ISRCTN55111436 https://doi.org/10.1186/ISRCTN55111436

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

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

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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 ≥ 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 ≥1.0 x 109/l on two consecutive testing without daily use of myeloid growth factor
6.2. Platelet ≥ 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 ≤15 s and PTT ≤40 s)
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 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 x 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 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
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S5 7AU

Sponsor information

Organisation
University of Birmingham

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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