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A first in human study to investigate the safety and tolerability of CV6-168 in combination with anti-cancer treatments in patients with advanced cancer.

Submission date
03/10/2023

Recruitment status
Recruiting

Registration date
06/02/2024

Overall study status
Ongoing

Last Edited
13/03/2025

Condition category
Cancer

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

Plain English Summary
Background and study aims
CV6-168 is a new experimental medicine to be given to humans for the first time. The study goal is to determine whether giving CV6-168 in combination with other anti-cancer treatments is a safe, tolerable, and effective treatment for patients with cancer. Different doses of CV6-168 and different anti-cancer treatments will be tested to see if there is an optimal dose and combination.

Who can participate?
Patients aged at least 18 years old with a diagnosis of an advanced cancer

What does the study involve?
This is a modular design study which consists of Module 1 and an optional Module 2. Each Module consists of Part A, B (Optional for Module 2), C (Optional) and D (Optional). Module 1 with Part A and Part B will be investigated first for the optimal combination doses of CV6-168 with other anti-cancer treatments.
The expected duration of the trial for each patient is up to 34 weeks for Part A and up to 31 weeks for Part B. Patients in both Parts A and B will be permitted 12 treatment cycles, based on the availability of IMP. Additional treatment with CV6-168 would be based on recommendation by the Investigator in agreement with the Sponsor. Part C will be investigated for dose optimisation and Part D will be investigated for dose expansion.

There will be substantial protocol amendments to provide additional modules.
Further Modules may explore:
1. Combinations with other standard-of-care anti-cancer treatments.
2. The effect of food on the bioavailability of CV6-168.
3. A switch of formulation of CV6-168.

The end of the study is defined as the last visit of the last patient participating in the study.

What are the possible benefits and risks of participating?
Blood Sampling:
Blood collection either by direct venepuncture or indwelling cannula may cause mild pain & bruising at the collection site. The placement of an indwelling catheter is proposed to minimise these effects for rapid PK sampling. Very rarely, a vein blockage or a small nerve injury can occur, resulting in numbness & pain which will resolve with time.

Harm to the unborn child:
Women of childbearing potential, any patient who is pregnant, breastfeeding or intending to become pregnant will not be eligible for participation. Women of childbearing potential, patients must agree to use two highly effective forms of contraception with their partner using a condom (if applicable) during the study & for at least 6 months following the last dose of study medication.
Male patients with partners of childbearing potential, must not father a child during this study or for a safety period of 6-months following the last dose of study medication. Patients must agree to use two highly effective forms of contraception with their partner using a condom (if applicable) during the study & for at least 6 months following the last dose of study medication. Male patients who have been sterilised or engage in non-vaginal intercourse should use a condom to prevent exposure of semen to any partner (male or female) until 6 months following the last dose of study medication. Patients must not donate sperm until 6 months following the last dose of study medication.

ECG:
A small number of people have a skin reaction to the stick electrode patches that attach to the chest for the electrocardiogram. Skin irritation usually disappears when patches are removed. Some men may need to have some chest hair shaved to ensure adequate contact between the electrodes & skin.

Echocardiogram:
During an echocardiogram, the patient may feel sick and dizzy, and experience some chest pain. There’s a small chance of the procedure triggering an irregular heartbeat or heart attack. Patients will be monitored carefully during the procedure, which will be stopped if there are any signs of problems.

Cardiac MRI:
A cardiac MRI is an optional assessment which can be used instead of an echocardiogram. It may involve an injection of contrast medium, which can cause some side effects, such as headache, feeling sick (nausea) or dizziness. These effects are most common, but only happen in less than 1 in every 200 patients & generally do not last long.

CT/MRI scans:
For tumour imaging, Computed Tomography (CT) is the preferred imaging modality, but Magnetic Resonance Imaging (MRI) or CT/MRI is also accepted. Contrast CT and/or MRI chest, abdomen and pelvis (CAP) should be performed, but non-contrast is accepted if patients cannot tolerate contrast. Brain CT/MRI will be performed only if clinically indicated. Generally, the amount of radiation exposure during each CT scan is the same as between a few months and a few years of exposure to natural radiation from the environment (including the sun). It's thought exposure to radiation during each CT scan could slightly increase the chances of developing cancer many years later, although this risk is very small (< 1 in 2,000). MRI uses radio waves and a strong magnetic field which is medically safe to provide images of internal organs and tissues. Radiation is not used for MRI, there is no risk of exposure to radiation during an MRI procedure.

If the patients have any metal parts in their body, there is a risk of interference, including heating & injury. Some patients may have a ‘closed in’ feeling while inside the imaging machine (s), the contrast dye may contain iodine which some people are allergic to, it may also make the patient feel sick or faint, and may cause pain, warmth, swelling, bruising, and/or a small blood clot or infection at the injection site.

Biopsies:
Most types of biopsies are painless once the anaesthetic starts to work, although this depends on where the sample is taken. Patients may experience nausea, vomiting & dull aches, which can be treated with painkillers. Risks of bleeding & infection can be treated on the doctor's or surgeon's advice. Mild pain is usually experienced, and the severity of pain may vary according to the site where the biopsy is being performed.

CV6-168:
CV6-168 is a new medicine that is being given to humans for the first time & there is limited information on what the potential side effects of CV6-168 could be in humans. CV6-168 has been considered to be safe to proceed into testing in humans, there have been several preclinical studies performed & concluded no major safety concerns. CV6-168 stimulates the immune system, patients may experience a general body reaction from the infusion. This may include difficulty breathing, low blood pressure, high blood pressure, headache, skin rashes and increased temperature. The study doctor will follow patients closely during the treatment and treat them accordingly if any reaction should occur.

Where is the study run from?
NHS Greater Glasgow and Clyde, Beatson West of Scotland Cancer Centre (UK)

When is the study starting and how long is it expected to run for?
September 2023 to December 2026

Who is funding the study?
CV6 Therapeutics (NI) Ltd

Who is the main contact?
Professor Richard Wilson, Richard.h.wilson@glasgow.ac.uk
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Contact information

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Principal Investigator

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number
1007859

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
CV6168-23-01-01, IRAS 1007859, CPMS 55993

Study information

Scientific Title
A first in human modular, open-label, phase I/IIa study to evaluate the safety, tolerability, pharmacokinetics and anti-tumour activity of the specific dUTPase inhibitor CV6-168 in combination with anti-cancer treatments in patients with advanced malignancies.

Study hypothesis
Core Study Primary Objectives:
1. To characterise the safety and tolerability of CV6-168 in combination with other anti-cancer agents.

Module 1: Part A Primary Objectives:
1. To establish an MTD/MFD of CV6-168 in combination with 5-FU infusions and bolus 5-FU and folinic acid for further development.
2. To characterise the safety and tolerability of CV6-168 in combination with 5-FU infusions and bolus 5-FU and folinic acid.

Module 1: Part B Primary Objectives:
1. To establish RP2D(s) and/or schedule(s) of CV6-168, in combination with bolus 5-FU and 5-FU infusions and folinic acid, for further development.

Core Study Secondary Objectives:
1. To establish the PK profile of CV6-168 alone and in combination with 5-FU infusions and bolus 5-FU and folinic acid.
2. To evaluate preliminary anti-tumour activity of CV6-168 in combination therapy with 5-FU infusions and bolus 5-FU and folinic acid.

Module 1: Part A Secondary Objectives:
1. Define dose(s)/schedule(s) of CV6-168 to be explored, in combination with 5-FU infusions and bolus 5-FU and folinic acid, in Part B of the module.

Ethics approval required
Ethics approval required

Ethics approval(s)
Approved 02/02/2024, South Central - Berkshire Research Ethics Committee (2 Redman Place, Stratford, London, E20 1JQ, United Kingdom; +44 (0)207 104 8178; berkshire.rec@hra.nhs.uk), ref: 23/SC/0366

Study design
First-in-human modular open-label study

Primary study design
Interventional

Secondary study design
Non randomised study

Study setting(s)
Hospital

Study type(s)
Safety, Efficacy

Participant information sheet

Condition
Advanced malignancies

Interventions
o This is a non-randomised study
o IMPs (Part A) = CV6-168, Folinic Acid, 5-FU

CV6-168: p.o.(dose range 50-900 mg)
• Cycle 1 on Days 8-10, 15-17 three times daily
• All other cycles on Days 1-3, three times daily

5-FU, i.v. bolus 400mg/m2 and i.v. infusion 2400mg/m2
• Cycle 1
o i.v. bolus Day 1, Day 15
o i.v. infusion Day 1-3, 15-17
• All other cycles

o i.v. bolus Day 1
o i.v. infusion Day 1-3

Folinic acid, i.v. infusion 350mg (d. l folinic acid) or 175mg (l folinic acid)
• Cycle 1
o Day 1, Day 15
• All other cycles
o Day 1

o Cycle duration is 4 weeks for Cycle 1 and 2 weeks for all other cycles. Each cycle starts the day after the previous cycle ends.
o Patients are followed for safety, tolerability, PK, efficacy and PD assessments as detailed in the Outcomes

Intervention Type
Drug

Pharmaceutical study type(s)
Pharmacokinetic, Pharmacodynamic, Dose response, Pharmacogenetic

Phase
Phase I

Drug/device/biological/vaccine name(s)
CV6-168 20 mg, 50 mg and 100 mg capsule [CV6-168]

Primary outcome measure
Core Study Primary Endpoints:
The following safety parameters will be assessed:
• Ongoing evaluation of AEs during treatment and follow up using the most recent version of NCI CTCAE
• Laboratory parameters
• Physical examination, vital signs and ECOG performance status
• 12-lead ECG and echocardiography

Module 1: Part A Primary End Points
1. Evaluation of DLT or MFD
2. The following safety parameters will be assessed:
• Ongoing evaluation of AEs during treatment and follow up using the most recent version of NCI CTCAE
• Laboratory parameters
• Physical examination, vital signs and ECOG performance status
• 12-lead ECG and echocardiography

Module 1: Part B Primary End Points
1. Evaluation of safety, tolerability, PK, PDc and tumour response data

AEs & SAEs from the time of informed consent up to & including 30 days after the last dose of study drug administered must be reported

Laboratory parameters
Screening, C1: D1, 8 & 15 (Part A only), Subsequent cycles: D1 & EOT

Physical examination, Vital signs and ECOG
Screening, C1: D1, 8 (Part A only), 15 & 22 (Part A only), Subsequent cycles: D1, 8 & EOT

12-lead ECG (in triplicate)
Screening, C1: D1, 8 & 15 (Part A only), Subsequent cycles: D1 & EOT

Echocardiography
Screening, Subsequent cycles: D1 (6 weeks after first echo)

DLT for Part A only
C1: D1, 2, 3, 8, 9, 10, 15, 16, 17, 22 and up to 28
C2: D1, 2, 3, 8 and up to 14

PK
C1: D1, 2, 3, 4, 8 (Part A only), 9 (Part A only), 10, 11 (Part A only), 15 (Part A only), 16, 17 & 18 (Part A only), Subsequent cycles (2, 4, 7 & 11): D1, 2, 3, 4 & EOT

Secondary outcome measures

Core Study Secondary Endpoints:
1. PK profile, potentially including but not limited to, supporting PK variables such as maximum concentration (Cmax), area under the curve (AUC), clearance, time to reach maximum observed concentration (tmax), elimination half-life (t1/2)
2. Tumour markers (patients with relevant tumour types) and assessment of anti-tumour activity using RECIST v1.1

Module 1: Part A Secondary End Points
1. Evaluation of safety, tolerability, PK and tumour response data

PK
C1: D1, 2, 3, 4, 8 (Part A only), 9 (Part A only), 10, 11 (Part A only), 15 (Part A only), 16, 17 & 18 (Part A only), Subsequent cycles (2, 4, 7 & 11): D1, 2 & 3, 4 and EOT

PDc
C1: D1, 2, 8 (Part A only), 9 (Part A only), 15 & 16 (Part A only),
C2: D1, 2
C3: D1, 2
C4: D1, 2

Tumour markers
Screening, C1: D15 (Part A only), Subsequent cycles: D1 and EOT

Tumour assessment
Screening, C1: D1 (C1D1 + every 8 weeks), Subsequent cycles: D1, EOT & FU

Overall study start date

29/09/2023

Overall study end date

29/12/2026

Eligibility

Participant inclusion criteria

Module 1 Inclusion Criteria: Inclusion Criteria for Part A (Dose Escalation) & Part B (Dose Expansion)
To be eligible for inclusion into this study, each patient must fulfil the following inclusion criteria within 28 days before C1D1:
1. Patients must be aged at least 18 years.
2. An ECOG Performance Score of 0-1.
3. A life expectancy of at least 12 weeks.
4. Patients must be able to swallow oral medications.
5. Women of childbearing potential (WOCBP) must have a negative serum test (minimum sensitivity 25 IU/L or equivalent units of HCG) during screening and within 48 hours prior to the start of investigational product and agree to have regular urine pregnancy testing throughout the trial. WOCBP must agree to use two effective forms of contraception (one highly effective form plus a barrier method) throughout the study and until 6 months after the last study medication administration. A woman is considered as WOCBP, i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. Post-menopause is defined as:
5.1. Amenorrhea ≥ 12 consecutive months without another cause, or
5.2. For women with irregular menstrual periods and on hormone replacement therapy (HRT), a documented serum follicle stimulating hormone (FSH) level >35 mIU/mL; however, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
5.3. For women who have had surgical bilateral oophorectomy (with or without hysterectomy) at least 6 weeks before screening. In the case of bilateral oophorectomy alone, the female patient is considered of non-childbearing potential only when the reproductive status of the patient has been confirmed by FSH hormone level assessment.
6. Male patients must agree to use a barrier method of contraception [condom plus spermicide] and refrain from donating sperm from the first administration of IMP, throughout the study and until 6 months after the last IMP administration. Men with partners of child-bearing potential must also be willing to ensure that their partner uses a highly effective method of contraception for the same duration. Men with pregnant or lactating partners should be advised to use barrier method contraception (e.g., condom plus spermicidal gel) to prevent exposure to the foetus or neonate.
7. Histological or cytological diagnosis of malignancy.
8. Clinical or pathological diagnosis of an advanced disease.
9. Adequate bone marrow function as defined by:
9.1. Absolute neutrophil count (ANC) ≥1.5 × 109/L
9.2. Platelet count ≥100 × 109/L
9.3. Haemoglobin ≥9 g/dL (transfusion allowed to achieve this but must be stable afterwards).
10. Adequate hepatic function as evidenced by a serum bilirubin ≤1.5X the upper limit of the normal range (ULN) (unless due to Gilbert's syndrome in which case up to 3 × ULN is permissible) and serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels ≤2.5X the ULN for the reference lab (≤5X the ULN if there is evidence of hepatic involvement by malignant disease).
11. Adequate renal function assessed as glomerular filtration rate ≥50 mL/min (calculated by the Cockcroft-Gault method).
12. Serum albumin ≥30 g/L.
13. Patients must have been advised to take measures to avoid or minimize exposure to UV light

for the duration of study participation and for a period of 4 weeks following the last dose of study medication.
14. Patients must have a disease that is evaluable as per RECIST V1.1 criteria and documented by CT/MRI. NOTE: Lesions to be used as a measurable disease for the purpose of response assessment must either:
14.1. Not reside in a field that has been subjected to prior radiotherapy, or
14.2. Have demonstrated clear evidence of radiographic progression since the completion of prior radiotherapy and prior to study enrolment.
15. Patients must have failed at least one standard therapy as part of the continuum of care for locally advanced or metastatic non-resectable solid tumours, unless no standard therapy exists; patients will not be denied any standard of care therapy as part of this continuum of care.
16. Patients must be treated for an indication where either fluropyrimidines are a recognised part of the continuum of care or may be a reasonable option when administered with CV6-168.
17. Absence of potentially deleterious DPYD polymorphisms associated with partial or complete DPYD deficiency, as assessed by mandatory DPYD screening in all patients (irrespective of previous 5-FU exposure).
18. Patients who have been previously treated with 5-FU that (in the opinion of the investigator) have tolerated the 5FU/folinic acid treatment without significant difficulty or any severe or unexpected toxicity that could reasonably be attributed to 5-FU therapy. Or (following a documented SRC decision to start cautiously including 5-FU naïve patients in later dose escalation cohorts), patients that in the opinion of the investigator are suitable for 5-FU treatment.
19. Ability to comply with protocol requirements.
20. Patients must be able to comprehend and provide written informed consent. Agreement, as part of the informed consent, to provide blood and archival tumour samples for molecular correlates, PK and PDc. Archival tumour tissue is mandatory, and patients where this is unavailable are excluded, unless they consent to a fresh tumour biopsy being taken.
21. Patients must be recovered to Grade 1 severity (the most recent version of NCI CTCAE) from the effects (including residual toxicities) of any prior therapy for their malignancies, excluding alopecia and residual Grade 2 neuropathy.
Additional Inclusion Criteria for Part A (Dose Escalation) Cohorts 1-3
22. Patients must have been previously treated with and tolerated 5-FU or capecitabine for at least 12 weeks without any dose reductions or delays attributed to 5-FU-related toxicities.

Participant type(s)
Patient

Age group
Mixed

Lower age limit
18 Years

Sex
Both

Target number of participants
141

Participant exclusion criteria

Module 1 Exclusion Criteria: Exclusion Criteria for Part A (Dose Escalation) & Part B (Dose Expansion)
To be eligible for inclusion into this study, each patient must violate none of the following exclusion criteria within 28 days before C1D1:
1. Patients who received treatment for the malignancy within 28 days before the first dose of IMP.
2. Patients with an active bacterial or viral infection (including Severe Acute Respiratory Syndrome Coronavirus 2 [SARS-CoV-2], Herpes Zoster, Varicella Zoster or chickenpox), including a major systemic infection requiring antibiotics or antivirals 1 week or less prior to the first dose of study drug.
3. Patients with known active hepatitis B or C (mandatory testing not required).
4. Patients with known Human Immunodeficiency Virus (HIV) infection (mandatory testing not required).
5. Patients with any other condition, including mental illness or substance abuse or abnormal laboratory results, deemed by the Investigator to be likely to interfere with a patient's ability to sign informed consent, cooperate and participate in the study, or interferes with the interpretation of the results. This includes (but is not limited to) the following:
5.1. Congestive heart failure (New York Heart Association Class III or Class IV).
5.2. Clinically significant coronary heart disease or myocardial infarction within 6 months of the first dose of study medication or high risk of uncontrolled arrhythmia.
5.3. Unstable or poorly controlled angina pectoris.
5.4. Complete left bundle branch, fascicular block or other clinically significant abnormal ECG finding.
5.5. QTc interval >470 milliseconds using the Fridericia formula.
5.6. History of or current risk factor for torsade de pointes (e.g., heart failure, hypokalaemia, or a family history of long QT syndrome).
5.7. History of severe skin reactions.
5.8. History of severe ocular disorders.
5.9. Interstitial pneumonitis or pulmonary fibrosis.
5.10. Diabetes mellitus with ketoacidosis or chronic obstructive pulmonary disease (COPD) requiring hospitalisation in the preceding 6 months; or any other intercurrent medical condition that contra-indicates treatment with CV6-168 or places the patient at undue risk for treatment-related complications.
6. Female patients who are pregnant or breastfeeding.
7. Patients who have had any active bleeding in the last ≤ 4 weeks or have an otherwise known bleeding diathesis.
8. History of hypersensitivity or current contra-indications or severe toxicity to 5-FU (irrespective of DPYD polymorphism status), FUdR or capecitabine.
9. Evidence of central nervous system (CNS) or leptomeningeal metastases.
10. Palliative radiotherapy during participation in the study is permitted but should not be concurrent with study treatment and recovery should be allowed to prevent overlapping toxicity. It should not include a target lesion.
11. No other prior malignancy is allowed except for the following: adequately treated basal cell or squamous cell skin cancer, curatively treated in situ cancer of the cervix, surgically excised or potentially curatively treated ductal carcinoma in situ of the breast or potentially curatively treated in situ melanoma, superficial bladder cancer, adequately treated Stage I or II cancer from which the patient is currently in complete remission, or any other cancer from which the patient has been disease-free for at least 3 years.
12. Thromboembolic event in the 6 months before inclusion (e.g., transitory ischemic stroke, stroke, subarachnoid haemorrhage) except deep vein thrombosis treated with therapeutic anticoagulants which have been discontinued and asymptomatic pulmonary emboli.
13. Acute intestinal obstruction, sub-acute obstruction in the preceding 4 weeks, or history of

uncontrolled inflammatory intestinal disease.
14. Received a live vaccination within four weeks of the first planned dose of study medication.
15. Known DPYD mutations associated with potential increased toxicity from fluoropyrimidines.
16. Required concomitant use of drugs known to prolong QT/QTc interval.
17. Patients who are on any dose of warfarin or are on full dose anticoagulation with other agents (including low molecular weight heparin, antithrombin agents, anti-platelet agents and more than 325 mg daily aspirin) within 7 days prior to first dose of study drug are excluded. Patients on prophylactic doses of low-molecular-weight heparin or aspirin at doses lower than 325 mg daily are allowed on study.

Recruitment start date
18/04/2024

Recruitment end date
30/09/2025

Locations

Countries of recruitment
England

Northern Ireland

Scotland

United Kingdom

Study participating centre
Beatson West of Scotland Cancer Centre
1053 Great Western Road
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Study participating centre
Belfast City Hospital
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Study participating centre
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Sponsor type
Industry

Funder(s)

Funder type
Industry

Funder Name
CV6 Therapeutics (NI) Ltd

Results and Publications

Publication and dissemination plan

1. Peer reviewed scientific journals
2. Internal report
3. Conference presentation
4. Publication on website
5. Other publication
6. Submission to regulatory authorities

The study data will be shared with relevant research groups and external stakeholders collaborating with the study sponsor to support the future development of the IMP within the boundaries of strict confidentiality agreements.

Intention to publish date

29/12/2027

Individual participant data (IPD) sharing plan

Not provided at time of registration

IPD sharing plan summary

Data sharing statement to be made available at a later date