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Comparing a new combination of medicines to the usual intensive chemotherapy treatment given to participants who have been recently diagnosed with acute myeloid leukaemia

Submission date
16/09/2025

Recruitment status
Not yet recruiting

Registration date
08/12/2025

Overall study status
Ongoing

Last Edited
07/10/2026

Condition category
Cancer

[X] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[X] Record updated in last year

Plain English summary of protocol

Background and study aims
This study is for people with a type of cancer of the bone marrow called Acute Myeloid Leukaemia (AML). The purpose of this study is to test the safety and effectiveness of a new combination of four medicines, tagraxofusp, venetoclax, cytarabine and cladribine compared with the normal standard of care intensive chemotherapy treatment, in fit adults with newly diagnosed AML either aged 18 and over with high-risk AML or older adults (aged 50 and over) with intermediate risk AML, with the aim of increasing the number of patients who can proceed to a potentially curative transplant.
There will be about 30 people taking part in the first part of this study (Part 1) and about 192 people taking part in the second part (Part 2), all patients will be from hospitals all over the UK. Patients in Part 1 will all receive the new combination of four medicines and in Part 2 will be assigned randomly to one of two groups (Arms A and B): Part 2, Arm A will receive the standard of care intensive chemotherapy treatment (abbreviated to either DA, DA+GO, CPX351 (Vyxeos) or FLAG-Ida) and Part 2, Arm B will receive the new combination of four medicines for intensive treatment: tagraxofusp, venetoclax, cytarabine and cladribine. Patients in both Arms will receive a minimum of two cycles of treatment. Patients will be recruited over approximately 15 months for Part 1 and 18 months for Part 2 and followed for up to 7 years. This study will consist of Screening, Study Treatment, Study Treatment Discontinuation, Long-Term Follow-Up and Survival Follow Up periods.

Who can participate?
Patients aged 18 years or older with Adverse risk AML, or aged 50 years or older with Intermediate risk AML.

What does the study involve?
Study design: The study design is based as closely as possible to the standard of care (SOC) pathway in this patient population; therefore, the additional burden to patients as a result of being on the study is minimal. Only the following assessments are additional to SOC in both

arms: bone marrow (BM) and peripheral blood (PB) sample repeated at screening for translational studies; pregnancy test for females of childbearing potential at treatment discontinuation; quality of life (QoL) questionnaires at 4-6 timepoints during the study. To help minimise the impact of the baseline molecular genetic testing and measurable residual disease (MRD) disease assessment (using the BM and PB), a separate Informed Consent Form (ICF) can be used, either prior to or following the patient's formal acute myeloid leukaemia (AML) diagnosis, to allow for these to be collected from the patient's diagnostic samples and to avoid having to repeat them at screening. This was implemented following widespread discussions with the proposed investigational sites. Possible side effects to participants if they need an extra BM and PB sample at screening (above SOC) include: bleeding, bruising, infection, pain and tingling of the leg. The SOC Part 2, Arm A treatment options were agreed following discussions with various UK consultant haematologists, to ensure this is a true reflection of the current UK patient population/treatment. Therefore, patients randomised to Part 2, Arm A will receive the same treatment they would receive if they chose not to join the study. Careful consideration has been given through statistical methods to minimise the risk to patients. Power calculations have been utilised to calculate the minimum required sample size whilst maintaining statistical power.

What are the possible benefits and risks of participating?
Benefits:
We cannot promise that participants will benefit directly from taking part in the study, but we believe that there is a good chance that the information we get from the study results will be valuable in evaluating new treatment options for patients with AML.

Risks:
Risk related to the IMP:
Part 2, Arm A will receive the standard of care intensive chemotherapy treatment of daunorubicin and cytarabine (DA), DA and gemtuzumab ozogamicin (DA+GO), a combination of daunorubicin and cytarabine called CPX-351 (Vyxeos), or fludarabine, cytarabine, granulocyte-colony stimulating factor (G-CSF) and idarubicin (FLAG-Ida). These treatments are abbreviated to DA, DA+GO, CPX351 (Vyxeos) or FLAG-Ida and since these treatments are standard of care, they reflect the current UK patient population treatment risk.

Part 1 and Part 2, Arm B will receive the new combination of four medicines for intensive treatment: tagraxofusp, venetoclax, cytarabine and cladribine (TAG/VEN/LDAC/CLAD).

TAG: Very Common AE's include low blood platelet count, anaemia, changes in levels of minerals in the blood such as low albumin, Capillary leak syndrome, which can lead to dangerous drops in blood pressure (Hypotension), nausea, vomiting, fatigue and elevated transaminases (a sign of liver stress). Other AE's are listed in the PIS.

VEN: Common AEs in people treated with VEN include: increased risk of infection, lung problems, anaemia, changes in levels of minerals in the blood, such as high potassium and phosphate and low calcium, diarrhoea or constipation, feeling or being sick, and fatigue. Occasional AEs are detailed in the PIS.

LDAC - low dose cytarabine: Most common AE's are gastrointestinal undesirable effects like swallowing problems, abdominal pain, nausea, vomiting, diarrhea etc. Cytarabine is toxic to the bone marrow and causes haematological undesirable effects like anaemia. LDAC can also commonly give eye disorders and skin disorders like rashes.

CLAD Common AE's include fever, fatigue, nausea, rash, headache, and administration site reactions.

Potential risks and burdens are described in the PIS so that potential patients can clearly understand what is involved if they consent to take part. Supportive medications will be given as per local practice.

Where is the study run from?
Accelerating Clinical Trials Ltd (UK)

When is the study starting and how long is it expected to run for?
September 2026 to October 2031

Who is funding the study?
Stemline Therapeutics (Netherlands)

Who is the main contact?
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Lay summary under review with external organisation

Contact information

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Public, Scientific

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Additional identifiers

Integrated Research Application System (IRAS)
1012553

Central Portfolio Management System (CPMS)
68990

Study information

Scientific Title
A phase I/II open-label cohort evaluating the safety and efficacy of a tagraxofusp, venetoclax, cladribine, cytarabine induction regimen, leading into a randomised open-label cohort evaluating safety and efficacy of a tagraxofusp, venetoclax, cladribine, cytarabine induction regimen compared with intensive chemotherapy in fit adults with newly diagnosed acute myeloid leukaemia

Acronym
FIDELIO (ACT-AML-901)

Study objectives
Primary objectives:
Part 1 - To assess the safety and tolerability of TAG/CLAD/VEN/LDAC chemotherapy and the clinical activity of the combination.
Part 2 - To compare the efficacy of TAG/CLAD/VEN/LDAC therapy (experimental arm) with standard of care IC (control arm) as measured by Event Free Survival.

Secondary objective:
To compare and evaluate the safety, efficacy and tolerability of TAG/CLAD/VEN/LDAC therapy (experimental arm) versus standard of care.

Ethics approval required
Ethics approval required

Ethics approval(s)
Approved 06/12/2025, North East - Newcastle & North Tyneside 1 Research Ethics Committee (2nd Floor, 2 Redman Place Stratford, London, E20 1JQ, United Kingdom; +44 207 104 8077; newcastlenorthtyneside1.rec@hra.nhs.uk), ref: 25/NE/0182

Primary study design
Interventional

Study design
Interventional randomized parallel group controlled trial

Study type(s)
Efficacy, Safety

Health condition(s) or problem(s) studied
Newly diagnosed Acute Myeloid Leukaemia

Interventions

The ACT-AML-901 study is a prospective, multi-centre, two-part open-label, Phase I/II, 2:1 randomized study comparing tagraxofusp, venetoclax, cytarabine and cladribine combination therapy with the current standard of care induction chemotherapy schedules in fit adults, with either newly diagnosed European LeukaemiaNet (ELN) 2022 adverse risk AML (18 years of age and over) or ELN 2022 intermediate-risk AML (50 years of age and over).
There will be about 30 participants enrolled on Part 1 (Experimental) of this study, and 192 participants randomly allocated to one of two treatment groups (2:1), Part 2, Arm B (Experimental) or Part 2, Arm A (Control).

Part 2, Arm A (control arm):
Two cycles, up to 42 days each, of standard-of-care intensive induction chemotherapy, with either daunorubicin and cytarabine (DA), DA with gemtuzumab ozogamicin (DA+GO), CPX-351 (Vyxeos) or FLAG-Ida (fludarabine, cytarabine, granulocyte-colony stimulating factor (G-CSF) and idarubicin.
Patients who achieve < 5% bone marrow blasts after 2 cycles of induction chemotherapy should be considered candidates for allogeneic stem cell transplantation (allo-SCT) as definitive therapy.
Patients may receive an additional 1-2 cycles of standard-of-care consolidation chemotherapy (high-dose cytarabine or Vyxeos) prior to allo-SCT as clinically indicated.
The above medications are defined as Non-Investigational Medicinal Products (NIMPs) in the context of this study, as these are only being given as per the standard of care to newly diagnosed AML patients.

Part 1 and Part 2, Arm B (Experimental arm):
Two cycles, up to 42 days each, of tagraxofusp, venetoclax, cytarabine and cladribine combination induction therapy.
Patients who achieve <5% bone marrow blasts after 2 cycles of tagraxofusp, venetoclax, cytarabine and cladribine induction chemotherapy should be considered candidates for allo-SCT.
Patients may receive additional cycles of venetoclax and azacitidine therapy prior to allo-SCT as clinically indicated.

The above medications are defined as Investigational Medicinal Products (IMPs) in the context of this study

A total of 222 adults with newly diagnosed AML who fulfil the eligibility criteria will be recruited.

Patients will be recruited over approximately 15 months for Part 1 and 18 months for Part 2 and followed for up to 7 years from the date of randomisation of the first patient. The entire study is expected to last approximately 7 years.

All patients who achieve < 5% bone marrow blasts after 2 cycles of induction chemotherapy will be followed for survival until death, withdrawal of consent, loss to follow-up, completion of survival follow-up, or study termination by the sponsor, whichever occurs first.
Patients who do not achieve < 5% bone marrow blasts after 2 cycles of induction chemotherapy will be withdrawn from the study.

Follow-up of all patients will be performed as follows: monthly during year 1 post allo-SCT, every 2 months during year 2 post allo-SCT and 6-monthly during year 3 onwards post allo-SCT.

Intervention Type

Drug

Phase
Phase II

Drug/device/biological/vaccine name(s)
Tagraxofusp, cladribine, venetoclax, cytarabine, azacitidine, daunorubicin, gemtuzumab ozogamicin, CPX-351, fludarabine, idarubicin, G-CSF

Primary outcome(s)
Superiority of the tagraxofusp, venetoclax, cladribine, cytarabine combination therapy versus standard of care intensive chemotherapy as measured by event free survival (EFS). The planned primary analysis will take place when 115 EFS events have occurred, or all patients have been followed for a minimum of 1 year, which is expected to occur approximately 30 months from the date of randomisation of the first patient into the study.

Key secondary outcome(s)
Current key secondary outcome(s) as of 13/08/2026:

Safety, efficacy and tolerability of TAG/CLAD/VEN/LDAC combination therapy (experimental arm) versus standard of care IC (control arm) as measured by:
1. Overall survival
2. Complete response (CR)
3. Composite CR (CR/CRi) rate
4. The overall response rate (defined as the proportion of patients with either CR, CRi, or morphologic leukaemia-free state [MLFS])
5. Proportion of participants achieving MRD negativity (CRMRD-)
6. Duration of CR
7. Duration of CR/CRi
8. Day 60 treatment-related mortality
9. Incidence of > CTCAE Grade 3 non-haematological adverse events (AEs)
10. Duration of hospitalisation in participants prior to allo-SCT
11. Rate of CRMRD- after two cycles of induction therapy and pre-transplant
12. Proportion of participants proceeding to allo-SCT
13. Day 100 transplant-related mortality (TRM) in participants proceeding to allograft
14. 2-year overall survival (OS) and 2-year relapse-free survival (RFS) in allografted participants
15. 2-year cumulative incidence of relapse (CIR) in allografted participants
16. CIR in the treated arms
17. Survival post allo-SCT
18. Transfusion independence
19. Time to transfusion independence
20. Health-related QoL throughout the study

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Previous key secondary outcome(s):

Safety, efficacy and tolerability of TAG/CLAD/VEN/LDAC combination therapy (experimental arm) versus standard of care IC (control arm) as measured by:
1. Overall Survival
2. Complete response (CR)
3. Composite CR (CR/CRi) rate
4. The overall response rate (defined as the proportion of patients with either CR, CRi, or

morphologic leukaemia-free state [MLFS])
5. Proportion of participants achieving MRD negativity (CRMRD-)
6. Duration of CR
7. Duration of CR/CRi
8. Day 60 treatment-related mortality
9. Incidence of >CTCAE Grade 3 non-haematological adverse events (AEs)
10. Duration of hospitalisation in participants prior to allo-SCT
11. Proportion of participants proceeding to allo-SCT
12. Day 100 transplant-related mortality (TRM) in participants proceeding to allograft
13. 2-year overall survival (OS) and 2-year relapse-free survival (RFS) in allografted participants
14. 2-year cumulative incidence of relapse (CIR) in allografted participants
15. Transfusion independence
16. Time to transfusion independence
17. Health-related QoL throughout the study

Completion date
01/10/2031

Eligibility

Key inclusion criteria
1. Adverse risk AML according to European Leukaemia Net (ELN) 2022 criteria (Döhner, et al., 2022), aged 18 years or older
2. Intermediate risk AML according to ELN 2022 criteria (Döhner, et al., 2022), aged 50 years or older
3. Evidence of CD123 expression on myeloid blast population
4. The participant is deemed by the treating physician to be fit for intensive chemotherapy
5. Eastern Cooperative Oncology Group (ECOG) performance status 0–2
6. Adequate renal, liver, and cardiac function
7. Participant agrees to use an adequate and medically accepted method of contraception throughout the study and for the required contraceptive period if they or their sexual partner are female-born of childbearing potential
8. Negative pregnancy test within 2 weeks prior to randomisation

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Mixed

Lower age limit
18 Years

Upper age limit
100 Years

Sex

All

Total final enrolment
0

Key exclusion criteria
Current key exclusion criteria as of 06/02/2026:
1. Have received previous cytotoxic chemotherapy (intensive or non-intensive), targeted therapies, hypomethylating agents, or venetoclax for the treatment of AML — except:
1.1. Hydroxycarbamide to control elevated white blood cell (WBC) count
1.2. Lenalidomide, Imetelstat, or luspatercept for the treatment of Myelodysplasia
2. Blastic transformation of chronic myeloid leukaemia (CML)
3. Clinical suspicion of active central nervous system (CNS) involvement with AML
4. Presence of a FLT3-ITD mutation or an NPM1 mutation during initial rapid diagnostic evaluation
5. Presence of a concurrent malignancy requiring active treatment (see Section 4.2 for exceptions)
6. Diagnosis of acute promyelocytic leukaemia (APL)
7. Known active, chronic or uncontrolled infections with human immunodeficiency virus (HIV), hepatitis B virus (HBV) or hepatitis C virus (HCV)
8. Significant disease or medical conditions, as assessed by the Investigator, which would substantially increase the risk-benefit ratio of participating in the study, including but not limited to:
8.1. History of myocardial infarction within 6 months of randomisation
8.2. Presence of unstable angina, cerebrovascular accident (CVA), transient ischemic attack (TIA), uncontrolled diabetes mellitus, significant active infections, and congestive heart failure (NYHA Class III–IV) within 3 months of randomisation
9. History of Wilson's disease or other copper-metabolism disorder
10. Pre-existing liver impairment with known cirrhosis
11. History of any of the following: drug-induced severe cutaneous adverse reaction (SCAR) including, but not limited to, Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN), or drug reaction with eosinophilia and systemic symptoms (DRESS), or dose-limiting immune-mediated reactions
12. Active infection, recently exposed to, or existing chicken pox or herpes zoster infection
13. Judgement by the local Investigator that the participant should not participate in the study, if the participant is unlikely to comply with study procedures, restrictions and requirements
14. Concomitant use of:
14.1. Any strong or moderate CYP3A inhibitors, except posaconazole or voriconazole
14.2. Note that participants subsequently enrolled/randomised to Part 1/Part 2 Arm B would be required to discontinue voriconazole, and instead receive posaconazole, prior to commencing treatment with VEN
14.3. Any strong or moderate CYP3A inducers
14.4. Preparations containing St John's Wort
15. Pregnant or lactating participants
16. Female-born participants of childbearing potential, or male-born participants with female partners of childbearing potential, not willing to use adequate contraception during study treatment and for the required contraceptive periods
17. Participants who are unable to swallow tablets whole
18. Unable to understand and therefore to give voluntary consent
19. Known hypersensitivity to any of the IMPs, the metabolites or formulation excipients
20. Current participation in another interventional clinical study. Participants in follow-up who

have not received the interventional treatment within 4 weeks of enrolment/randomisation may enrol.
21. Participants receiving any live vaccine within 4 weeks prior to initiation of study treatments
22. Participants known to require vaccination with a live vaccine during the treatment period or for 3 months after the end of study treatment
23. Participants who have had a major surgery within the 4 weeks prior to the start of treatment
24. Participants with uncontrolled, clinically significant pulmonary disease (e.g. COPD, pulmonary hypertension, etc.) that, in the opinion of the Investigator, would put the subject at significant risk for pulmonary complications during the study
25. Participants who have experienced Grade 3 or Grade 4 capillary leak syndrome (CLS) in the past for any reason.

Previous key exclusion criteria:
1. Have received previous cytotoxic chemotherapy (intensive or non-intensive), targeted therapies, hypomethylating agents, or venetoclax for the treatment of AML — except:
1.1. Hydroxycarbamide to control elevated white blood cell (WBC) count
1.2. Lenalidomide, Imetelstat, or luspatercept for the treatment of Myelodysplasia
2. Blastic transformation of chronic myeloid leukaemia (CML)
3. Clinical suspicion of active central nervous system (CNS) involvement with AML
4. Presence of a FLT3-ITD mutation or an NPM1 mutation during initial rapid diagnostic evaluation
5. Presence of a concurrent malignancy requiring active treatment (see Section 4.2 for exceptions)
6. Diagnosis of acute promyelocytic leukaemia (APL)
7. Known newly diagnosed or uncontrolled HIV, hepatitis B, or hepatitis C infection
8. Significant disease or medical conditions, as assessed by the Investigator, which would substantially increase the risk-benefit ratio of participating in the study, including but not limited to:
8.1. History of myocardial infarction within 6 months of randomisation
8.2. Presence of unstable angina, cerebrovascular accident (CVA), transient ischemic attack (TIA), uncontrolled diabetes mellitus, significant active infections, and congestive heart failure (NYHA Class III–IV) within 3 months of randomisation
9. History of Wilson’s disease or other copper-metabolism disorder
10. Pre-existing liver impairment with known cirrhosis
11. Concomitant use of:
11.1. Any strong or moderate CYP3A inhibitors, except posaconazole or voriconazole
11.2. Any strong or moderate CYP3A inducers
11.3. Preparations containing St John’s Wort
12. Pregnant or lactating participants
13. Participants who are unable to swallow tablets whole
14. Participants receiving any live vaccine within 4 weeks prior to initiation of study treatment
15. Participants known to require vaccination with a live vaccine during the treatment period or for 3 months after the end of study treatment

Date of first enrolment
30/11/2026

Date of final enrolment
01/06/2029

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
Churchill Hospital
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Study participating centre
University College London Hospital
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Study participating centre
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Study participating centre
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Study participating centre
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Sponsor information

Organisation
DIDACT Foundation

Funder(s)

Funder type
Industry

Funder Name
Stemline Therapeutics

Results and Publications

Individual participant data (IPD) sharing plan
All data generated or analysed during this study will be included in the subsequent results publication

IPD sharing plan summary
Published as a supplement to the results publication