A Phase 1 Open-Label, Dose Escalation and Expansion Trial to Investigate the Safety, pharmacokinetics and Pharmacodynamics of CB307, a Trispecific Humabody® T-cell Enhancer, in Patients with PSMA+ Advanced and/or Metastatic Solid Tumours (POTENTIA)

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Primary Objective:To assess the safety and tolerability and determine the MTD and the RP2D of CB307 in patients with PSMA+ tumoursSecondary Objectives:• To characterise the serum PK of CB307• To characterise the immunogenic potential of CB307 and...

Ethical review	Approved WMO
Status	Completed
Health condition type	Miscellaneous and site unspecified neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON52294

Source
ToetsingOnline

Brief title
POTENTIA

Condition

- Miscellaneous and site unspecified neoplasms malignant and unspecified

Synonym

advanced tumours, Metastatic tumours

Research involving
Human

Sponsors and support

Primary sponsor: Crescendo Biologics Limited
Source(s) of monetary or material Support: Crescendo Biologics;Ltd.

Intervention

Keyword: Advanced Solid Tumours, Metastatic Solid Tumours, PSMA, T-cell enhancer

Outcome measures

Primary outcome

The nature and frequency of any DLTs during the DLT-monitoring period assessed

based on NCI CTCAE v5.0.

Secondary outcome

1. Tumour response based on the RECIST v1.1

2. Tumour response and PSA response according to PCWG3

3. Serum CB307 PK parameters

4. Overall Survival

5. Change from baseline in anti-CB307 antibodies (ADA).

Study description

Background summary

This is a FIH dose escalation and expansion study to assess safety, tolerability, PK, pharmacodynamics and immunogenicity, to determine MTD and RP2D and to assess preliminary anti-tumour activity of CB307 in patients with advanced and/or metastatic PSMA+ solid tumours following weekly IV administration.
CB307 is a trispecific Humabody® that binds to CD137, PSMA and HSA. CB307 will bind to PSMA on tumour cells and CD137 on immune cells to enhance the

anti-tumour immune response.
CD137 (4-1BB) is a co-stimulatory receptor that is induced on T cells and NK cells. It is expressed on T cells that have undergone antigen recognition, and subsequent ligation of CD137 induces T-cell effector functions. CD137 signalling is initiated by clustering brought about by trimeric CD137 ligand; this can also occur with anti-CD137 antibody engagement. The consequence for T cells is enhanced proliferation, proinflammatory cytokine secretion, increased tumour cytotoxicity and prolonged T cell survival. PSMA is highly upregulated on tumour cells and tumour neovasculature in prostate cancer and other solid tumours, including lung (NSCLC), kidney (clear cell RCC), bladder and colorectal cancers (Salas Fragomeni et al. 2018). Therefore, by simultaneously binding to PSMA and CD137, CB307 not only enables the bridging of the tumour cell and T cell for immune recognition, but also directs T cell co-stimulation to the tumour microenvironment by a *conditional* mechanism that is dependent upon the co localisation of both targets. Thus, CB307 has no agonistic activity in the absence of PSMA. Furthermore, CB307 lacks an antibody fragment crystallisable (Fc) domain so it does not drive CD137 clustering via non-specific interactions with FcγR on immune cells. The dependency on PSMA and lack of FcγR binding are thought to reduce the risk of potential off target immune pathology including potential hepatotoxicity seen with urelumab (Segal et al. 2017).
Human serum albumin is an abundant serum protein with long circulatory half-life. CB307 engages HSA to enable extension of its half-life and to promote drug distribution into tissue and tumours.
As seen with bispecific antibodies in haematological malignancies (Bargou et al. 2008), engaging T cells in solid tumours is expected to result in T cell expansion at tumour sites and lead to a durable response. It is worth noting that there is no cytokine release syndrome (CRS) reported for CD137 agonistic antibodies including urelumab and utomilumab (Segal et al. 2017, Segal et al. 2018). Urelumab was effective as monotherapy at a higher dose but due to the dose-dependent hepatotoxicity observed (Segal et al. 2017), urelumab has been further evaluated at a lower dose. The observed hepatotoxicity is likely due to CD137 cross-linking via FcγRIIb-expressing liver-resident cells such as hepatic myeloid and sinusoidal endothelial cells. It is not expected that CB307 will have this effect due to the lack of an Fcγ region. In addition, unlike CD3 targeting bispecific molecules, there was no CRS or neurotoxicity reported for CD137 a targeting bispecific molecule (Piha-Paul et al. 2019). CB307 engages only antigen experienced T cells and thus is expected to reduce the cytokine release syndrome often observed in T-cell-redirecting treatment.
PSMA is known to express in normal prostate as well as duodenal mucosa and a subset of proximal renal tubules (Silver et al. 1997). However, CD137 positive, antigen experienced T cells are rarely observed in the normal tissues (Wang et al. 2008). Indeed, there is no neurotoxicity or critical on target, off tumour toxicities reported in PSMA targeting CD3 bispecific molecules tested in clinic (Bendell et al. 2020; Hummel et al. 2019). While seizure (n = 1) and syncope (n = 1) were observed with HPN424, the details of these events and their cause have not been disclosed (Piha-Paul et al. 2019). Overall, CB307 may have a

better safety profile than CD3 targeting T-cell bispecific antibodies, opening the potential for a range of combination therapies and delivering durable anti tumour responses for PSMA+ solid tumours.
PSMA is frequently expressed in prostate cancer and corelates with poor prognosis. High Gleason score and castration resistance is positively correlated with membrane PSMA expression. Interestingly, CRPC with high DNA damage repair mutation including BRCA1/2 or ATM also associates with PSMA expression (Paschalis et al. 2019). Recent data suggests that BRCA1/2 mutation or CDK12 loss in CRPC is known to have more T cell infiltration in tumour among immune-cold prostate cancer (Jenzer et al. 2019, Hegde et al. 2020, Yi-Mi et al. 2018).

Study objective

Primary Objective:
To assess the safety and tolerability and determine the MTD and the RP2D of CB307 in patients with PSMA+ tumours
Secondary Objectives:
• To characterise the serum PK of CB307
• To characterise the immunogenic potential of CB307 and assess the relationship with safety endpoints
• To evaluate the preliminary CB307 dose/anti-tumour activity relationship
• To evaluate clinical efficacy in mCRPC patients with known or likely deleterious genetic alterations in any of: breast cancer susceptibility genes (BRCA1/ BRCA2), ataxia telangiectasia mutated (ATM) genes, cyclin-dependent kinase 12 (CDK12) genes or patients with tumours that are defective in DNA mismatch repair for example that display a microsatellite instability-high (MSI-high) phenotype.
Exploratory Objectives:
• To assess tumour response by CT or MRI based on RECIST 1.1 for PSMA-PET positive lesion(s) at baseline.
• To assess and characterise the treatment-induced pharmaco-dynamic effects of CB307 (change from baseline and on study treatment) on the following:
o Peripheral blood lymphocytes
o Soluble serum markers
• To assess and characterise the treatment-induced pharmaco-dynamic effects of CB307 (change from baseline and on study treatment) in the tumour microenvironment (if tissue is available)
• To identify the biologically active dose of CB307, defined as the dose at which maximal pharmacodynamic changes in blood and the tumour are induced
• To evaluate the response of tumours with BRCA1/2 and/or CDK12, and/or ATM alterations to treatment in metastatic prostate cancer patients compared to patients with tumours that do not have any of these alterations.
• To assess PSMA-PET signal change after CB307 treatment.

Study design

This is a FIH, Phase 1, open-label, multi centre, non randomised study of CB307, a trispecific Humabody® T-cell enhancer, in patients with advanced and/or metastatic PSMA+ solid tumours.
The study will consist of a dose escalation phase (Part 1) and a cohort expansion phase (Part 2). Up to 50 patients will participate (approximately 20-30 patients in Part 1 and the remainder in Part 2). The study population will be the same in both parts, and dosing will continue until loss of clinical benefit, intolerable toxicity is observed, withdrawal of consent or the study is stopped, whichever comes first.
Patients will receive CB307 IV infused over 60 minutes starting on Cycle 1 Day 1 every 7 days, until loss of clinical benefit, unacceptable toxicity or end of study. The duration of the infusion may be adapted by the SRC pending clinical experience and safety review.
Part 1 Dose escalation phase:
Part 1 will evaluate escalating doses of CB307 starting at 1.0 mg. The following doses will be tested:1.0, 3.0, 10, 25, 50, 100 and 200 mg.
Initially, in the accelerated titration phase of the study (single patient cohorts), CB307 doses will be escalated from the starting dose of 1.0 mg up to and including the 10 mg dose level or until a treatment-related grade 2 or higher toxicity is observed during the 21-day DLT assessment period, whichever occurs first. If a DLT or any treatment-related grade >=2 toxicity is observed, the sponsor will immediately employ 3 patients per cohort to further assess the observed safety data. Once a DLT is observed, mCRM will be applied to estimate the next dose level.
Dose escalation decisions will be guided by a BLRM and EWOC algorithm. For the remainder of Part 1 (starting with a dose of 25 mg), cohorts of 3 patients per dose level will be enrolled, unless a DLT is observed in which case the mCRM will be applied. If no DLT is observed in the single patient accelerated titration phase at 10 mg, the next cohort will enrol 3 patients at 25 mg.
The first patient in each cohort will not be enrolled until all patients at the immediately lower cohort have completed the DLT-monitoring period and the SRC has reviewed the safety data to decide whether to proceed to the next dose level.
The duration of a treatment cycle is defined as 21 days (3 doses administered plus 7 days), in line with a DLT-monitoring period of 3 doses of CB307 plus 7 days (21 days). In Part 1, the MTD and RP2D will be determined in approximately 20-30 patients.
Intra-patient dose escalation may be possible to the declared safe dose level (i.e., 1 dose level below the dose level currently under DLT assessment) at the discretion of the investigator and in agreement with the sponsor and/or medical monitor. If the declared safe dose level is increased subsequently, an intra-patient dose increase may be allowed to the new declared safe dose level.

Guide of Dose Escalation Steps:
Dose Level Dose (mg) Next Dose (mg), (Increment Between Dose Levels [%] if no DLT)
1 1.0 3.0 (200)

2 3.0 10 (233)
3 10 25 (150)
4 25 50 (100)
5 50 100 (100)
6 100 200 (100)
7 200
Note: Subsequent dose escalation steps will be guided by the emerging safety data

After all patients in a cohort of Part 1 have completed the DLT monitoring period, an SRC will review the safety data generated to date to decide whether to proceed to the next dose level. The SRC will also be able to de-escalate to an intermediate dose level in between the current and previous dose levels, should this be deemed necessary to investigate at a dose not specified in the table above. An SRC can also recommend enrolling more patients in the declared safe dose levels as well as suggest alternative dosing schedule (e.g., Q2W) to explore further efficacy without impacting on dose escalation decision. Each dose escalation/de-escalation will be agreed by the SRC and recommended to the investigators.
Once the CB307 dose escalation is confirmed as having reached the MTD and/or RP2D, enrolment will close within Part 1 and enrolment into the Part 2 expansion cohort will commence at one of these doses/schedules (as agreed by the SRC).
The sponsor may recommend an RP2D less than or equal to the MTD. The RP2D is further defined as a dose (less than or equal to the MTD) with confirmed biological or clinical activity and acceptable tolerability.
Part 1 enrolment will end after the last patient*s DLT-monitoring period is completed, at which time Part 2 may commence. At screening, patients will provide an historical IHC tumour sample and/or a fresh biopsy sample, if available. These samples will also be utilised for various exploratory endpoints.
Any somatic mutations in CRPC tumours of sponsor*s interest (including BRCA1/2 and/or CDK12, and/or ATM) will also be assessed at screening, if the tumour is available for testing. Where genetic results are already known from either germline, ctDNA or tumour analysis, a copy of the genetics report is requested to be shared with the sponsor, if the patient consents. If somatic mutation testing (mutations, deletion or frame shift) for BRCA1/BRCA2/ATM/CDK12 has already been performed, then the sponsor has the discretion to accept these results without additional testing. Otherwise, if tissue is available, this will be tested by the sponsor.

Part 2 Dose expansion phase:
Part 2 will be initiated after the MTD/RP2D decision and is a cohort expansion phase to explore efficacy signals in PSMA+ solid tumours. Part 2 will evaluate safety and preliminary efficacy at the MTD or RP2D determined in Part 1. Up to 20 patients will be enrolled in Part 2 (up to a maximum of 50 patients across the entire study in Parts 1 and 2). Patients will receive

CB307 at the SRC-approved dose (MTD or RP2D). Patients in Part 1 can continue on their current dosing schedule after Part 2 commences or adjust to the determined dosing and schedule for Part 2, if deemed appropriateby the investigator and approved by the sponsor.
Although Part 2 is aimed at exploring the preliminary clinical efficacy as well as assessing safety in various PSMA+ solid tumours, the sponsor anticipates that a minimum of 3 patients who have prostate cancer with either BRCA1/2 and/or CDK12 and/or ATM mutations will be enrolled.
After the end of treatment with CB307, survival follow-up information will be collected via telephone calls, patient medical records and/or clinic visits every 12 weeks until withdrawal of consent or the study is stopped, whichever comes first.

Intervention

Infusion of CD307

Study burden and risks

There is no clinical data available for CB307 to date. Preclinical studies suggest that activation CD137-positive T cells is observed with CB307 in the presence of PSMA-expressing tumours. Hepatotoxicity observed in urelumab may be mitigated, as CB307 does not contain an Fc region and does not induce nonspecific macrophage activation. In addition, the starting dose of the first in human study is selected carefully based on the toxicology and pharmacology studies. Based on the preliminary result of PRS343, a CD137 targeting bispecific agent and the results of AMG212 and HPN424, both PSMA-and CD3 targeting bispecific molecules, CB307 may demonstrate efficacy in a clinical trial with an acceptable safety profile and it is considered that the potential benefits outweigh the potential risks.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Capable of understanding the written informed consent, provides signed and witnessed written informed consent and agrees to comply with protocol requirements.
2. Aged at least 18 years at the time of signing informed consent.
3. Has documented histologically confirmed diagnosis of advanced or metastatic solid tumours.
4.Meets at least one of the following PSMA-based eligibility criteria:
For patients with non-prostate cancer:
At least one of the following:
a. PSMA positivity by IHC in an FFPE sample obtained prior to the initiation of study enrolment (defined as availability of a representative archived pre-treatment tumour specimen for submission to central reader). Brushing, cell pellet from ascites or pleural effusion or lavage samples are not acceptable. Samples of bone lesion or samples that require a decalcification procedure are acceptable.
b. PSMA positivity by IHC in a fresh tumour biopsy sample set in formalin including decalcification of bone metastases (brushing, cell pellet from pleural effusion or lavage samples are not acceptable) obtained prior to initiation of study treatment for submission to central reader.
-Provision of fresh tumour samples is a preferable option even if FFPE is available and site can submit both FFPE and fresh samples.
For patients with prostate cancer:
At least one of the following:
a.Documented PSMA+ lesion determined by local PSMA-PET scan obtained between the last anti-cancer treatment and prior to commencing CB307 study treatment.
-Note that while a positive PSMA test result by IHC is not required for

eligibility if PSMAPET positive status is confirmed locally, provision of a fresh tissue sample or archival tumour sample is still requested form retrospective PSMA-IHC analysis on-study.
b.PSMA positivity by IHC in an FFPE newly obtained biopsy or archival sample prior to the initiation of study enrolment. Brushing, cell pellet from ascites or pleural effusion or lavage samples are not acceptable.
Samples of bone lesion or samples that require a decalcification procedure are acceptable.
-Provision of fresh tumour samples is a preferable option even if FFPE is available; sites may submit both FFPE and fresh samples.
5. Has an Eastern Cooperative Oncology Group Performance Status 0 or1.
6. Has adequate organ function.
For further information, please refer to the clinical protocol.

Exclusion criteria

- Has evidence of autoimmune or significant, uncontrolled concomitant diseases that could affect compliance with the protocol or interpretation of results.
- Has discontinued from anti-cytotoxic lymphocyte-associated protein 4, anti-PD1 or anti-PD-L1 antibody because of intolerable toxicity according to the investigator*s assessment.
- Has brain metastasis including leptomeningeal metastasis or primary brain tumour.
- Has encephalitis, meningitis, or uncontrolled seizures in the year prior to informed consent.
- Has current or history of CNS disease, such as stroke, epilepsy, CNS vasculitis or a neurodegenerative disease.
- Has uncontrolled pleural effusion, pericardial effusion or ascites that require regular recurrent drainage procedures.
- Is currently receiving bisphosphonate therapy for symptomatic hypercalcaemia.
- Has active second malignancy.
-Has significant cardiovascular/cerebrovascular vascular disease within 6 months prior to the first dose of CB307, including any of the following: hypertensive
crisis/encephalopathy, uncontrolled hypertension (systolic >150 mm Hg and/or diastolic >100 mm Hg), unstable angina, transient ischaemic attack/stroke, congestive heart failure (NYHA III or greater), serious cardiac arrhythmia requiring treatment (exceptions are atrial fibrillation, paroxysmal supraventricular tachycardia), history of thromboembolic events (such as myocardial infarction, stroke or pulmonary embolism).
- Has known HIV-1, HBV or HCV infection.
- Has known active or uncontrolled bacterial, viral, fungal, mycobacterial, parasitic or other infection (excluding fungal infections of nail beds) or any major episode of infection requiring treatment with IV antibiotics or hospitalisation (relating to the completion of the course of antibiotics,

except if for tumour fever) within 28 days prior to the first dose of CB307.
- Has a history of chronic liver disease or evidence of hepatic cirrhosis.
- Has any other diseases, metabolic dysfunction, physical examination finding or clinical laboratory finding that give reasonable suspicion of a disease or condition that would contraindicate the use of an investigational drug or that may affect the interpretation of the results or render the patient at high risk from treatment complications, in the opinion of the investigator.
- Has had major surgery or significant traumatic injury within 28 days prior to the first dose of CB307 (excluding biopsies) or anticipation of the need for major surgery during study treatment or 3 months after the last dose.
- Administered a live attenuated vaccine within 28 days prior to the first dose of CB307 or anticipation that such a live attenuated vaccine will be required during the study or 3 months after the last dose.
- Has dementia or altered mental status that would prohibit informed consent.
- Has a known hypersensitivity to any of the components of CB307 or history of severe hypersensitivity reactions to antibodies (NCI CTCAE v5.0 grade >=3).
- Adverse events (grade 1 or baseline) not recovered from previous anticancer treatment.
- Last dose with any of the following agents: etanercept, infliximab, tacrolimus, cyclosporine, mycophenolic acid, alefacept, efalizumab or similar systemic immune modulator within 28 days or 5 half-lives, whichever is longer, prior to the first dose of CB307.
- Has regular immunosuppressive therapy (e.g., for organ transplantation, chronic rheumatologic disease).
- Requires long-term use of systemic steroids or use of high doses of systemic corticosteroids (>10 mg of prednisone or equivalent) within 7 days prior to the first dose of CB307.
- Has severe dyspnoea at rest due to complications of advanced malignancy or requiring supplementary oxygen therapy.
- Has had prior allogeneic haematopoietic stem cell transplantation or prior solid organ transplantation.

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	01-10-2021
Enrollment:	20
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	CB307
Generic name:	-

Ethics review

Approved WMO Date:	04-01-2021
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	15-06-2021
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	21-10-2021
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	06-12-2021
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	20-01-2022
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO	

Date:	03-03-2022
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	15-03-2022
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	11-04-2022
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	18-06-2022
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	06-07-2022
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	05-11-2022
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	12-12-2022
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	02-02-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	16-02-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO	

Date:	08-05-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	26-05-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Not approved Date:	16-06-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	27-07-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
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Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	14-02-2024
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	17-04-2024
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2019-004584-46-NL
CCMO	NL75993.042.20

Study results

Date completed: 18-07-2024

Results posted: 17-12-2024

First publication
02-12-2024