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Goldilocks - determining if personalised drug monitoring of fludarabine in children and young adults with acute lymphoblastic leukaemia who are undergoing CAR-T therapy is feasible and can improve outcome whilst minimising toxicity

Submission date 20/09/2025	**Recruitment status** Not yet recruiting	[X] Prospectively registered [_] Protocol
Registration date 30/10/2025	**Overall study status** Ongoing	[_] Statistical analysis plan [_] Results
Last Edited 03/12/2025	**Condition category** Cancer	[_] Individual participant data [X] Record updated in last year

Plain English summary of protocol

Background and study aims

Acute lymphoblastic leukaemia (ALL) is a type of blood cancer that primarily affects about 400 young people a year in the UK. For around 90% of these the outlook is positive, but 15-20% of these patients may experience a relapse. Relapsed ALL patients are challenging to treat, and each relapse typically leads to poorer outcomes.

One promising treatment for these difficult cases is CAR T-cell therapy. This therapy involves modifying the patient's own immune cells (T-cells) in a lab so they can better target and fight the cancer. Before administering CAR T-cell therapy, it is necessary to deplete the patient's normal T-cells. This is done by giving them chemotherapy drugs called fludarabine and cyclophosphamide in the week leading up to the therapy.

Recent research indicates that administering an optimal level of fludarabine can reduce the chance of relapse within a year after CAR T-cell therapy to less than 30%. In contrast, if fludarabine levels are too low, the likelihood of relapse jumps to at least double and in one study up to 100%. Unfortunately, around 40% of patients receiving CAR T-cell therapy have insufficient fludarabine levels.

To address this, we aim to personalise the dosing of fludarabine for CAR T-cell therapy patients in real time, ensuring they receive the optimal levels needed for effective treatment.

Who can participate?

Patients less than 25 years old receiving fludarabine and cyclophosphamide as lymphodepletion before CD19 CAR T-cell therapy

What does the study involve?

Blood samples taken on the first day will be sent to the Newcastle Cancer Centre Pharmacology Group (NCCPG) to measure fludarabine levels, allowing us to adjust doses for the following days to achieve optimal levels.

What are the possible benefits and risks of participating?
This research aims to enhance treatment outcomes by personalising fludarabine dosing and may help the NHS by reducing treatment failures, thus saving money and resources. The benefit of this study for the individual suffering from life-threatening r/r B-ALL is the potential for a cure by optimizing CAR T outcomes. The median overall survival has been reported as 7.5 months in paediatric patients with r/r ALL. In addition, affected patients often report poor general and mental health and functional impairment. Children and young people with B-ALL experience a range of debilitating symptoms including fatigue feeling weak or breathless, bony pain, fevers, easy bruising/bleeding, headaches and visual loss. It also significantly affects the ability of both the patient and their caregivers to do daily tasks and maintain employment or education. While tisagenlecleucel has changed the treatment landscape for r/r B ALL, the outcome of patients with treatment failure is dismal. Real-time monitoring has the potential to reduce treatment failure associated with fludarabine underexposure (< 14mg/L.h) and toxicities associated with overexposure. Patients treated at centres within the UK will obtain an immediate benefit from this study.
Additional blood sampling is unlikely to cause inconvenience to the participant as they will have a central line and already be an inpatient in the hospital due to undergoing the lymphodepletion prior to their CAR-T treatment. Samples for fludarabine monitoring will be taken at the same time as clinical samples where possible.
Discussion of the trial with the participants and their families may cause distress at what is already a very difficult time for them. It is felt that this would be minimal as the potential benefits of the trial far outweigh the risks.
There is also a risk of breach of confidentiality. For the trial patient personal data is pseudo anonymised with the patients date of birth the only information recorded on patient registration forms. Following registration, patients are allocated a unique study number (study ID number), a copy of which will be sent to the relevant site for their records. All further communication regarding the patient, and clinical information collected on the patient will use the study ID number only. Data will be retained at the Newcastle Cancer Centre Pharmacology Group (NCCPG) and will be subject to the Data Protection Act 2018.

Where is the study run from?
Newcastle upon Tyne Hospitals NHS Foundation Trust (UK)

When is the study starting and how long is it expected to run for?
September 2025 to September 2028

Who is funding the study?
The Little Princess Trust (UK)

Who is the main contact?
1. Dr Shelby Barnett, shelby.barnett@nhs.net
2. Dr Geoff Shenton, geoff.shenton1@nhs.net

Plain English summary under review with external organisation

Contact information

Type(s)
Scientific

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Additional identifiers

Integrated Research Application System (IRAS)
1012095

Protocol serial number
NCCPG/2025/01

Central Portfolio Management System (CPMS)
68955

Study information

Scientific Title
Implementation of real-time fludarabine therapeutic drug monitoring analysis in the United Kingdom for relapsed/refractory B-cell acute lymphoblastic leukaemia patients undergoing chimeric antigen receptor (CAR) T-cell therapy

Acronym
Goldilocks

Study objectives

Primary objectives:
To investigate if it is feasible to modify the dosing of fludarabine given to patients prior to their CAR T treatment so that the levels they achieve will reduce toxicity whilst improving how effective the treatment is.
Fludarabine is only given for 4 days before the chimeric antigen receptor (CAR) T-cell treatment - so we want to see if it's possible to measure the amount of fludarabine in the patient's blood on day 1 and get results back to the doctors so that they can change the dose of fludarabine given (if needed) on either days 3 or 4 to make sure the patient achieves the right amount of the drug.

Secondary objectives:
To investigate if the levels of fludarabine a patient achieves by changing the dose given has any effect on how well their CAR T Treatment works. We will compare the information gained, with information already available on patients who have not had their fludarabine levels adjusted.
We will investigate if there is any link between the concentrations of cyclophosphamide in the patients' blood with how well their CAR T treatment worked.
We will also look at how well the patients white blood cells have been destroyed by the fludarabine and cyclophosphamide prior to their CAR T treatment and how much toxicity the patient has experienced.

Ethics approval required
Ethics approval required

Ethics approval(s)
approved 27/10/2025, North West - Liverpool Central Research Ethics Committee (2 Redman Place, Stratford, London, E20 1JQ, United Kingdom; -; liverpoolcentral.rec@hra.nhs.uk), ref: 25/NW/0306

Study design
Single-arm trial

Primary study design
Interventional

Study type(s)
Efficacy

Health condition(s) or problem(s) studied
Acute lymphoblastic leukaemia

Interventions
A single-arm trial including real-time therapeutic drug monitoring of fludarabine to ensure all patients achieve a target cumulative exposure of 16-20mg/L.h during the lymphodepletion regimen. Observation pharmacokinetic analysis will be performed for cyclophosphamide. Patients will be followed up for 1 year following CAR T-cell therapy.

Intervention Type
Drug

Phase
Phase IV

Drug/device/biological/vaccine name(s)
Fludarabine, cyclophosphamide

Primary outcome(s)
Feasibility of implementation is measured by the proportion of enrolled patients in whom real-time PK-guided fludarabine monitoring and dose adjustments have been successfully implemented at the close of the study

Key secondary outcome(s))
Secondary and exploratory:
Benefit of implementation is measured by assessing the impact of fludarabine and cyclophosphamide exposure on patient outcomes compared to a historical cohort with no dose intervention at 1 year following CAR T cell infusion:
1. Overall survival (OS)
2. Event-free survival (EFS)
3. Leukaemia-free survival (LFS) (*Stringent EFS)
4. Cumulative incidence of relapse
5. Cumulative incidence of loss of B cell aplasia
6. Cumulative incidence of cytokine relapse syndrome (CRS)
7. Cumulative incidence of grade 3-4 immune effector cell-associated neurotoxicity syndrome (ICANS)
8. The associated haematological toxicity

Mechanistic:
The impact of fludarabine exposure and cytokine profile at 0, +7 and +14 days will be measured by patient outcomes (as above) at 1 year following CAR T cell infusion

Completion date
01/09/2028

Eligibility

Key inclusion criteria
1. Age >28 days and <25 years old
2. Receiving fludarabine (30 mg/m2/day for 4 days) & cyclophosphamide (500 mg/m2/day for 2 days) as lymphodepletion prior to CD19 CAR T-cell therapy*
3. Capacity for the patient or the patient’s guardian/ legal representative to provide written informed consent

*This indicates the standard lymphodepletion regimen, dose modifications from this standard regimen for renal impairment and young age do not impact the eligibility for inclusion

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Mixed

Lower age limit
28 days

Upper age limit
25 years

Sex
All

Total final enrolment
0

Key exclusion criteria
1. Contraindications which would prevent fludarabine or cyclophosphamide being used as lymphodepletion agents
2. Pregnancy or breastfeeding in patients
3. Inclusion in other interventional CAR T trials

Date of first enrolment
01/02/2026

Date of final enrolment
31/08/2028

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
Great North Children's Hospital
Royal Victoria Infirmary
Newcastle upon Tyne
England
NE1 4LP

Study participating centre
Northern Centre for Cancer Care
Freeman Road
High Heaton
Newcastle upon Tyne
England
NE7 7DN

Study participating centre
Royal Manchester Children's Hospital
Oxford Road
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M13 9WL

Study participating centre
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Study participating centre
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Sponsor information

Organisation

Newcastle upon Tyne Hospitals NHS Foundation Trust

ROR
https://ror.org/05p40t847

Funder(s)

Funder type
Charity

Funder Name
Little Princess Trust

Alternative Name(s)
The Little Princess Trust, LPT

Funding Body Type
Private sector organisation

Funding Body Subtype
Trusts, charities, foundations (both public and private)

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study will be available upon request from Shelby Barnett (shelby.barnett@nhs.net) on completion of the trial. No identifiable patient information will be shared. Data will be shared for academic research purposes only and will be at the discretion of the Newcastle Cancer Centre Pharmacology Group (NCCPG).

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes