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CRISTAL-APC - a trial of chemokine receptor inhibition for patients with pancreatic cancer

Submission date 03/10/2024	**Recruitment status** Recruiting	[X] Prospectively registered [_] Protocol
Registration date 17/01/2025	**Overall study status** Ongoing	[_] Statistical analysis plan [_] Results
Last Edited 10/02/2026	**Condition category** Cancer	[_] Individual participant data [X] Record updated in last year

Plain English summary of protocol
https://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-trial-looking-at-vp-002-and-chemotherapy-for-advanced-pancreatic-cancer-cristal-apc#undefined

Background and study aims
Pancreatic ductal adenocarcinoma (PDA) is an aggressive form of cancer associated with poor survival. Patients with metastatic PDA (mPDA) if they are fit enough, are generally treated with chemotherapy, but even with this their average life expectancy is under 1 year, so improvements in treatment are much needed. This study will investigate VP-002 in patients with mPDA. This drug blocks a protein called the CCR1 receptor, which can affect features of the immune system, such as chemicals and cells. In laboratory models of mPDA, VP-002 can slow down cancer growth, especially when combined with chemotherapy. It has been tested previously in humans, but not in patients with mPDA and not with chemotherapy. CRISTAL-APC is a medical study (clinical trial) led by Cambridge University Hospitals and the University of Cambridge. The study will see if VP-002 can be combined with chemotherapy to improve its effectiveness for patients with mPDA.

Who can participate?
Patients aged 18 years and over with advanced PDA. In total, the study aims to treat about 120 patients on the trial across the country at several hospitals.

What does the study involve?
The trial will combine VP-002 with two chemotherapies called nab-paclitaxel and gemcitabine, which are both standard treatments given to patients to treat their PDA. The chemotherapies are given as a drip (infusion) every week, for three in every four weeks. VP-002 is taken as a tablet twice a day. The study has two stages: in the first stage (Phase I trial), the goal is to work out the best doses of VP-002 and the chemotherapies together. In the second stage (Phase II trial), the goal is to assess how
well this new combination of VP-002 when given chemotherapy works compared to the standard chemotherapies without VP-002.

In the Phase I trial, everyone will be allocated a particular dose of VP-002 and the chemotherapy drugs. Different doses will be tried to select the best one by checking for any side effects,

effects in the blood or the cancer tissue, and any signs of cancer shrinkage and survival. Participants will be asked questions about their health and symptoms, looking for changes in blood tests using imaging scans and where possible, looking for changes inside the cancer itself by taking biopsies. They will be monitored closely throughout the treatment; this will involve extra tests and visits to the hospital, but the goal is to catch any side effects so they can be managed early.

In the Phase II trial, participants will be randomly split into two groups: some will receive all three drugs (VP-002 plus), and some will receive nab-paclitaxel plus gemcitabine chemotherapies that are used in standard care. This choice will be selected by a computer. After all the patients in the trial have finished treatment, we will compare the two groups to see which has better effectiveness.

Anyone on the trial will be free to stop at any time and can withdraw information about themselves from the study. The treatments will be given for 6 months initially and participants can be treated for more than this (up to a year) depending on the benefit and how the treatment is tolerated. Treatment may stop early if the drugs are causing bad side effects or not helping shrink the cancer. A detailed information sheet will be provided for potential volunteers who are interested in taking part.

If the addition of VP-002 to the standard chemotherapies nab-paclitaxel and gemcitabine looks more effective than just the standard chemotherapies alone, then the new combination may be further tested in larger studies to see whether it could become a new and approved option for treating patients with mPDA.

What are the possible benefits and risks of participating?
Participants may suffer side effects of treatment. Side effects for the trial medication are listed in the Participant Information Sheet. All adverse events will be checked as per the visit schedule outlined in the protocol and participants will be regularly followed up for any adverse events until resolution, stabilisation or 28 days from last trial treatment. To mitigate these side effects, the trial team will be encouraged to prescribe medication to ease any side effects of the trial medication experienced by the participants. Dose interruptions are permitted, for a maximum of 4 weeks as well as dose reduction (down to 600 mg or intermittent schedules) to manage toxicities related to trial medication. In case of severe reactions, trial treatment will be discontinued. Participants will be given contact details of their site study team, printed on the Participant Information Sheet. Participants will also receive a Participant ID card with local contact details. These contact details will also include an Out-of-hours service, in line with local site arrangements.

Participants will be asked to self-administer oral medication twice a day. There is a risk that participants may lose the medication or overdose/underdose. Participants will be given a diary with clear instructions and will be asked to keep a record of the tablets they take. Participants will have contact with the site study team at regular intervals, where the diary will be checked and/or talked through. Participants will also be asked to return used and unused or empty medication bottles for trial drug reconciliation purposes.

Participants are asked to attend up to 30 trial appointments. Whilst some of those appointments (especially follow-up visits) will happen at similar time points as normal clinic visits for active surveillance, this is a higher number of hospital encounters compared to standard of care. It may therefore be an increased burden compared with the standard of care. The protocol is designed to allow flexibility to conduct as many tests and assessments remotely as possible to keep additional visits to a minimum. Where extra financial costs are incurred as a result of

participating in the trial, participants will be reimbursed for reasonable travel expenses and subsistence during their participation.

Participants are asked to undergo CT scans every 8 weeks from the date of registration. Some CT scans will coincide with scans that patients would have as part of their routine care (dependent on standard of care practice at local sites). Before CT scans, patients will be asked to drink or have an injection of dye which will highlight areas of their body more clearly on the scan. If dye is given by injection, they may experience pain and/or bruising in the arm from the insertion of the cannula used to give the dye. They may also experience a warm feeling or metallic taste during the injection. If oral contrast is given, it may have a bitter taste to it. Participants will be informed of the procedure while joining the study.

Magnetic resonance imaging (MRI) may be undertaken in place of a CT scan if the patient is known to be allergic to contrast. Most MRI scans are painless. However, some participants may find it uncomfortable to stay still. It is normal for the area of the body being imaged to feel slightly warm. Participants have been asked to speak to the local trial team if this bothers them. When the images are being recorded, they may hear and feel loud thumping sounds as the scanner can be noisy. They will be provided with earplugs or headphones to reduce the noise made by the scanner.

Participants may experience mild discomfort/pain and/or bruising from where a trial blood sample is taken and from the insertion of the cannula used to give IVs.
Participants are asked to undergo up to 3 (phase 1) or 4 (phase II) research biopsies as part of the trial until disease progression. Biopsies can cause discomfort and carry some risks (for example bleeding and infection) which participants will be aware of from their diagnostic biopsy procedure. As the biopsy for this study will be done at a specific time point, this may be an additional procedure for some participants as there is a chance they would not need a biopsy as part of their routine care. This procedure will be performed by delegated and trained members of staff who will conduct the needle biopsy and fully inform participants of the procedure beforehand.

Where is the study run from?
Cambridge Clinical Trials Unit (CCTU) (UK)

When is the study starting and how long is it expected to run for?
October 2024 to December 2030

Who is funding the study?
Cycle Pharmaceuticals (UK)

Who is the main contact?
Dr Bristi Basu (Chief Investigator), bb313@cam.ac.uk

Contact information

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Public, Scientific

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Central Portfolio Management System (CPMS)
60446

Integrated Research Application System (IRAS)
1009418

Protocol serial number
CCTU0442

Study information

Scientific Title
A multi-centre, open-label Phase I/randomised Phase II study of VP-002, a C-C motif chemokine receptor 1 (CCR1) inhibitor, given orally in combination with nab-paclitaxel and gemcitabine (nPG) to patients with advanced pancreatic ductal adenocarcinoma

Acronym
CRISTAL-APC

Study objectives

The CRISTAL-APC Phase I trial aims to propose a recommended dose of VP-002 when given with nab-paclitaxel and gemcitabine (nPG).

The CRISTAL-APC Phase II trial aims to compare overall survival in patients with untreated metastatic pancreatic cancer when administered VP-002 in combination with nab-paclitaxel and gemcitabine (nPG) versus nPG alone.

Phase I:
1. To assess the safety and toxicity profile of VP-002 alone and when given with nPG
2. To assess the early signals of anti-tumour activity of VP-002 when given with nPG
3. To assess VP-002 pharmacokinetics alone and in combination with nPG

Phase II:
1. To assess the safety and toxicity profile of VP-002 when given with nPG
2. To assess the efficacy of VP-002 when given with nPG first-line therapy
3. To assess VP-002 pharmacokinetics alone and in combination with nPG

Ethics approval required
Ethics approval required

Ethics approval(s)
approved 30/12/2024, London-Surrey Borders Research Ethics Committee (Equinox House, City Link, Nottingham, NG2 4LA, United Kingdom; +44 (0)2071048057; surreyborders.rec@hra.nhs.uk), ref: 24/LO/0787

Study design
Open randomized controlled parallel-group trial

Primary study design
Interventional

Study type(s)
Efficacy, Safety

Health condition(s) or problem(s) studied
Advanced pancreatic ductal adenocarcinoma

Interventions
CRISTAL-APC is split into two (2) phases and the participants will receive the following treatments:

Phase I: Dose Escalation Phase
CRISTAL-APC will evaluate VP-002 at a total daily dose of 600mg to a maximum of 1,800mg per day in combination with nab-paclitaxel and gemcitabine. Nab-paclitaxel will be administered at the allocated dose level of either 100mg/m2 or 125mg/m2. Gemcitabine will be administered at the allocated dose level of either 800mg/m2 or 1000mg/m2.
Cycle 0 is a 14-day monotherapy cycle where patients will self-administer VP-002 only. It will be taken once a day on day 1 and twice daily on days 2-14.
Cycles 1-6: Patients will self-administer VP-002 twice daily on days 1-28 of a 28-day cycle. Intravenous (IV) nab-paclitaxel 30-minute infusion followed immediately by IV gemcitabine 30-minute infusion will be administered on days 1, 8 and 15 of a 28-day cycle.

Phase II: Dose Expansion Phase
Patients will be randomised using a Web-based randomisation system into one of the following arms:
Experimental Arm A:
The dose levels of VP-002, nab-paclitaxel and gemcitabine will be decided from the phase I dose escalation.
Cycles 1-6: Patients will self-administer VP-002 twice daily on days 1-28. Intravenous (IV) nab-paclitaxel 30-minute infusion followed immediately by IV gemcitabine 30-minute infusion will be administered on days 1, 8 and 15 of a 28-day cycle.
Control Arm B:
Cycles 1-6: Intravenous (IV) nab-paclitaxel 30-minute infusion followed immediately by IV gemcitabine 30-minute infusion will be administered on days 1, 8 and 15 of a 28-day cycle.
The trial drugs will continue in both phases until disease progression, unacceptable toxicity that precludes further treatment or patient withdrawal, pregnancy, or choice. Patients may continue treatment in phases I and II for another 6 cycles at the investigator's discretion after discussing with the sponsor.

Intervention Type
Drug

Phase
Phase II

Drug/device/biological/vaccine name(s)
VP-002, nab-paclitaxel, gemcitabine

Primary outcome(s)
Phase I:
1. MTD (Maximum Tolerated Dose) based on the occurrence of DLTs (Dose Limiting Toxicities) in cycle 0 and cycle 1 (around six weeks from the start of treatment)
2. Incidence of Treatment-Emergent Adverse Events (TEAEs), identified by symptoms, physical examination, ECGs and through clinical laboratory blood and urine sample evaluations (according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0) throughout all cycles of the study
3. Incidence of TEAEs leading to study drug modifications (e.g., interruptions) and discontinuation of the study drug throughout all cycles of the study

Phase II:
Median overall survival (OS), calculated from the date of randomisation to the date of death for all evaluable patients in each treatment arm across the study

Key secondary outcome(s))
Phase I:
Safety and tolerability:
1. The frequency of AEs (Grades 3, 4 and 5), and the number of SAEs and DLTs considered at least possibly related to VP-002 occurring in cycle 0 and cycle 1 (around six weeks from the start of treatment), according to NCI CTCAE version 5.0.

Anti-tumour activity:
1. ORR (Objective Response Rate), defined as the rate of CR (Complete Response) plus PR (Partial Response) according to Response Evaluation Criteria in Solid Tumours Version 1.1,

(RECIST V1.1) This will be measured by CT imaging every 8 weeks from screening, until the end of the study.
2. Best overall response (BOR), the best radiological response from the start of study treatment according to RECIST v1.1 until the end of the study.
3. Changes in CA19.9 from baseline measured in the blood each cycle of treatment until disease progression

Pharmacokinetics:
1. Pharmacokinetics of VP-002 including, but not limited to maximum (or peak) plasma concentration (Cmax), time to reach Cmax (Tmax), minimal plasma concentration (Cmin), area under the plasma concentration-time curve (AUC), apparent clearance (CL/F), apparent volume of distribution (V/F) from blood samples taken in cycle 0, cycle 1 and cycle 2.

Phase II:
Safety and tolerability:
1. Frequency of AEs and SAEs considered at least possibly related to VP-002 and the number of Grade 3, 4 and 5 AEs considered at least possibly related to VP-002 according to NCI CTCAE version 5.0, assessed throughout all cycles until the end of the study.

Efficacy:
1. Progression-free survival (PFS): time from the date of randomising VP-002 plus nPG to the date of disease progression or date of death, whichever occurs first. This will be measured by imaging according to RECIST V1.1 every 8 weeks from randomisation until progression or end of study. Surviving patients without progression will be censored at the date of their last clinical follow-up at the time of analysis.
2. Overall survival (OS) at 12 months from randomisation.
3. Disease control rate (DCR): best response of CR, PR or SD (Stable disease) measured by imaging according to RECIST V1.1 at 3,6 9 and 12 months after randomisation.
4. ORR at weeks 8, 16, 24, and 52, defined as rate of CR plus PR according to RECIST V1.1
5. Best overall response (BOR), best radiological response according to RECIST v1.1 from the start of the treatment across all visits until disease progression.
6. Changes in CA19.9 from baseline until end of study.
7. Changes in Quality of Life scores from baseline until disease progression with the European Organisation for Research and Treatment of Cancer (EORTC) quality of life questionnaire (QLQ)-C30 and QLQ-PAN26 serially

Pharmacokinetics:
1. Pharmacokinetics of VP-002 including, but not limited to maximum (or peak) plasma concentration (Cmax), time to reach Cmax (Tmax), minimal plasma concentration (Cmin), and area under the plasma concentration-time curve (AUC) measured in blood samples taken at cycle 1 day 1, 8 & 15, and cycle 2 day 1.

Completion date
31/12/2030

Eligibility

Key inclusion criteria
1. Histologically or cytologically (based on local assessment and per local guidelines) confirmed PDAC and variants. Either of the following:
1.1. Adenosquamous carcinoma

1.2. Ductal adenocarcinoma
1.3. Intraductal papillary mucinous neoplasm (IPMN) with an associated invasive carcinoma
1.4. Mucinous adenocarcinoma
1.5. Mucinous cystic neoplasm (MCN) with an associated invasive carcinoma
1.6. Undifferentiated carcinoma
2. Aged 18 years and over
3. Radiologically confirmed stage IV disease
4. Measurable disease by RECIST version 1.1
4.1. If the patient has received prior radiotherapy to the lesion, it should have progressed since irradiation to be included as a measurable lesion:
5. ECOG PS 0 or 1
6. Estimated life expectancy ≥12 weeks at screening
7. Adequate bone marrow function:
7.1. Absolute neutrophil count (ANC) ≥1.5 x 10^9 /L
7.2. Haemoglobin (Hb) ≥90 g/L for Phase I; ≥100 g/L for Phase II, with no blood transfusions in the preceding 14 days
7.3. Platelets ≥100 x 10^9 /L
8. Adequate liver function:
8.1. Aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) ≤2.5 x upper limit of normal range (ULN) (<5 x ULN in presence of liver metastasis)
8.2. Total bilirubin <1.5 x ULN
8.3. Total albumin ≥28 g/L
9. Adequate renal function:
9.1. Calculated creatinine clearance by Cockcroft Gault of ≥50 mL/min
10. Women of childbearing potential (WoCBP), male participants and their partners are required, and must be willing, to use 1 highly effective form PLUS 1 effective form of contraception for the duration of the trial and for six (6) months after the completion of the trial treatment.
11. Patient is willing and able to comply with the visit schedule outlined in the protocol for the duration of the trial
12. Absence of any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule; those conditions should be discussed with the patient before registration in the trial
13. Have given written informed consent
14. Be enrolled/registered in the Precision-Panc Master Protocol study

Inclusion Criteria – Phase I Specific:
In addition to the inclusion criteria for Phase I and Phase II above:
1. Tumour site amenable to biopsy
2. Confirmation of adequate tumour tissue sample: archival tissue if taken within 8 weeks with no intervening therapy and the site must confirm if >100 cells are present in the sample, or a baseline tumour biopsy
3. Gemcitabine and Nab-paclitaxel deemed reasonable treatment or re-treatment options:
3.1. Have not received it previously OR
3.2. Have received it previously and tolerated treatment without significant dose.

Inclusion Criteria – Phase II Specific:
1. Received no prior systemic therapy for stage IV disease; or received prior systemic anti-cancer therapy as neo-adjuvant or adjuvant therapy AND such treatment was completed at least 6 months previously
2. Confirmation of adequate tumour tissue sample: archival tissue within 2 years of study entry. This can include a primary resection specimen, or consented for baseline tumour biopsy, or a baseline tumour biopsy

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Mixed

Lower age limit
18 years

Upper age limit
100 years

Sex
All

Total final enrolment
0

Key exclusion criteria
Phase I and Phase II:
1. Patients with operable or locally advanced PDAC
2. Other invasive malignancies with the exception of adequately treated carcinoma in situ of the cervix or non-melanoma skin cancer. Cancer survivors who have undergone potentially curative treatment for a prior malignancy, have no recurrence within the last 2 years and are deemed at negligible risk for recurrence are eligible for trial
3. Significant acute or chronic medical or psychiatric condition, disease or laboratory abnormality which in the judgment of the investigator would place the patient at undue risk or interfere with the trial. Examples include, but are not limited to:
3.1. Patients who have had a venous thromboembolic event who are not appropriately anticoagulated or have had a significant bleeding episode in the 3 weeks prior to randomization
3.2. Patients with symptoms of severe chronic obstructive airways disease or significant shortness of breath at rest AND have an Forced expiratory volume (FEV)1 < 1.0 L within the last 6 months
3.3. Patients with a history of interstitial lung disease, sarcoidosis, silicosis, idiopathic pulmonary fibrosis, pulmonary hypersensitivity pneumonitis, cystic fibrosis or bronchiectasis
3.4. Patients with uncontrolled ischaemic heart or other cardiovascular event (myocardial infarction, new angina, stroke transient ischaemic attack (TIA), or new congestive cardiac failure (CCF) within the last 6 months
3.5. Patients with stable but significant cardiovascular disease defined by heart failure (New York Heart Association Functional Classification (NYHF) III or IV) or frequent angina
3.6. Presence of active infection
3.7. Cirrhotic liver disease, known chronic active or acute hepatitis B, or hepatitis C
3.8. Known allergy or hypersensitivity to gemcitabine or nab-paclitaxel or CCR1 inhibitors or the components of VP-002. Components of VP-002 are Kollidon SR, lactose monohydrate, fumaric acid, magnesium stearate, Opadry II Yellow
4. Women who are pregnant, plan to become pregnant or are lactating during the trial period
5. Resting ECG with mean QTc interval of >480 ms msec (confirmation of any prolongation to be

used based on the average QT interval by Fridericia (QTcF) value of 3 reads within a 30-minute time period). Concomitant use of medications known to prolong QT interval, or with factors that increase the risk of QTc prolongation or risk of arrhythmic events (such as heart failure, hypokalaemia, congenital long QT syndrome, family history of long QT syndrome), or unexplained sudden death under 40 years of age. Inability to discontinue medication with agents designated as having a risk of Torsades de Pointes due to QT prolongation
6. Concurrent participation in an interventional clinical trial (observational studies allowed)
7. Patients that have not been enrolled onto the Precision Panc Master Protocol

Exclusion Criteria – Phase I Specific:
1. Any unresolved toxic effects Grade ≥2 according to NCI CTCAE v 5.0 from prior chemotherapy administered for locally advanced or metastatic disease (with the exception of alopecia, Gr 2 peripheral neuropathy and haemoglobin ≥90g/L with no blood transfusions in the preceding 28 days

Exclusion Criteria – Phase II Specific:
1. Prior chemotherapy for locally advanced or metastatic pancreatic adenocarcinoma
2. Any unresolved toxic effects Grade ≥2 according to NCI CTCAE v 5.0 from previous treatment for cancer (adjuvant or neoadjuvant) before randomization, except for alopecia, grade 2 peripheral neuropathy, and haemoglobin level ≥100 g/L, with no blood transfusions in the preceding 28 days

Date of first enrolment
04/04/2025

Date of final enrolment
31/01/2028

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
Cambridge University Hospitals NHS Foundation Trust
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Study participating centre
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Study participating centre
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Sponsor information

Organisation
Cambridge Clinical Trials Unit (CCTU)

Funder(s)

Funder type
Industry

Funder Name
Cycle Pharmaceuticals

Results and Publications

Individual participant data (IPD) sharing plan

The data-sharing plans for the current study are unknown and will be made available at a later date

De-identified datasets from the trial will be made available to the study funders and may also be made available to other researchers in line with national and international data transparency initiatives (using an open-access model). This information is in the patient information sheet and consent will be provided for this.

IPD sharing plan summary

Available on request