# A double-blind randomised trial to compare oral azacitidine (CC-486) with placebo in adults with acute myeloid leukaemia and myelodysplasia who are undergoing allogeneic stem cell transplantation

Submission date	Recruitment status  No longer recruiting	[X] Prospectively registered		
25/02/2019		☐ Protocol		
Registration date	Overall study status	Statistical analysis plan		
25/02/2019 Last Edited	Ongoing  Condition category	Results		
		Individual participant data		
23/05/2025	Cancer	[X] Record updated in last year		

#### Plain English summary of protocol

https://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-trial-looking-at-azacitidine-for-acute-myeloid-leukaemia-or-myelodysplasia-amadeus

#### Study website

https://www.impactpartnership.org.uk/the-trials/amadeus/

#### Contact information

#### Type(s)

Scientific

#### Contact name

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#### Additional identifiers

#### **EudraCT/CTIS** number

2018-001012-30

IRAS number

ClinicalTrials.gov number

NCT04173533

Secondary identifying numbers

41275

# Study information

#### Scientific Title

A double-blind, phase III, randomised study to compare the efficacy and safety of oral azacitidine (CC-486) versus placebo in subjects with acute myeloid leukaemia or myelodysplastic syndromes as maintenance after allogeneic haematopoietic stem cell transplantation

#### Acronym

**AMADEUS** 

#### Study objectives

The aim of the study is to find out if there is a difference in the relapse free survival of patients with AML or high risk MDS treated with maintenance therapy of oral azacitidine versus placebo after stem cell transplantation.

#### Ethics approval required

Old ethics approval format

#### Ethics approval(s)

Approved 02/05/2019, East Midlands - Leicester Central Research Ethics Committee (The Old Chapel, Royal Standard Place, Nottingham, NG1 6FS; Tel: +44 (0)207 1048098; Email: nrescommittee.eastmidlands-leicestercentral@nhs.net), ref: 19/EM/0063

#### Study design

Randomised; Interventional; Design type: Treatment, Drug

#### Primary study design

Interventional

#### Secondary study design

Randomised controlled trial

#### Study setting(s)

Hospital

#### Study type(s)

Treatment

#### Participant information sheet

Not available in web format, please use the contact details to request a patient information sheet

#### Health condition(s) or problem(s) studied

Acute myeloid leukaemia, myelodysplastic syndromes

#### **Interventions**

Patients will be randomised 1:1 to either treatment with oral azacitidine (CC-486) or matching placebo. Patients will take a dose of 200 mg once daily from days 1 – 14 of a 28-day cycle. Patients will commence therapy between days 42 and 84 post-transplant up to a maximum of 12 months from the date of transplant. Patients will be followed up for 2 years for survival information.

#### Intervention Type

Drug

#### Phase

Phase III

#### Drug/device/biological/vaccine name(s)

Azacitidine (CC-486)

#### Primary outcome measure

Relapse free survival; Timepoint(s): Date of first relapse (including morphological, cytogenetic or molecular relapse) or death from any cause. Patients who are progression free and still alive at the end of the trial will be censored at their date of last follow-up

#### Secondary outcome measures

- 1. Overall survival is defined as the time from date of randomisation to date of death, from any cause. Patients who are alive at the end of the trial will be censored at their date last seen.
- 2. Cumulative incidence of relapse is defined as the time from date of randomisation to date of relapse. Patients who die without relapse will be considered a competing risk, at their date of death. Patients who are alive and relapse free at the end of the trial will be censored at their date last seen.
- 3. Non-relapse mortality is defined as the time from date of randomisation to date of any death not following relapse. Patients who die post relapse will be considered a competing event at their date of death and patients who are alive at the end of the trial will be censored at their date last seen.
- 4. Incidence of acute and chronic GVHD of any grade reported throughout the trial.
- 5. Time to early treatment discontinuation is defined as the time from date of randomisation to date of treatment discontinuation, for any reason. Patients who take the full year of treatment will be censored at 12 months.
- 6. Safety will be collected in accordance with CTCAE criteria version 4.0 and defined as the number of patients who experience one or more adverse event.
- 7. Quality of life measured using the EORTC-QLQ-C30 and EQ-5D questionnaires at randomisation i.e. baseline and at 3, 6, 12 (end of treatment) and 24 months post randomisation 8. GVHD-free and relapse-free survival defined as time from date of randomisation to date of

first event or death. An event is defined as GVHD or relapse (including molecular relapse and progression). Patients who are alive and event free at the end of the trials will be censored at their date last seen

#### Overall study start date

07/07/2017

#### Completion date

31/03/2027

# **Eligibility**

#### Key inclusion criteria

Current participant inclusion criteria as of 24/02/2021:

- 1. Age  $\geq$  16 years at the time of signing the informed consent form
- 2. Patients with a diagnosis of any of the below and undergoing allo-SCT using MAC or RIC preparative regimens, and with either peripheral blood or bone marrow as the source of hematopoietic stem cells:
- 2.1. AML (CR1 or CR2) according to WHO classification
- 2.2. Secondary AML (defined as a previous history of MDS, antecedent hematological disease, or chemotherapy exposure; CR1 or CR2)
- 2.3. Advanced or high-risk MDS with an IPSS-R of ≥3.5 (intermediate 3.5 or higher) including intermediate or high-risk CMML (e.g. CPSS int-2 or high risk)
- 3. At the time of allo-SCT
- 3.1. No prior allo-SCT
- 3.2. No more than 1 antigen mismatch at HLA-A, -B, -C, -DRB1 or -DQB1 locus for either related or unrelated donor
- 3.3. No haplotype or cord blood donor
- 3.4. Bone marrow blast <5% for AML and <10% for MDS patients
- 4. Able to commence study therapy between 42 to 84 days following allo-SCT
- 5. Post-transplant bone marrow:
- 5.1. AML patients blast count ≤5% confirmed within 28 days prior to starting study therapy
- 5.2. MDS patients confirmation of CR post-transplant with blast count ≤5% in bone marrow
- 6. Adequate neutrophil and platelet engraftment within 14 days prior to starting study therapy defined as:
- 6.1. ANC  $\geq$ 1.0 x 109/l on two consecutive testing without daily use of myeloid growth factor
- 6.2. Platelet  $\geq$  50 x 109/l on two consecutive testing without platelet transfusion within 1 week 7. Adequate organ function:
- 7.1. Serum AST or ALT <3 x upper limit of normal (ULN)
- 7.2. Serum bilirubin <2 x ULN. Higher levels are acceptable if these can be attributed to active red blood cell (RBC) precursor destruction within the bone marrow (i.e., ineffective erythropoiesis) or Gilbert's syndrome.
- 7.3. Serum creatinine <2 x ULN
- 8. Adequate coagulation (PT  $\leq$ 15 s and PTT  $\leq$ 40 s)
- 9. Eastern Cooperative Oncology Group (ECOG) performance status of  $\leq 2$
- 10. Patients with adequately controlled GVHD (defined as GVHD grade <II with concurrent use of corticosteroids equivalent of prednisone at a dose  $\le$ 0.5 mg/kg) can be included
- 11. Females of childbearing potential may participate, providing they meet the following conditions:
- 11.1. Agree to use at least two effective contraceptive methods (oral, injectable, or implantable hormonal contraceptive; tubal ligation; intra-uterine device; barrier contraceptive with

spermicide; or vasectomised partner) or practice true abstinence throughout the study, and for 3 months following the last dose of study therapy

- 11.2. Have a negative serum or urine pregnancy test (sensitivity of at least 25 mIU/mL) at screening
- 11.3. Have a negative serum or urine (investigator's discretion) pregnancy test (sensitivity of at least 25 mIU/ml) within 72 h prior to starting study therapy. This applies even if the subject practices complete abstinence from heterosexual contact.
- 12. Male patients with a female partner of childbearing potential must agree to the use of at least two physician-approved contraceptive methods throughout the course of the study and should avoid fathering a child during the course of the study and for 3 months following the last dose study therapy
- 13. Understand and voluntarily sign an informed consent form (ICF) prior to any study-related assessments or procedures being conducted
- 14. Able to adhere to the study visit schedule (i.e., clinic visits at the study sites are mandatory unless noted otherwise for study visits) and other protocol requirements

#### Previous participant inclusion criteria:

- 1. Age > = 16 at the time of signing the informed consent form
- 2. Patients with a diagnosis of AML (CR1 or CR2) according to WHO classification or high risk MDS (as per IPSS-R) undergoing allo-SCT using MAC or RIC preparative regimens, and with either peripheral blood or bone marrow as the source of hematopoietic stem cells.
- 3. At the time of allo-SCT:
- 3.1. No prior allo-SCT; and
- 3.2. No more than 1 antigen mismatch at HLA-A, -B, -C, -DRB1 or -DQB1 locus for either related or unrelated donor; and
- 3.3. No haplotype or cord blood donor; and
- 3.4. Bone marrow blast < 5% for AML and < 10% for MDS patients
- 4. Able to commence study therapy between 42 to 84 days following allo-SCT
- 5. Post-transplant bone marrow
- 5.1. AML patients blast count < = 5% confirmed within 28 days prior to starting study therapy
- 5.2. MDS patients confirmation of CR post-transplant with blast count < = 5% in bone marrow
- 6. Adequate neutrophil and platelet engraftment within 14 days prior to starting study therapy defined as:
- 6.1. ANC  $> = 1.0 \times 10^9/L$  on two consecutive testing without daily use of myeloid growth factor; and
- 6.2. Platelet > = 50 x 10^9/L on two consecutive testing without platelet transfusion within 1 week
- 7. Adequate organ function:
- 7.1. Serum AST and ALT  $< 3 \times 10^{-5}$  x upper limit of normal (ULN)
- 7.2. Serum bilirubin < 2 x ULN. Higher levels are acceptable if these can be attributed to active red blood cell (RBC) precursor destruction within the bone marrow (i.e., ineffective erythropoiesis) or Gilbert's syndrome
- 7.3. Serum creatinine < 2 x ULN
- 8. Adequate coagulation (PT < = 15 seconds, PTT < = 40 seconds, and/or INR < = 1.5)
- 9. Eastern Cooperative Oncology Group (ECOG) performance status of < = 2
- 10. Patients with adequately controlled GVHD (defined as GVHD grade < II with concurrent use of corticosteroids equivalent of prednisone at a dose < = 0.5 mg/kg) can be included
- 11. Females of childbearing potential (FCBP) may participate, providing they meet the following conditions:
- 11.1. Agree to use at least two effective contraceptive methods (oral, injectable, or implantable hormonal contraceptive; tubal ligation; intra-uterine device; barrier contraceptive with spermicide; or vasectomised partner) throughout the study, and for 3 months following the last

dose of study therapy and

- 11.2. Have a negative serum pregnancy test (sensitivity of at least 25 mIU/mL) at screening; and
- 11.3. Have a negative serum or urine (investigator's discretion) pregnancy test (sensitivity of at least 25 mIU/mL) within 72 hours prior to starting study therapy. This applies even if the subject practices complete abstinence from heterosexual contact.
- 12. Male patients with a female partner of childbearing potential must agree to the use of at least two physician-approved contraceptive methods throughout the course of the study and should avoid fathering a child during the course of the study and for 3 months following the last dose study therapy
- 13. Understand and voluntarily sign an informed consent form (ICF) prior to any study related assessments or procedures being conducted
- 14. Able to adhere to the study visit schedule (i.e., clinic visits at the study sites are mandatory, unless noted otherwise for study visits) and other protocol requirements

#### Participant type(s)

Patient

#### Age group

Adult

#### Sex

Both

#### Target number of participants

Planned Sample Size: 324; UK Sample Size: 324

#### Total final enrolment

326

#### Key exclusion criteria

Current participant exclusion criteria as of 24/02/2021:

- 1. Use of any of the following after transplantation and prior to starting study therapy:
- 1.1. Any agents (chemotherapy or targeted agents) used for adjuvant therapy (note that prophylactic use of these agents is allowed in this study, e.g., methotrexate for GVHD or rituximab for EBV reactivation)
- 1.2. Unlicensed investigational agents/therapies used within 28 days prior to starting study therapy
- 1.3. Azacitidine, decitabine or other hypomethylating agent (HMA)
- 1.4. Lenalidomide, thalidomide and pomalidomide used within 28 days prior to starting study therapy
- 1.5. Any chemotherapy used for adjuvant therapy
- 2. Subjects who have undergone a haploidentical or cord blood transplant
- 3. Active GVHD grade II or higher (acute GVHD Clinical Staging and Grading)
- 4. Concurrent use of corticosteroids equivalent of prednisone at a dose > 0.5 mg/kg
- 5. Known active viral infection with Human Immunodeficiency Virus (HIV), Hepatitis B Virus (HBV) or Hepatitis C Virus (HCV)
- 6. Active uncontrolled systemic fungal, bacterial, or viral infection (defined as ongoing signs /symptoms related to the infection without improvement despite appropriate antibiotics, antiviral therapy, and/or other treatment)
- 7. History of inflammatory bowel disease (e.g., Crohn's disease, ulcerative colitis), celiac disease (i.e., sprue), prior gastrectomy or upper bowel removal, or any other GI disorder or defect that

may interfere with the absorption, distribution, metabolism or excretion of the investigational medicinal products (IMPs) and/or predispose the subject to an increased risk of gastrointestinal toxicity prior to allo-SCT

- 8. Idiopathic thrombocytopenic purpura (ITP), disseminated intravascular coagulation, haemolytic uremic syndrome, thrombotic thrombocytopenic purpura (TTP)
- 9. History of prior malignancies. However, the following will be exceptions:
- 9.1. Fully resected basal cell or squamous cell carcinoma of skin
- 9.2. Treated cervical carcinoma in situ
- 9.3. Lobular breast carcinoma in situ,
- 9.4. Incidental histologic finding of prostate cancer (T1a or T1b using the tumor, node, metastasis clinical staging system)
- 9.5. Previous Myelodysplastic Syndrome (MDS), Chronic Myelomonocytic Leukemia (CMML), Myeloproliferative Neoplasm (MPN) resulting in secondary acute myeloid leukaemia (AML)
- 9.6. Cancer treated with curative intent ≥5 years previously
- 10. Significant active cardiac disease within the previous 6 months, including:
- 10.1. New York Heart Association (NYHA) class III or IV congestive heart failure
- 10.2. Unstable angina or angina requiring surgical or medical intervention; and/or
- 10.3. Myocardial infarction
- 11. Known or suspected hypersensitivity to azacitidine or mannitol
- 12. Pregnant or lactating females
- 13. Any significant medical condition, laboratory abnormality, or psychiatric illness that would prevent the patient from participating in the study.
- 14. Any condition including the presence of laboratory abnormalities, which places the patient at unacceptable risk if he/she were to participate in the study
- 15. Any condition that confounds the ability to interpret data from the study

#### Previous participant exclusion criteria:

- 1. Use of any of the following after transplantation and prior to starting study therapy:
- 1.1. Any agents (chemotherapy or targeted agents) used for adjuvant therapy (note that prophylactic use of these agents is allowed in this study, e.g., methotrexate for GVHD or rituximab for EBV reactivation)
- 1.2. Unlicensed investigational agents/therapies used within 28 days prior to starting study therapy
- 1.3. Azacitidine, decitabine or other hypomethylating agent (HMA)
- 1.4. Lenalidomide, thalidomide and pomalidomide used within 28 days prior to starting study therapy
- 2. Subjects who have undergone a haploidentical or cord blood transplant
- 3. Active GVHD grade II or higher (acute GVHD Clinical Staging and Grading)
- 4. Concurrent use of corticosteroids equivalent of prednisone at a dose > 0.5 mg/kg
- 5. Known active viral infection with Human Immunodeficiency Virus (HIV), Hepatitis B Virus (HBV) or Hepatitis C Virus (HCV)
- 6. Active uncontrolled systemic fungal, bacterial, or viral infection (defined as ongoing signs /symptoms related to the infection without improvement despite appropriate antibiotics, antiviral therapy, and/or other treatment)
- 7. History of inflammatory bowel disease (e.g., Crohn's disease, ulcerative colitis), celiac disease (i.e., sprue), prior gastrectomy or upper bowel removal, or any other GI disorder or defect that may interfere with the absorption, distribution, metabolism or excretion of the investigational medicinal products (IMPs) and/or predispose the subject to an increased risk of gastrointestinal toxicity prior to allo-SCT
- 8. Idiopathic thrombocytopenic purpura (ITP), disseminated intravascular coagulation, haemolytic uremic syndrome, thrombotic thrombocytopenic purpura (TTP)
- 9. Prior history of/concurrent malignancies (including CMML). However, subjects with the

following history/concurrent conditions are allowed:

- 9.1. Basal or squamous cell carcinoma of the skin
- 9.2. Carcinoma in situ of the cervix
- 9.3. Carcinoma in situ of the breast
- 9.4. Incidental histologic finding of prostate cancer (T1a or T1b using the tumor, node, metastasis (TNM) clinical staging system)
- 10. Significant active cardiac disease within the previous 6 months, including:
- 10.1. New York Heart Association (NYHA) class III or IV congestive heart failure
- 10.2. Unstable angina or angina requiring surgical or medical intervention; and/or
- 10.3. Myocardial infarction
- 11. Known or suspected hypersensitivity to azacitidine or mannitol
- 12. Pregnant or lactating females
- 13. Any significant medical condition, laboratory abnormality, or psychiatric illness that would prevent the patient from participating in the study.
- 14. Any condition including the presence of laboratory abnormalities, which places the patient at unacceptable risk if he/she were to participate in the study
- 15. Any condition that confounds the ability to interpret data from the study

#### Date of first enrolment

14/06/2019

Date of final enrolment

27/03/2023

#### Locations

#### Countries of recruitment

England

Scotland

United Kingdom

Wales

Study participating centre Beatson West of Scotland Cancer Centre

Glasgow United Kingdom G12 0YN

Study participating centre King's College Hospital London United Kingdom SE5 9RS

#### Study participating centre St. James's University Hospital

Leeds United Kingdom LS9 7TF

Study participating centre Manchester Royal Infirmary Manchester United Kingdom M13 9WL

Study participating centre Freeman Hospital Newcastle-Upon-Tyne United Kingdom NE7 7DN

Study participating centre Churchill Hospital Oxford United Kingdom OX3 7LE

Study participating centre Queen Elizabeth Hospital Birmingham United Kingdom B15 2TH

Study participating centre St Bartholomew's Hospital London United Kingdom EC1A 7BE

Study participating centre

#### Bristol Haematology and Oncology Centre

Bristol United Kingdom BS2 8ED

#### Study participating centre University College London Hospitals

London United Kingdom NW1 2BU

#### Study participating centre Addenbrookes Hospital

Cambridge United Kingdom CB2 0QQ

# Study participating centre University Hospital of Wales

Cardiff United Kingdom CF14 4XW

#### Study participating centre Christie Hospital

Manchester United Kingdom M20 4BX

#### Study participating centre Hammersmith Hospital London

United Kingdom W12 0HS

#### Study participating centre

#### Leicester Royal Infirmary

Leicester United Kingdom LE1 5WW

# Study participating centre The Clatterbridge Cancer Centre Liverpool United Kingdom CH63 4JY

Study participating centre Nottingham City Hospital Nottingham United Kingdom NG5 1PB

Study participating centre
Derriford Hospital
Plymouth
United Kingdom
PL6 8DH

Study participating centre The Royal Marsden Hospital London United Kingdom SW3 6JJ

Study participating centre Royal Hallamshire Hospital Sheffield United Kingdom S5 7AU

# Sponsor information

#### Organisation

University of Birmingham

#### Sponsor details

Research Support Group Aston Webb Building Edgbaston Birmingham England United Kingdom B15 2TT +44 (0)121 371 7858 amadeus@trials.bham.ac.uk

#### Sponsor type

University/education

#### **ROR**

https://ror.org/03angcq70

# Funder(s)

#### Funder type

Charity

#### Funder Name

IMPACT (funded by NHS Blood & Transplant, Anthony Nolan and Leuka)

#### Funder Name

Celgene

#### Alternative Name(s)

Celgene Corporation

#### **Funding Body Type**

Private sector organisation

#### **Funding Body Subtype**

For-profit companies (industry)

#### Location

United States of America

### **Results and Publications**

#### Publication and dissemination plan

Planned publication in a high-impact peer reviewed journal

#### Intention to publish date

31/03/2027

#### Individual participant data (IPD) sharing plan

The data sharing plans for the current study are unknown and will be made available at a later date.

#### IPD sharing plan summary

Data sharing statement to be made available at a later date

#### **Study outputs**

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			28/06/2023	No	No