ISRCTN12595783 https://doi.org/10.1186/ISRCTN12595783

# NG-350A plus chemoradiotherapy for locally advanced rectal cancer

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| **Submission date**<br>19/11/2024 | **Recruitment status**<br>Recruiting | [ ] Prospectively registered<br>[ ] Protocol |
| **Registration date**<br>04/04/2025 | **Overall study status**<br>Ongoing | [ ] Statistical analysis plan<br>[ ] Results |
| **Last Edited**<br>28/01/2026 | **Condition category**<br>Cancer | [ ] Individual participant data<br>[X] Record updated in last year |

## Plain English summary of protocol

Background and study aims
Worldwide, almost 10 million deaths in 2020 were estimated to be due to cancer. Despite the introduction of multiple new therapies, the overall burden of cancer incidence and mortality is growing worldwide and there remains a critical need for new and effective treatments.

NG-350A is an experimental gene therapy medicinal product derived from a virus. The added gene is information in the form of deoxyribonucleic acid (DNA) required for making proteins or other molecules. This additional drug is called an 'anti-CD40 antibody' and is designed to help the immune system to attack cancer cells:

1. The virus (study drug) infects only tumour cells
2. The virus (study drug) forces tumour cells to produce another drug (anti-CD40 antibody)
3. This additional drug is designed to help activate the immune system
4. Activated immune cells then further attack the cancer cells.

NG-350A can multiply in and kill cancer cells, but it is not expected to have an effect on normal cells.

Who can participate?
Patients with locally advanced rectal cancer.

What does the study involve?
The study will include approximately 30 patients with locally advanced rectal cancer (LARC) that will all receive NG-350A. The trial is designed so that the initial anti-cancer effect of NG-350A plus standard chemotherapy and radiotherapy can be tested during a short active study treatment period of 12 weeks, while hospital sites can give additional standard-of-care treatment during the trial follow-up period.

The study will determine the number of patients that achieve a complete response in 12, 18 and 36 weeks after starting NG-350A. The study will also investigate what side effects people have and what percentage of people experience these.

The estimated duration of follow up during the study from joining to the end is at least 1 year up to a maximum follow-up of three years.

What are the possible benefits and risks of participating?
Benefits:
Not provided at time of registration
Risks:
It is not possible to predict all side-effects but based on prior studies/literature. Kidney damage, breathing problems, intestinal blockages, abnormal blood clotting tests (not associated with bleeding/clotting) and cytokine release syndrome (see ICF) are considered important risks in this study. Successful mitigation strategies have been established to reduce the risk of these side-effects (e.g. not enrolling patients most at risk, extra monitoring & modifying dosing schedules). In the first stage of this study, patients will be enrolled one at a time with gaps of 14 days between at least the first two patients in a cohort to allow safety to be closely assessed. Capecitabine and radiotherapy is approved for treating the cancer type in this study; further unknown risks may occur when it is combined with NG-350A. Prior studies with related viral vectors + capecitabine have not identified new risks. A complete list of potential risks and side effects are provided in the ICF. Patients will be closely monitored during the study and if The patient's condition worsens or disease progression occurs, study treatment will be discontinued. As relatively frequent visits are required, visit windows are in place to allow patients to attend at the most convenient times for them; some visits may be by phone.
Patients need to have routine blood draws (max 95 mL drawn per visit), CT or MRI scans and biopsies.
These are all common procedures which would likely be carried out as part of the patient's routine care.
All procedures will be carried out by trained professionals.
Biopsies can cause pain and so the area to be biopsied is numbed with a local anaesthetic and painkillers may be prescribed. The effect of NG-350A on babies before they are born, or on breastfeeding children is not known. Patients who are pregnant, planning pregnancy or are breastfeeding, will not be included in the study. A number or requirements are in place to prevent pregnancy.

Where is the study run from?
Akamis Bio Ltd. (UK)

When is the study starting and how long is it expected to run for?
November 2024 to December 2028

Who is funding the study?
Akamis Bio Ltd. (UK)

Who is the main contact?
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# Additional identifiers

**Integrated Research Application System (IRAS)**
1011106

**ClinicalTrials.gov (NCT)**
NCT06459869

**Protocol serial number**
NG-350A-03

Central Portfolio Management System (CPMS)
65610

# Study information

## Scientific Title
A multicentre, open-label, non-randomized, phase 1b trial of NG-350A, a tumour-selective anti-CD40-expressing adenoviral vector, in combination with chemoradiotherapy in locally advanced rectal cancer (FORTRESS)

## Acronym
Fortress NG-350A-03

## Study objectives
Primary objective:
To determine the proportion of patients achieving a complete response to NG-350A in combination with CRT

Secondary objectives:
1. To characterize the safety and tolerability of NG-350A in combination with CRT in patients with LARC
2. To further characterize the anti-tumour effects of NG-350A in combination with CRT

## Ethics approval required
Ethics approval required

## Ethics approval(s)
approved 28/01/2025, North East- York Research Ethics Committee (2 Redman Place, Stratford, London, E20 1JQ, United Kingdom; +44 207 104 8079; york.rec@hra.nhs.uk), ref: 24/NE/0216

## Study design
Interventional non randomized

## Primary study design
Interventional

## Study type(s)
Efficacy, Safety

## Health condition(s) or problem(s) studied
Medical condition: Histologically confirmed clinical stage II-III adenocarcinoma of the rectum with at least one pre-specified risk factor for recurrence

## Interventions
The study will include approximately 30 patients with locally advanced rectal cancer (LARC) that will all receive NG-350A. The trial is designed so that the initial anti-cancer effect of NG-350A plus standard chemotherapy and radiotherapy can be tested during a short active study treatment period of 12 weeks, while hospital sites can give additional standard-of-care treatment during the trial follow-up period.

### Intervention Type
Drug

### Phase
Phase I

### Drug/device/biological/vaccine name(s)
NG-350A

### Primary outcome(s)
Proportion of patients achieving a complete response in 12, 18 and 36 weeks after starting NG-350A.

### Key secondary outcome(s))
12, 18 and 36 weeks, and at study end (other timepoints may be utilized):
1. Incidence of AEs, SAEs, AEs leading to discontinuation of study treatment or trial discontinuation, and AEs resulting in death
2. Incidence of AEs causing delays to planned CNCT (patients undergoing CNCT only)
3. Incidence of AEs causing delays to planned surgery (patients undergoing surgery only)
4. Proportion of patients completing CRT without a clinically relevant delay (within 7 days of planned intervention timing)
5. Proportion of patients completing 3 cycles of NG-350A
6. Clinical response outcome 12, 18, and 36 weeks after initiating NG-350A plus CRT (cCR, ncCR, poor response)
7. mrTRG 12, 18, and 36 weeks after initiating NG-350A plus CRT (response [Grade 1-2] vs non-response [Grade 3-5])

### Completion date
31/12/2028

## Eligibility

### Key inclusion criteria
Disease-specific criteria
1. Histologically confirmed adenocarcinoma of the rectum.
2. Locally advanced disease (clinical stage II-III based on pelvic MRI) selected by a multidisciplinary team for treatment with neoadjuvant CRT (which may be followed by CNCT to comprise planned TNT).
- Note: Patients with oligometastatic disease are permitted provided that the site-specific multidisciplinary team deems them suitable for radical treatment/chemoradiation.
- Note: While considered unlikely, tumours with a location or size likely to present a risk of intestinal obstruction if tumour flare occurs require close monitoring for tumour changes or obstruction, but do not exclude patient participation.
3. At least one of the following risk factors for recurrence:
3.1. Compromised circumferential resection margin/MRF+ disease, and/or
3.2. Any regional N2 disease, and/or
3.3. cT3a-d, N0-2 tumours of the lower rectal third (within 5 cm of the anal verge), and/or
3.4. Extramural vascular invasion (EMVI+).
4. Confirmed microsatellite stable (MSS)/proficient mismatch repair (pMMR) status.

Patient-specific criteria
5. Provide written informed consent to participate.
6. Willing and able to comply with the protocol-scheduled biopsy, all protocol-specified visits, and examinations for the duration of the trial.
7. Aged 18 years or over on day of signing informed consent.
8. ECOG Performance Status 0 or 1.
9. Must not be pregnant or breastfeeding.
9.1. Female patients of childbearing potential must have a negative serum pregnancy test ≤24 hours before the first dose of study treatment.
10. Patients who are sexually active (with either sex) must agree to use a highly effective method of contraception (where they or their partner are of childbearing potential), as well as barrier contraception (irrespective of childbearing potential) during treatment and for at least 6 months following the last dose of study treatment (see Appendix 2, Contraception). Additionally, all patients (male or female) must ensure any male partners use a male condom with spermicide.
10.1. Patients must be willing to refrain from egg or sperm donation during treatment and for at least 6 months following the last dose of study treatment.

Organ function criteria
11. Adequate lung reserve, defined as oxygen saturation on ambient air at sea level ≥95% or the equivalent based on altitude (i.e. ≥90% at 5000 feet). This should be assessed ≤10 days prior to first dose.
12. Adequate renal function (assessed ≤10 days prior to first dose):
12.1. Creatinine ≤1.5 × upper limit of normal (ULN).
12.1.1. Patients with creatinine >1.5 × institutional ULN remain eligible if measured or calculated creatinine clearance is ≥45 mL/minute (per institutional standard) and considered fit for CRT.
12.2. Proteinuria dipstick ≤1+ or spot albumin:creatinine ratio (ACR) ≤300 mg/g or a 24-hour urinary protein assessment <1 g/24 h at screening and baseline assessment.
12.2.1. Patients with a dipstick >1+ are permissible for inclusion with a spot ACR ≤300 mg/g or 24-hour urinary protein assessment of <1 g/24 h.
12.2.2. Patients with a spot ACR >300 mg/g are permissible for inclusion with a 24-hour urinary protein assessment of <1 g/24 h.
13. Adequate hepatic function (assessed ≤10 days prior to first dose):
13.1. Total bilirubin ≤1.5 × ULN OR direct bilirubin ≤1 × ULN (for patients with Gilbert's syndrome ULN for total bilirubin is considered to be <3.0 mg/mL).
13.2. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤2.5 × ULN range.
14. Adequate bone marrow/haematological function (assessed ≤10 days prior to first dose):
14.1. Absolute neutrophil count (ANC) ≥1.5 × 10^9/L (≥1500/μL).
14.2. Platelets ≥100 × 10^9/L (100,000/μL).
14.3. Haemoglobin ≥90 g/L (9 g/dL) or ≥5.6 mmol/L.
14.3.1. Haemoglobin criteria must be met without packed red blood cell transfusion within the prior 2 weeks. Patients can be on stable dose of erythropoietin (≥ approximately 3 months).

## Participant type(s)
Patient

## Healthy volunteers allowed
No

## Age group
Adult

## Sex
All

## Total final enrolment
0

## Key exclusion criteria
Disease-specific criteria
1. Recurrent rectal cancer.
2. Distant metastatic disease not amenable to radical treatment/chemoradiation.

Prior medical history exclusions
3. Other prior malignancy active within the previous 3 years, except for local or organ confined early-stage cancer that has been definitively treated with curative intent, does not require ongoing treatment, has no evidence of residual disease, and has a negligible risk of recurrence and is therefore unlikely to interfere with the primary and secondary endpoints of the trial, including response rate and safety.
4. Known dihydropyridine dehydrogenase (DPYD) deficiency.
5. Prior or planned allogeneic or autologous bone marrow or tissue/organ transplantation.
6. Splenectomy (patients with prior partial resection remain eligible if the Investigator considers splenic function to not be significantly compromised).
7. Active infections requiring antibiotics or physician monitoring, or recurrent fevers (>38.0˚C [100.4°F]) associated with a clinical diagnosis of active infection. Infections requiring systemic therapy within 1 week of the anticipated first dose of study drug.
8. Known history of hepatitis B infection or human immunodeficiency virus (HIV) infection, or active hepatitis C infection (no testing for HIV, hepatitis B, or hepatitis C is required unless mandated by local health authority).
9. Active autoimmune disease that has required systemic therapy in the past 2 years, immunocompromised status in the opinion of the Investigator, or current treatment with systemic immunosuppressive therapy.
9.1. Patients with vitiligo, type I diabetes mellitus, asthma/atopy, residual hypothyroidism due to autoimmune disease (which only requires hormone replacement therapy), or conditions not expected to recur in the absence of an external trigger are permitted to enrol if they comply with all other eligibility criteria. Use of inhaled corticosteroids, topical corticosteroids, local steroid injection, steroid eye drops, or oral corticosteroids (≤10 mg/day prednisone equivalent) is allowed.
10. History of prior Grade 3–4 acute kidney injury or other clinically significant renal impairment.
11. Any ongoing Common Terminology Criteria for Adverse Events (CTCAE) Grade ≥2 coagulation abnormality/coagulopathy.
12. History of clinically significant interstitial lung disease (including pneumonitis).
13. Infectious or inflammatory bowel disease in the 3 months before the first dose of study treatment.
14. Any clinically significant cardiovascular, peripheral vascular, cerebrovascular, or thromboembolic event in the last 1 month before the first dose of study treatment.
15. Grade 3 or 4 gastrointestinal bleeding (or risk factors for gastrointestinal bleeding), haemoptysis, or any history of bleeding requiring transfusion or hospitalization in the last 1 month before the first dose of study treatment.
16. Major surgery in the 14 days before the first dose of study treatment or any surgical wounds that are not fully healed and free of infection or dehiscence.

Prior treatment criteria
17. Any prior surgery for rectal cancer or pelvic radiotherapy.
18. Any other anti-cancer or experimental therapy within the previous 12 months or that is planned during the active study treatment period.
- Note: patients may receive anti-cancer therapy during the follow-up period irrespective of disease progression.
19. Treatment with any other enadenotucirev-based virus (parent virus or transgene-modified variants), or anti-CD40 antibody at any time.
20. Treatment with any coronavirus disease 2019 (COVID-19) vaccine in the 30 days before first dose of study drug, unless confirmed to not be based on an adenoviral vector (e.g. messenger ribonucleic acid [mRNA]-based vaccines, for which only exclusion criterion 21 applies).
21. Treatment with any other vaccine (including non-adenoviral COVID-19 vaccines) in the 7 days before first dose of study drug.
22. Treatment with the anti-viral agents: ribavirin, adefovir, lamivudine, cidofovir, or paxlovid within 10 days prior to the first dose of study treatment; or pegylated interferon (IFN) in the 4 weeks before the first dose of study treatment.
23. Known hypersensitivity to both cidofovir and valacyclovir.

Additional patient exclusions
24. Positive pregnancy test prior to treatment (serum test to be performed ≤24 hours before the first dose of study treatment).
25. Any condition, therapy, laboratory abnormality, or other circumstance that might jeopardize participation for the full duration of the trial, confound trial results, or make participation in the trial not in the best interest of the patient, in the opinion of the treating Investigator.
26. Known psychiatric or substance abuse disorder that would interfere with the patient's ability to cooperate with the requirements of the trial.

### Date of first enrolment
15/02/2025

### Date of final enrolment
30/11/2026

## Locations

### Countries of recruitment
United Kingdom

England

### Study participating centre
**University College London Hospitals NHS Foundation Trust**
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**Study participating centre**
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# Sponsor information

**Organisation**
Akamis Bio Ltd.

# Funder(s)

**Funder type**
Industry

**Funder Name**
Akamis Bio Ltd.

# Results and Publications

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

**IPD sharing plan summary**
Data sharing statement to be made available at a later date