Y, Lv N, et al. Correlation between isocitrate dehydrogenase gene aberrations and prognosis of patients with acute myeloid leukemia: a systematic review and meta-analysis. *Clin Cancer Res*. 2017;23(15):4511–4522. doi: 10.1158/1078-0432.CCR-16-2628
- Marcucci G, Maharry K, Wu YZ, et al. IDH1 and IDH2 gene mutations identify novel molecular subsets within de novo cytogenetically normal acute myeloid leukemia: a cancer and leukemia group B study. *J Clin Oncol*. 2010;28(14):2348–2355. doi: 10.1200/JCO.2009.27.3730
- Issa GC, DiNardo CD. Acute myeloid leukemia with IDH1 and IDH2 mutations: 2021 treatment algorithm. *Blood Cancer J*. 2021;11(6):107. doi: 10.1038/s41408-021-00497-1
- Sargas C, Ayala R, Chillon MC, et al. Networking for advanced molecular diagnosis in acute myeloid leukemia patients is possible: the PETHEMA NGS-AML project. *Haematologica*. 2021;106(12):3079–3089. doi: 10.3324/haematol.2020.263806
- Paschka P, Schlenk RF, Gaidzik VI, et al. IDH1 and IDH2 mutations are frequent genetic alterations in acute myeloid leukemia and confer adverse prognosis in cytogenetically normal acute myeloid leukemia with NPM1 mutation without FLT3 internal tandem duplication. *J Clin Oncol*. 2010;28(22):3636–3643. doi: 10.1200/JCO.2010.28.3762
- Tallman MS, Wang ES, Altman JK, et al. Acute myeloid leukemia, version 3.2019, NCCN clinical practice guidelines in oncology. *J Natl Compr Canc Netw*. 2019;17(6):721–749. doi: 10.6004/jnccn.2019.0028
- Burnett AK, Milligan D, Prentice AG, et al. A comparison of low-dose cytarabine and hydroxyurea with or without all-trans retinoic acid for acute myeloid leukemia and high-risk myelodysplastic syndrome in patients not considered fit for intensive treatment. *Cancer*. 2007;109(6):1114–1124. doi: 10.1002/cncr.22496
- Heuser M, Fernandez C, Hauch O, et al. Therapies for acute myeloid leukemia in patients ineligible for standard induction chemotherapy: a systematic review. *Future Oncol*. 2023;19(11):789–810. doi: 10.2217/fon-2022-1286
- Popovici-Muller J, Lemieux RM, Artin E, et al. Discovery of AG-120 (ivosidenib): a first-in-class mutant IDH1 inhibitor for the treatment of IDH1 mutant cancers. *ACS Med Chem Lett*. 2018;9(4):300–305. doi: 10.1021/acsmchemlett.7b00421
- Montesinos P, Recher C, Vives S, et al. Ivosidenib and azacitidine in IDH1-mutated acute myeloid leukemia. *N Engl J Med*. 2022;386(16):1519–1531. doi: 10.1056/NEJMoa2117344
- The AGILE study is a pivotal trial demonstrating improved survival with ivosidenib + azacitidine versus placebo + azacitidine in patients with newly-diagnosed IDH1 AML who were ineligible for IC.**
- De Botton S, Montesinos P, Vives S, et al. Updated efficacy and safety data from the AGILE study in patients with newly diagnosed acute myeloid leukemia treated with ivosidenib + azacitidine compared to placebo + azacitidine. *J Clin Oncol*. 2023;41(16_suppl):7012. doi: 10.1200/JCO.2023.41.16_suppl.7012
- Smith BD, Lachowicz CA, Ambinder AJ, et al. A comparison of acute myeloid leukemia (AML) regimens: hypomethylating agents combined with ivosidenib or venetoclax in newly diagnosed patients with IDH1 mutations: a real-world evidence study. *Blood*. 2023;142(Supplement 1):971–971. Presented at ASH. doi: 10.1182/blood-2023-173033
- Nier S, Pelouchova J, Hills R, et al. Patient involvement in the design of ALIDHE: a study of ivosidenib + azacitidine in newly diagnosed IDH1 mutant AML. *Future Oncol*. 2025. doi: 10.1080/14796694.2025.2587002
- Dohner H, Wei AH, Appelbaum FR, et al. Diagnosis and management of AML in adults: 2022 recommendations from an international expert panel on behalf of the ELN. *Blood*. 2022;140(12):1345–1377. doi: 10.1182/blood.2022016867
- A revised European LeukemiaNet (ELN) genetic risk classification, revised response criteria and treatment recommendations are included among recently updated guidelines developed by an international expert panel convened by ELN.**
- U.S Department of Health and Human Services. Common terminology criteria for adverse events (CTCAE) version 5.0. 2017. Available from: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf
- Goswami P, Salek S, Fielding AK, et al. Development of a novel patient-reported outcome measure in haematological malignancy for use in routine clinical practice: item generation. *Blood*. 2016;128(22):5985. doi: 10.1182/blood.V128.22.5985.5985
- Devlin NJ, Shah KK, Feng Y, et al. Valuing health-related quality of life: an EQ-5D-5L value set for England. *Health Econ*. 2018;27(1):7–22. doi: 10.1002/hec.3564
- Golics CJ, Basra MK, Finlay AY, et al. The development and validation of the family reported outcome measure (FROM-16)^(c) to assess the impact of disease on the partner or family member. *Qual Life Res*. 2014;23(1):317–326. doi: 10.1007/s11136-013-0457-y