

A study to test the safety, tolerability and effect of ZI-MA4-1 for patients with locally advanced or metastatic solid malignancies

Submission date 19/12/2025	Recruitment status Recruiting	☒ Prospectively registered ☐ Protocol
Registration date 01/05/2026	Overall study status Ongoing	☐ Statistical analysis plan ☐ Results
Last Edited 29/07/2026	Condition category Cancer	☐ Individual participant data ☒ Record updated in last year

Plain English summary of protocol

Background and study aims

This study will recruit patients with the following cancer indications: ovarian cancer, squamous non-small cell lung cancer, synovial sarcoma and head and neck cancer, with inoperable locally advanced or metastatic solid tumours. Currently, these patients have a poor prognosis and a relatively short overall survival. There is a lack of meaningful, effective therapies available that improve the outcome for these patients. The treatment being investigated in this study is ZI-MA4-1, an allogeneic cell therapy product. This is the first time ZI-MA4-1 will be administered to humans. The study is planned to consist of two parts (A and B). Part A includes up to four dose escalation cohorts and aims to identify the maximum tolerated dose of ZI-MA4-1 and give insight into the recommended Phase 2 dose (RP2D). Part B consists of an expansion cohort and is designed to further evaluate the RP2D identified in Part A across one or more indications. The study procedures and eligibility criteria will be the same for participants in Parts A and B, except for the dose level of ZI-MA4-1.

Who can participate?

Adult patients aged with inoperable locally advanced or metastatic solid tumours.

What does the study involve?

All participants will receive ZI-MA4-1 administered via IV infusion 3 times per 33-day treatment cycle at their assigned dose. It is planned that all participants in the study will get a minimum of one treatment cycle and up to a maximum of two treatment cycles. Prior to receiving ZI-MA4-1, participants will be given fludarabine and cyclophosphamide to temporarily reduce lymphocytes in the body (lymphodepletion).

The total duration for participation is approximately 5 years & 2 months.

What are the possible benefits and risks of participating?

The possible benefit of participating is unknown. It is not known if taking part in this study will improve patients' condition and there is no guarantee of any such improvement. It is possible that the study medication may address the underlying cause or some symptoms of their cancer.

However, it is not known for how long any benefit may last and any benefit may not be long-lasting or permanent.

This is the first time the study medication (ZI-MA4-1) has been given to humans, so the risks are unknown.

ZI-MA4-1 is a cell therapy. Different types of similar treatments have been used before to treat cancer.

Some of the known side effects from this type of treatment are:

- Cytokine release syndrome
- Confusion, dizziness, or headaches, or (in rare cases) neurological damage
- Feeling or being sick, and loss of appetite
- Tiredness
- Changes to the levels of certain substances in your blood.

Risks associated with lymphodepletion include:

- High chance of infection due to the reduction in white blood cells (neutropenia)
- Feeling tired, weak and breathless due to a reduction in red blood cells (anaemia)
- Bruising, bleeding gums or nosebleeds due to a reduction in the platelets (thrombocytopenia), which help blood clot
- Fever

Other study procedure risks include:

- biopsy risks (pain or discomfort where the sampling tool enters)
- blood sample risks (minor pain, bleeding, and/or bruising)
- CT scan risks (feeling unwell due to contrast dye)

Where is the study run from?

Zelluna Immunotherapy AS

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

May 2026 to December 2032

Who is funding the study?

Zelluna Immunotherapy AS

Who is the main contact?

Medical and Product Information Enquiry, ctinfo@zelluna.com

Contact information

Type(s)

Principal investigator

Contact name

Dr Fiona Thistlethwaite

ORCID ID

<https://orcid.org/0000-0002-4832-7008>

Contact details

The Christie NHS Foundation Trust
Wilmslow Road, Withington
Manchester
United Kingdom
M20 4BX

Type(s)

Public, Scientific

Contact name

None Medical and Product Information Enquiry .

Contact details

Ullernchausséen 64
Oslo
Norway
0379

-

ctinfo@zelluna.com

Additional identifiers**Integrated Research Application System (IRAS)**

1013415

Central Portfolio Management System (CPMS)

71922

Study information**Scientific Title**

A phase 1, dose-escalation, open-label study, evaluating the safety and tolerability of ZI-MA4-1, a TCR-NK cell therapy, in HLA A*02:01 positive patients with inoperable, locally advanced, or metastatic MAGE-A4 expressing solid malignancies

Acronym

ZIMA-101

Study objectives

Primary objective:

To evaluate the safety and tolerability of ZIMA41 when administered to human leukocyte antigen (HLA)-A*02:01 positive participants with advanced solid tumour malignancies expressing melanomaassociated antigen (MAGE)A4

Secondary objective:

Safety:

1. To determine the maximum tolerated dose (MTD) and the recommended Phase 2 dose (RP2D)

of ZI-MA4-1

2. Long term safety

3. To identify the minimum biologically active dose (MBAD)

Efficacy:

1. To evaluate the efficacy of ZI-MA4-1 in HLA-A*02:01 positive participants with MAGE-A4 expressing solid malignancies

Pharmacokinetics:

1. Evaluation of persistence of ZI-MA4-1 in the blood

Ethics approval required

Ethics approval required

Ethics approval(s)

Approved 09/02/2026, North East – York Research Ethics Committee (2 Redman Place, Stratford, London, E20 1JQ, United Kingdom; -; york.rec@hra.nhs.uk), ref: 26/NE/0005

Primary study design

Interventional

Allocation

N/A: single arm study

Masking

Open (masking not used)

Control

Uncontrolled

Assignment

Single

Purpose

Treatment

Study type(s)

Efficacy, Safety

Health condition(s) or problem(s) studied

Ovarian cancer, squamous non-small-cell lung cancer, synovial sarcoma, head and neck cancer.

Interventions

This is an open-label, first-in-human, Phase 1 dose-escalation study (3+3 design) evaluating the safety and tolerability of ZI-MA4-1, an allogeneic TCR-NK cell therapy, in patients with advanced solid tumours. There are no randomised treatment arms.

All participants receive lymphodepleting chemotherapy consisting of cyclophosphamide (300 mg /m²/day) and fludarabine (30 mg/m²/day), administered intravenously prior to study treatment. ZI-MA4-1 is administered intravenously in three doses on Days 1, 4 and 8 of Cycle 1. Dose levels are evaluated sequentially in a 3+3 dose-escalation design to determine the maximum tolerated dose and/or recommended Phase 2 dose. An optional second treatment cycle may be

administered following safety review.

Participants are hospitalised during the dosing period for monitoring.

The primary evaluation period includes a dose-limiting toxicity (DLT) assessment window through Day 28 of Cycle 1. Participants are subsequently followed for response and safety for up to 2 years after first dose, with long-term follow-up for up to 5 years.

No randomisation is performed in this study.

Intervention Type

Drug

Phase

Phase I

Drug/device/biological/vaccine name(s)

ZI-MA4-1

Primary outcome(s)

1. Safety and tolerability of ZI-MA4-1 from baseline through end of study visit measured using clinical assessments and adverse event reporting recorded in the eCRF, including dose-limiting toxicities (DLTs), treatment-emergent adverse events (TEAEs), and treatment-related adverse events (TRAEs), assessed at baseline through Day 28 and throughout the study up to 5 years

Key secondary outcome(s)

Completion date

01/12/2032

Eligibility

Key inclusion criteria

Pre-Screening Inclusion Criteria

1. Participant has signed the Pre-Screening ICF
2. Participant is HLA-A*02:01 positive (assessed by the hospital's own laboratory vendor)
3. Participant's tumour(s) show expression of the MAGE-A4 protein of $\geq 30\%$ tumour cells at $\geq 2+$ intensity (assessed by sponsors central lab)
4. Participant meets, or is expected to comply with all Screening Inclusion Criteria

Screening Inclusion Criteria (Part A and Part B)

5. Participant must be capable of giving signed informed consent as described in Section 10.3 which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.
6. 18 to ≤ 75 years of age, at the time of signing the informed consent.
7. Histopathological or cytological diagnosis of inoperable Locally Advanced or Metastatic malignant disease: ovarian cancer, squamous non-small cell lung cancer (NSCLC), synovial sarcoma or head and neck cancer.
8. No approved therapy with demonstrated clinical benefit is indicated or available to treat the patients, or the patient is intolerant of or has refused standard of care therapy. Patients should not have been withdrawn from any treatment (considered necessary for the clinical management of the patient) with the only purpose being fulfilling the study eligibility criteria.
9. Patients must have documented imaging confirmed disease progression while on or within 6 months after the end of the most recent therapy.

10. Patients must have received ≥ 2 prior lines of cancer therapy except for patient with synovial sarcoma for whom ≥ 1 prior lines of cancer therapy are required.

11. Patients have measurable disease according to RECIST v1.1 criteria.

12. An ECOG PS of 0 or 1 with no deterioration over the previous 2 weeks, and an anticipated life expectancy of >3 months following lymphodepletion.

13. Adequate haematological, renal, and hepatic function within 7 days of the start of lymphodepletion

14. Patients must not have evidence of rapidly progressive disease that would preclude patient from completing at least 1 cycle of ZI-MA4-1 treatment.

The lymphodepletion regimen comprises cyclophosphamide and fludarabine which are teratogenic and may impair fertility, appropriate contraception and pregnancy precautions are required.

Contraceptive guidance is consistent with the respective Summaries of Product Characteristics (SmPCs) for cyclophosphamide and fludarabine. Contraceptive use by participants or participants' partners should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies

15. Female participants are eligible to participate if they are not pregnant or breastfeeding, and one of the following conditions applies:

- o Participant is a woman of nonchildbearing potential (WONCBP) as defined in Section 13.1.1

- OR
- o WOCBP must have negative pregnancy test and agree to use a highly effective contraceptive method Note: Breastfeeding is prohibited during treatment and for at least 6 months following the last dose of ZIMA41. See Section 8.3.5 for pregnancy testing schedule.

The investigator should evaluate the potential for contraceptive method failure (e.g., noncompliance, recently initiated).

16. A WOCBP must have a negative hCG serum pregnancy test at screening and a negative urine /serum pregnancy test within 24 hours of lymphodepletion (requirements for pregnancy testing during and after the study are provided in Section 8.3.5).

- o If a urine test cannot be confirmed as negative (e.g., an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.

- o The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

17. Male participants are eligible to participate if they agree to the following during the intervention period and for at least 6 months after the last dose of ZIMA41:

- o Refrain from donating sperm or fresh unwashed semen;

AND in addition, either:

- Be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a longterm and persistent basis) and agree to remain abstinent;

OR

- Agree to use contraception/barrier as follows:

Use a male condom when having sexual intercourse with a woman of childbearing potential (WOCBP) who is not currently pregnant. Female partners must use an additional highly effective contraceptive method with a failure rate of $<1\%$ per year as described in Section 13.1.2.

18. Able and willing to give consent for biopsy collection. An exception may be granted if the biopsy procedure poses a safety risk to the patient or if the lesion's location precludes the collection of tumour tissue; however, such an exception requires prior consultation with the sponsor

Healthy volunteers allowed

No

Age group

Mixed

Lower age limit

18 Years

Upper age limit

75 Years

Sex

All

Total final enrolment

0

Key exclusion criteria**Pre-Screening Exclusion Criteria**

1. Participant currently meets, or is expected to meet, any of the Main Exclusion Criteria.

Screening Exclusion Criteria (Part A and Part B)

1. Patients have received any prior cellular or gene therapy.
2. Receiving experimental investigational products within 4 weeks of lymphodepletion.
3. Recent therapies prior to lymphodepletion including:
 - a. Within 4 weeks or 5 halflives (whichever is longer) of the start of lymphodepletion: biologic agents (such as monoclonal antibodies including marketed drugs), anti-cancer immunotherapy including monoclonal antibodies against PD-1 receptor or ligand.
 - b. Within 4 weeks of lymphodepletion: Bone/soft tissue directed palliative radiotherapy,
 - c. Within 3 weeks of lymphodepletion: Cytotoxic chemotherapy or loco-regional therapy, liver directed radiation therapy within 3 months.
 - d. Within 2 weeks of lymphodepletion: Systemic corticosteroids, other types of radiotherapy not stated above, or any other immunosuppressive therapy.
 - e. Any other therapy, which in the opinion of the investigator presents as a contra indication to lymphodepletion.
 - f. Treatment with biologic agents (such as monoclonal antibodies including marketed drugs) within 4 weeks or 5 halflives (whichever is longer) of the start of lymphodepletion in this study.
4. Residual toxicities ≥ 2 CTCAE grade due to prior therapy, that in the opinion of the investigator may interfere with study conduct.
5. Patients have had any other active malignancy besides the tumour under study within 3 years prior to screening except for in situ removal of basal cell carcinoma or adequately treated cervix carcinoma in-situ.
6. Active or documented history of autoimmune disease or any other diseases requiring immunosuppressive therapy or corticosteroid therapy (defined as >10 mg/day prednisone or equivalent). Physiological replacement, topical, and inhaled steroids are permitted.
7. Significant CNS disorders including Uncontrolled seizures and CNS metastases, within 3 months of enrolment.
8. Myocardial infarction, cardiac angioplasty or stenting, cardiac arrhythmia requiring medication, unstable angina, New York Heart Association Class II or greater congestive heart failure, cardiac atrial or ventricular lymphoma involvement, or other clinically significant cardiac disease within 6 months of enrolment.
9. Active fungal, bacterial viral, or other infection requiring intravenous antibiotic, antifungal, or antiviral medication within 7 days prior to lymphodepletion, including acute symptoms of COVID-

19 infection or positive covid test.

10. Received or planned to receive a live vaccine ≤ 6 weeks before the planned start date of lymphodepletion.

11. Severe or uncontrolled medical condition (e.g., severe chronic obstructive pulmonary disease, interstitial lung disease, severe Parkinson's disease, active inflammatory bowel disease) or psychiatric condition, which in the opinion of the investigator would interfere with study activities.

12. Active bleeding diatheses, including but not limited to therapeutic anticoagulation, and treatment with major surgery within 28 days before lymphodepletion (minor surgical procedures such as lymph node biopsy/excision or catheter placement are permitted).

13. Patients have significant immunosuppression

14. Known significant hepatic or biliary abnormalities. Active infection with hepatitis B (HbsAg positive), hepatitis C (anti-HCV positive). A history of hepatitis B or hepatitis C is permitted if the viral load is undetectable per quantitative polymerase chain reaction (PCR) and/or nucleic acid testing. Patients that are HbsAg negative but hepatitis B core antibody positive must receive prophylaxis against viral reactivation prior to lymphodepletion therapy. If Hep B core positive and Ag negative then prophylaxis needed.

15. Any medical, psychological, or social condition, drug or alcohol abuse that would make it difficult for the patient to participate in the study and comply with the study procedures, restrictions, and requirements. History of allergic reactions to compounds chemically or biologically similar to cyclophosphamide, fludarabine or other agents used in the study

16. QTc > 450 msec for male participants or > 470 msec for female participants

17. Medical conditions, such as anti-coagulation, which is not suitable for reversal which, at the opinion of the investigator, preclude or make the patient a poor candidate for biopsy

18. Personal history of allergies or intolerance to local anaesthetic.

19. Recent treatment with immunosuppressive agents

20. Residual toxicities ≥ 2 Common Terminology Criteria for Adverse Events (CTCAE) grade due to prior therapy, that in the opinion of the investigator may interfere with study conduct

Date of first enrolment

15/05/2026

Date of final enrolment

01/12/2027

Locations

Countries of recruitment

United Kingdom

England

Study participating centre

The Christie NHS Foundation Trust

550 Wilmslow Road

Withington

Manchester

England

M20 4BX

Study participating centre
The Royal Marsden NHS Foundation Trust
Fulham Road
London
England
SW3 6JJ

Sponsor information

Organisation
Zelluna Immunotherapy AS

Funder(s)

Funder type

Funder Name
Zelluna Immunotherapy AS

Results and Publications

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Not expected to be made available