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A first-in-human, phase 1/2, multicenter, open-label, dose escalation, confirmation and expansion study to evaluate the safety, pharmacokinetics and antitumor activity of TH9619 in subjects with advanced solid tumors (ODIN)

Submission date 18/12/2024	**Recruitment status** Recruiting	[X] Prospectively registered [ ] Protocol [ ] Statistical analysis plan [ ] Results [ ] Individual participant data [X] Record updated in last year
Registration date 26/02/2025	**Overall study status** Ongoing	
Last Edited 02/07/2026	**Condition category** Cancer	

Plain English summary of protocol

Background and study aims
This is a Phase 1a (dose escalation)/Phase Ib (dose expansion) single arm study of TH9619 in patients with selected tumor types who have been treated with available standard of care therapies. This study drug, TH9619, was tested in laboratory and animal studies and will now be tested for the first time in humans to evaluate its safety, antitumor activity and pharmacokinetics (PK) in patients. PK is an analysis of how a drug is absorbed, distributed, and eliminated from the body. A single-arm study is one in which the activities of the study drug are not compared to those of another.

Who can participate?
Patients aged 18 years or above, with selected tumor types, who meet the inclusion criteria.

What does the study involve?
The study has two parts (Phase 1a and Phase 1b). Phase 1a is a dose escalation study, a study that determines the best dose of a new drug or treatment. In a dose-escalation study, the dose of the test drug is increased a little at a time in different groups of people until the highest dose that does not cause harmful side effects (maximum tolerated dose [MTD]) is found.
Phase 1b is a dose expansion study, a study in which an additional number of patients are treated at the estimated MTD or minimal reproducibly active dosage (MRAD) in order to collect more data on the antitumor activity and safety of the study drug.
All subjects will be administered weekly infusions (into a vein) on Days 1, 8 and 15 followed by one week without infusion, of a 28-day cycle until disease progression (worsening of cancer) or unacceptable toxicity, or until the study doctor determines that it is no longer in the best interest of the patient to continue on the study. Subjects will be followed for disease

progression and survival status for a maximum of 2 years.
The study drug, TH9619, is a molecule that blocks enzymes inducing cancer cells to be deprived of folate. The blocking of the enzymes occurs only in cancer cells and causes DNA damage and the death of cancer cells. Normal cells are not dependent on this mechanism and are therefore not affected.

What are the possible benefits and risks of participating?
Benefits: Published data from non-clinical studies show that TH9619 has anti-tumor activity, and so it is possible that the cancer will respond positively. However, this cannot be guaranteed, and it is also possible that there is no benefit from this treatment. Even if there might not be a direct benefit from being in this study, participating may help patients get better care in the future
Risks: Data from non-clinical studies indicate that TH9619 should be safe within the dose range selected for this study.
Possible side effects:
- Anemia due to vitamin B deficiency. The study doctor will check vitamin B levels on a regular basis and will provide treatment.
- The subjects will undergo on-study imaging assessments exposing them to radiation having the potential to increase a subject's risk of getting cancer.
- Additional risks with the imaging assessments include allergies to contrast fluids and specific attention to dosing of contrast fluids needs to be given to subjects with renal failure.
- Common risks with tumor biopsies include bleeding, pain and discomfort, and infections. Less common risks include scarring and damage to surrounding tissues, allergic reactions to anesthesia and in cases of lung biopsies, pneumothorax.
The subjects will be informed of the risks related to these procedures and given the advanced stage of cancer and the frequency of assessments these subjects will have at the clinic, they will be sufficiently monitored for any risks experienced from these procedures.
- Sensitivity to sunlight. It is recommended to avoid direct sunlight and wear a hat and sunscreen SPF 50.

Where is the study run from?
One-carbon Therapeutics AB

When is the study starting and how long is it expected to run for?
August 2025 to September 2027

Who is funding the study?
One-carbon Therapeutics AB

Who is the main contact?
Prof Ruth Plummer, ruth.plummer@newcastle.ac.uk

Contact information

Type(s)
Public, Scientific

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Type(s)
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Additional identifiers

ClinicalTrials.gov (NCT)
NCT07151040

Clinical Trials Information System (CTIS)
2024-519639-40

Integrated Research Application System (IRAS)
1011422

Central Portfolio Management System (CPMS)
70892

Protocol serial number
TH9619-0101

Study information

Scientific Title
A first-in-human, phase 1/2, multicenter, open-label, dose escalation, confirmation and expansion study to evaluate the safety, pharmacokinetics and antitumor activity of TH9619 in subjects with advanced solid tumors (ODIN)

Acronym
ODIN

Study objectives

Primary objective:
To assess the overall safety and tolerability profile and determine the MTD/maximum administered dose and RP2DS (recommended dose(s)) of TH9619 as monotherapy in patients with selected solid tumors.

Secondary objectives:
1. To characterize the pharmacokinetics (PK) of TH9619 after repeated administration.
2. To determine the minimal reproducibly active dosage (MRAD) of TH9619 in subjects with advanced cancer.
3. To assess the anti-tumor activity of TH9619.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 20/02/2025, West Midlands - Edgbaston Research Ethics Committee (2 Redman Place, Stratford, E20 1JQ, United Kingdom; 0207 104 81 55; edgbaston.rec@hra.nhs.uk), ref: 25WM0008

Primary study design
Interventional

Study design
Interventional non randomized

Study type(s)
Efficacy, Safety

Health condition(s) or problem(s) studied
Advanced solid tumors

Interventions
Phase 1a - DOSE ESCALATION
Description:
Single arm dose escalation of TH9619 as monotherapy.
TH9619 will be administered as an intravenous infusion. Multiple doses will be tested.
Dosing will be given per body size (m2) applying the DuBois formula.
Subjects will be administered weekly infusions on Days 1, 8 and 15 of a 28-day cycle.

Phase 1b - DOSE EXPANSION
Description:
Single arm dose expansion of TH9619 as monotherapy in selected tumor types.
The objectives and endpoints for the expansion cohort(s) will be defined in a protocol amendment,
once data from Phase 1a are available.

Intervention Type
Drug

Phase
Phase I

Drug/device/biological/vaccine name(s)
TH9619

Primary outcome(s)
1. Frequency of treatment-emergent adverse events (TEAEs) is measured using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v5.0 at baseline, C1D1, safety follow-up visit (EOT), or early withdrawal
2. Severity of treatment-emergent adverse events (TEAEs) is measured using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v5.0 at baseline, C1D1, safety follow-up visit (EOT), or early withdrawal
3. Causality of treatment-emergent adverse events (TEAEs) is measured using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v5.0 at baseline, C1D1, safety follow-up visit (EOT), or early withdrawal
4. Frequency of serious adverse events (SAEs) is measured using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v5.0 at baseline, C1D1, safety follow-up visit (EOT), or early withdrawal
5. Severity of serious adverse events (SAEs) is measured using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v5.0 at baseline, C1D1, safety follow-up visit (EOT), or early withdrawal
6. Causality of serious adverse events (SAEs) is measured using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v5.0 at baseline, C1D1, safety follow-up visit (EOT), or early withdrawal
7. Clinically significant findings on clinical laboratory tests at baseline, C1D1, safety follow-up visit (EOT), or early withdrawal
8. Clinically significant findings on vital signs parameters at baseline, C1D1, safety follow-up visit (EOT), or early withdrawal
9. Clinically significant findings on electrocardiogram (ECG) at baseline, C1D1, safety follow-up visit (EOT), or early withdrawal
10. Clinically significant findings on physical examinations at baseline, C1D1, safety follow-up visit (EOT), or early withdrawal
11. Tolerability is assessed by treatment-emergent adverse events (TEAEs) leading to dose interruption, reduction, and/or discontinuation using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v5.0 at baseline, C1D1, safety follow-up visit (EOT), or early withdrawal
12. Adverse events (AEs) from first dosing on C1D1 up until the safety follow-up visit (EOT), or early withdrawal
13. Serious adverse events (SAEs) from the time of the informed consent being signed up until 90 days after EOT, or 30 days after EOT if new anticancer therapy is initiated
14. Adverse events of special interest (AESIs) from the time of the informed consent being signed up until 90 days after EOT, or 30 days after EOT if new anticancer therapy is initiated

Key secondary outcome(s)
1. Maximum concentration (Cmax) is measured using pharmacokinetic (PK) analysis at baseline, C1D1, and at specified timepoints post-dose
2. Time to maximum concentration (Tmax) is measured using pharmacokinetic (PK) analysis at baseline, C1D1, and at specified timepoints post-dose
3. Area under the curve (AUC) is measured using pharmacokinetic (PK) analysis at baseline, C1D1, and at specified timepoints post-dose
4. Maximum percentage tumor shrinkage from baseline is measured using imaging (e.g., CT/MRI) at baseline and at specified intervals during treatment
5. Objective Response Rate (ORR) is measured using Response Evaluation Criteria in Solid

Tumors (RECIST) v1.1 by Investigator assessment at baseline and at specified intervals during treatment
6. Duration of response (DOR) is measured using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 by Investigator assessment at baseline and at specified intervals during treatment
7. Progression Free Survival (PFS) is measured using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 by Investigator assessment at baseline and at specified intervals during treatment
8. Clinical benefit rate (CBR) is measured using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 by Investigator assessment at baseline and at specified intervals during treatment
9. Time to response (TTR) is measured using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 by Investigator assessment at baseline and at specified intervals during treatment
10. Overall Survival (OS) is measured using survival status assessments at baseline and at specified intervals up to 2 years
11. Disease progression is measured using imaging (e.g., CT/MRI) and clinical assessments at baseline and at specified intervals up to 2 years
12. Survival status is measured using follow-up assessments at baseline and at specified intervals up to 2 years

Completion date
30/09/2027

Eligibility

Key inclusion criteria
Current inclusion criteria as of 14/05/2025:

1. Willing and able to give written informed consent for participation in the study before performance of any study-specific screening procedures
2. Male or female subject aged ≥18 years of age
3. Histopathologically confirmed CRC, HNSCC, NSCLC, and gastric cancer with metastatic and/or unresectable disease (not amenable to treatment with curative intent), except for:
3.1. NSCLC with EGFR driver mutations including but not limited to del19, L858R
3.2. Gastrointestinal Stromal cell Tumors (GIST)
3.3. CRC with MSI-H
4. Treatment with at least one prior line of cytotoxic systemic therapy for metastatic /unresectable disease, including but not limited to pemetrexed, capecitabine, MTX, 5-FU, tegafur, oxaliplatin, irinotecan, cisplatin, and carboplatin
5. Prior systemic neoadjuvant or adjuvant therapy will be considered as one line of therapy if radiological progression occurred either during that treatment or within 6 months of completion
6. Progressive disease as per investigator assessment after latest given therapy
7. At least one measurable lesion by RECIST v1.160
8. Must have tumor lesion(s) or metastases amenable to biopsy, excluding bone metastases, as confirmed by a radiologist, if appropriate, and as deemed safe by the investigator
9. Mandatory pre-treatment and on-treatment biopsies (except for subjects treated at the lowest dose levels within the accelerated titration
10. Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1
11. Life expectancy of at least 12 weeks as judged by the investigator
12. The following safety laboratory parameters must be met during screening (within 15 days) and also immediately before first IMP administration:
12.1. Total bilirubin ≤1.5 x upper limit of normal (ULN), or unconjugated bilirubin of ≤ 3 x ULN in subjects diagnosed with Gilbert’s syndrome

12.2. Aspartate aminotransferase (ASAT) and alanine aminotransferase (ALAT) ≤ 3.0 x ULN (≤5 x ULN allowed in patients with metastases in the liver)
12.3. Renal function: Estimated creatinine clearance by eGFR ≥50 mL/min
12.4. Absolute neutrophil count (ANC) ≥1500 cells/mm³ (1.5 x 10^9/L)
12.5. Platelet count ≥100000 cells/mm³ (100 x 10^9/L)
12.6. Hemoglobin ≥90 g/L
12.7. Albumin levels 3.4-5.4 g/dL in the normal range of institutional standards
12.8. Folic acid levels 3.1-17.5 ng/mL (7.0-39.7 nmol/L) in the normal range of institutional standards
12.9. Vitamin B12 levels of >250 pg/mL (>185 pmol/L)
13. Contraceptive measures
13.1. Women of childbearing potential (WOCBP) must:
13.1.1. Have a negative pregnancy test within 1 week before first dose of study drug
13.1.2. Use highly effective method(s) of birth control consistently and correctly during the study and for at least 6 months after the last dose of treatment
13.1.3. Agree to not donate eggs (ova, oocytes) for the purposes of assisted reproduction during the study and for at least 6 months after the last study drug administration
13.1.4. Agree to not breastfeed and not plan to become pregnant during the study and for at least 6 months after the last study drug administration
13.2. Males who are sexually active must:
13.2.1. Agree to use a condom with spermicidal foam/gel/film/cream/suppository during the study and for at least 90 days after the last study drug administration
13.2.2. Agree to not donate sperm during the study and for at least 90 days after the last study drug administration
13.2.3. Have no plan to father a child during the study and for at least 90 days after the last study drug administration

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Previous inclusion criteria:

1. Willing and able to give written informed consent for participation in the study before performance of any study-specific screening procedures
2. Male or female subject aged ≥18 years of age
3. Histopathologically confirmed CRC, HNSCC, NSCLC, and gastric cancer with metastatic and/or unresectable disease (not amenable to treatment with curative intent), except for:
3.1. NSCLC with EGFR driver mutations including but not limited to del19, L858R
3.2. Gastrointestinal Stromal cell Tumors (GIST)
3.3. CRC with MSI-H
4. Treatment with at least one prior line of cytotoxic systemic therapy for metastatic /unresectable disease, including but not limited to pemetrexed, capecitabine, MTX, 5-FU, tegafur, oxaliplatin, irinotecan, cisplatin, and carboplatin
5. Prior systemic neoadjuvant or adjuvant therapy will be considered as one line of therapy if radiological progression occurred either during that treatment or within 6 months of completion
6. Progressive disease as per investigator assessment after latest given therapy
7. At least one measurable lesion by RECIST v1.160
8. Must have tumor lesion(s) or metastases amenable to biopsy, excluding bone metastases, as confirmed by a radiologist, if appropriate, and as deemed safe by the investigator
9. Mandatory pre-treatment and on-treatment biopsies (except for subjects treated at the lowest dose levels within the accelerated titration
10. Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1
11. Life expectancy of at least 12 weeks as judged by the investigator

12. The following safety laboratory parameters must be met during screening (within 15 days) and also immediately before first IMP administration:
12.1. Total bilirubin ≤1.5 x upper limit of normal (ULN), or unconjugated bilirubin of ≤ 3 x ULN in subjects diagnosed with Gilbert's syndrome
12.2. Aspartate aminotransferase (ASAT) and alanine aminotransferase (ALAT) ≤ 3.0 x ULN (≤5 x ULN allowed in patients with metastases in the liver)
12.3. Renal function: Estimated creatinine clearance by eGFR ≥50 mL/min
12.4. Absolute neutrophil count (ANC) ≥1500 cells/mm³ (1.5 x 10^9/L)
12.5. Platelet count ≥100000 cells/mm³ (100 x 10^9/L)
12.6. Hemoglobin ≥90 g/L
12.7. Albumin levels 3.4-5.4 g/dL in the normal range of institutional standards
12.8. Folic acid levels 3.1-17.5 ng/mL (7.0-39.7 nmol/L) in the normal range of institutional standards
12.9. Vitamin B12 levels of >250 pg/mL (>185 pmol/L)
13. Contraceptive measures
13.1. Women of childbearing potential (WOCBP) must:
13.1.1. Have a negative pregnancy test within 1 week before first dose of study drug
13.1.2. Use highly effective method(s) of birth control consistently and correctly during the study and for at least 90 days after the last dose of treatment
13.1.3. Agree to not donate eggs (ova, oocytes) for the purposes of assisted reproduction during the study and for at least 90 days after the last study drug administration
13.1.4. Agree to not breastfeed and not plan to become pregnant during the study and for at least 90 days after the last study drug administration
13.2. Males who are sexually active must:
13.2.1. Agree to use a condom with spermicidal foam/gel/film/cream/suppository during the study and for at least 90 days after the last study drug administration
13.2.2. Agree to not donate sperm during the study and for at least 90 days after the last study drug administration
13.2.3. Have no plan to father a child during the study and for at least 90 days after the last study drug administration

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Mixed

Lower age limit
18 Years

Upper age limit
99 Years

Sex
All

Total final enrolment
0

Key exclusion criteria

1. History of any clinically significant disease or disorder which, in the opinion of the Investigator, may either put the subject at risk because of participation in the study, or influence the results or the subject's ability to participate in the study
2. Any clinically significant illness, medical/surgical procedure or trauma within 4 weeks of first administration of IMP, as judged by the Investigator
2.1. Any toxicities from prior treatment(s) (incl surgery, RT and systemic therapies) grade >2 by NCI CTCAE v5.0 criteria prior to first dose of study treatment
2.2. Clinically significant cardiovascular disease, defined as any of the following:
2.2.1. Major ECG abnormalities (e.g., symptomatic or sustained atrial or ventricular arrhythmias, second- or third-degree atrioventricular block, clinically significant bundle branch blocks, clinically significant ventricular hypertrophy)
2.2.2. Including dihydropyrimidine dehydrogenase polymorphisms (DDP) and fluoropyrimidine toxicity
3. Primary brain malignancy or known, untreated central nervous system (CNS) or leptomeningeal metastases, or symptoms suggesting CNS involvement for which treatment is required. Screening of asymptomatic patients without history of CNS metastases is not required. Subjects with previously treated brain metastases are eligible, provided they have not experienced a seizure, had no significant change in neurological status, and have not required steroids for management of brain metastases in the last 2 weeks prior to enrollment
4. Active known second malignancy with the exception of any of the following:
4.1. Adequately treated basal cell carcinoma, squamous cell carcinoma of the skin, or in situ cervical cancer
4.2. Adequately treated Stage 1 cancer from which the patient is currently in remission and has been in remission for ≥2 years
4.3. Low-risk prostate cancer with a Gleason score <7 and a prostate-specific antigen (PSA) level <10 ng/mL
4.4. Any other cancer from which the patient has been disease-free for ≥3 years. Malignancy (other than the one diagnosed) within the past 5 years, with the exception of any other malignancy that has been treated with no signs of relapse within 3 years (e.g., superficial melanoma, low grade cervix cancer)
5. Any planned major surgery within the duration of the study (i.e., from screening to end of study visit)
6. Active and uncontrolled infection requiring intravenous antibiotic or antiviral treatment within 2 weeks prior to first IMP administration
7. Subjects with known active HBV (screening for HBV is not required for subjects who do not have a history of HBV, unless required by local regulations) and with treated/chronic HBV are eligible provided they meet the following criteria:
7.1. Subjects with positive HBsAg must be on permitted suppressive antiviral therapy prior to first IMP administration, remain on the same antiviral treatment throughout the study and should follow local standards for continuation of therapy after completion of IMP
7.2. Note: while HBsAg-negative, anti-HBc–positive subjects are at lower risk of HBV reactivation compared with HBsAg-positive subjects, risk of HBV reactivation should be considered in all subjects and the need for anti-HBV prophylaxis should be carefully assessed prior to the initiation of the IMP
7.3. Undetectable HBV DNA ≤ 14 days of C1D1
7.4. Note: subjects who are HBsAg positive and HBV DNA positive (detectable) will be excluded
8. Known hepatitis C or human immunodeficiency virus (HIV) infection
8.1. Subjects with known positivity for HIV and who have well-controlled HIV infection/disease
8.1.1. Subject with a history of Kaposi Sarcoma and/or multicentric Castleman Disease is excluded
8.2. Subjects with known active HCV and previously treated for HCV

9. Prolonged QTcF (> 450 ms), or any clinically significant abnormalities in the resting ECG at the time of screening, as judged by the Investigator
10. History of severe allergy/hypersensitivity or ongoing allergy/hypersensitivity, as judged by the Investigator, or history of hypersensitivity to drugs with a similar chemical structure or class to TH9619
11. Any anti-cancer therapy (chemotherapy, targeted agents, radiotherapy, immunotherapy) within 28 days or 5 times the half-life (whichever is shorter) before study treatment
12. Planned treatment or treatment with another investigational drug within 28 days or 5 times the half-life such as other anti-cancer therapy prior to first IMP administration. Subjects consented and screened but not dosed in previous Phase 1 studies will not be excluded
13. Current alcohol and/or drug abuse, as judged by the Investigator
14. The Investigator considers the subject unlikely to comply with study procedures, restrictions and requirements

Date of first enrolment
22/08/2025

Date of final enrolment
01/03/2027

Locations

Countries of recruitment
United Kingdom

France

Spain

Study participating centre
Newcastle University
-
Newcastle-upon-Tyne
England
NE1 7RU

Study participating centre
Sir Bobby Robson Cancer Trials Research Centre
Northern Centre for Cancer Care, Level 2, Freeman Hospital
Newcastle-upon-Tyne
England
NE7 7DN

Sponsor information

Organisation
One-carbon Therapeutics AB

Funder(s)

Funder type
Industry

Funder Name
One-carbon Therapeutics AB

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated and analysed during the current study will be held in Clinical.Net, a proprietary system of the One-carbon Therapeutics AB delegate OPIS s.r.l., based in Italy. During the study data will be held by One-carbon Therapeutics AB, processed and analysed by OPIS s.r.l. and shared with the investigators and safety committee members involved in the study. The data that will be shared prior to the committee meetings will be through a password protected repository and available to the committee members during the course of the study, for their continuous assessment of data affecting participant safety. All participants in the study will have been informed of the type of data that is being collected and that their data is being pseudonymised, with limited access to identifying data for the sponsor and its delegates.

IPD sharing plan summary
Published as a supplement to the results publication, Stored in non-publicly available repository