A Phase I/IIA, Multi-Centre, Open-Label, Dose-Escalation Study with Expansion Arms to Assess the Safety, Tolerability, Pharmacokinetics and Preliminary Efficacy of CB-103 Administered Orally in Adult Patients with Advanced or Metastatic Solid Tumours and Haematological Malignancies Characterised by Alterations of the NOTCH Signalling Pathway

Published: 11-07-2017
Last updated: 13-04-2024

Primary ObjectivesThe primary objectives of this study are:Phase I, Part A - Dose Escalation:• To determine the maximum tolerated dose (MTD) or recommended phase 2 dose (RP2D) of CB-103 as a single agent when administered orally and with repeat...

Ethical review	Approved WMO
Status	Will not start
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON48760

Source
ToetsingOnline

Brief title
CB103-C-101

Condition

- Other condition
- Metastases

Synonym
advanced or metastatic solid tumours and haematological malignancies

Health condition

metastatic solid tumours and haematological malignancies characterised by alterations of the NOTCH signalling pathway

Research involving
Human

Sponsors and support

Primary sponsor: Cellestia Biotech AG
Source(s) of monetary or material Support: Cellestia Biotech AG

Intervention

Keyword: advanced or metastatic solid tumours and haematological malignancies characterised, dose-escalation study, NOTCH signalling pathway, open label, safety

Outcome measures

Primary outcome

The primary objectives of this study are:

Phase I, Part A - Dose Escalation:

• To determine the maximum tolerated dose (MTD) or recommended phase 2 dose

(RP2D) of CB-103 as a single agent on adult patients with advanced or

metastatic solid tumours and haematological malignancies, who have progressed

despite curative therapy or for whom no curative therapy exists.

Phase IIA, Part B - Expansion:

• To assess preliminary anti-tumour and anti-lymphoma activity of single agent

CB-103 in the different expansion arms across the different indications.

Secondary outcome

The secondary objectives for parts A and B of this study are:

• To characterise the pharmacokinetic (PK) characteristics of CB-103 in patients after single and repeated administration at various dose levels.

• Part A only:

o To characterise safety and tolerability of the MTD/RP2D of CB-103 in patients with selected solid tumours and haematological malignancies

o To assess preliminary anti-tumour and anti-lymphoma activity of single agent CB-103

• Part B only:

o To characterise safety and tolerability of the MTD/RP2D of CB-103 in patients with selected solid tumours and haematological malignancies, stratified into separate expansion arms for the respective indications and with tumours characterised by genetic alterations and activation of the NOTCH pathway.

Study description

Background summary

NOTCH signalling plays a key role in many cellular processes during develop-ment. NOTCH is a developmental pathway characterized by cell to cell commu-nication and activation via ligand-receptor interaction. The pathway is known to play critical roles during embryonic development as well as for the regulation of self-renewing tissues. Aberrant activation of NOTCH signalling leads to deregu-lation of the self-renewal process resulting in sustained proliferation, evasion of cell death, loss of differentiation capacity, invasion and metastasis, and re-sistance to chemotherapy, all of which are

hallmarks of cancer. Over-activation of the NOTCH signalling pathway can lead to cancer development, or, if it occurs during the course of the disease, it may contribute to the de-differentiation of can¬cer, promoting progression, development of metastasis, escaping apoptosis or to even cause resistance against chemotherapy or other targeted therapies.
Aberrant or over-activation of the NOTCH signalling pathway, in particular the constitutive activation of NOTCH signalling (independent of ligand/receptor ex-pression) can be found in many solid tumour indications and various haematological malignancies. The level of oncogenic activation of NOTCH signalling is correlated with a more aggressive course of disease, resulting in poorer survival rates with a more rapid disease progression compared to the overall survival seen in patients with the same tumours not hav¬ing any aberration or dysregulation of the NOTCH pathway.
Altogether, the correlation and dependency of the patient*s life expectancy with the NOTCH status in their tumours confirms the important role of NOTCH signal¬ling in human malignancies indicating that a strong rationale exists for the devel¬opment of NOTCH-tailored therapies.
(Ref. see Investigators Brochure section 2 (introduction) for more information)

This Phase I/IIA study is a first-in-human (FIH), open-label study investigating the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD) and preliminary efficacy of the pan-NOTCH inhibitor CB-103 in adult patients with advanced or metastatic solid tumours and haematological malignancies. CB-103 is an orally administered, small molecule targeting the NOTCH signalling pathway by a novel mode of action (protein-protein interaction inhibition) with binding to the NOTCH-specific transcription complex located at the nucleus of tumour cells. The study is divided into two parts with Part A (the Phase I component of the study) being the dose escalation part of the study to determine the maximum tolerated dose (MTD) or recommended Phase II dose (RP2D). Part B (the Phase IIA component of the study) is the expansion part of the study with several expansion arms to confirm MTD/RP2D of CB-103 in patients with selected tumour indications and to explore preliminary clinical efficacy and PD of CB-103 in these indications. While in Part A no patient enrichment for NOTCH will be implemented, in Part B the patients in all expansion arms must have tumours characterised by a functionally over-activated NOTCH signalling pathway determined by molecular and/or biochemical biomarkers in their tumours. (Ref. see Protocol section 1 (Introduction) for more information)

Study objective

Primary Objectives
The primary objectives of this study are:
Phase I, Part A - Dose Escalation:
• To determine the maximum tolerated dose (MTD) or recommended phase 2 dose (RP2D) of CB-103 as a single agent when administered orally and with repeat dosing to adult patients with advanced or metastatic solid tumours and

haematological malignancies, who have progressed despite curative therapy or for whom no curative therapy exists.
Phase IIA, Part B - Expansion:
• To assess preliminary anti-tumour, anti-lymphoma and anti-myeloma activity of single agent CB-103 when administered orally and with repeat dosing in the different expansion arms across the different indications.

Secondary Objectives
The secondary objectives for parts A and B of this study are:
• To characterise the pharmacokinetic (PK) characteristics of CB-103 in patients after single and repeated administration at various dose levels.
• Part A only:
o To characterise safety and tolerability of the MTD/RP2D of CB-103 in patients with selected solid tumours and haematological malignancies
o To assess preliminary anti-tumour, anti-lymphoma and anti-myeloma activity of single agent CB-103 when administered orally and with repeat dosing.
• Part B only:
o To characterise safety and tolerability of the MTD/RP2D of CB-103 in patients with selected solid tumours and haematological malignancies, stratified into separate expansion arms for the respective indications and with tumours characterised by genetic alterations and activation of the NOTCH pathway.
Exploratory Objectives
The exploratory objectives for parts A and B of this study are:
• To explore potential correlations between PK and parameters of efficacy (e.g. tumour response, tumour shrinkage), pharmacodynamic (PD) markers (genes and proteins) and safety (e.g. occurrence of adverse events, relationship of CB 103 concentration versus electrocardiogram [ECG] change from baseline QT interval corrected for heart rate using the Fridericia*s correction factor [QTcF], heart rate [HR], PR interval [PR] and QRS complex [QRS]).
• To investigate plasma levels of metabolite(s) when feasible.
• To assess changes in NOTCH target and downstream PD markers (genes, proteins) in pre- and post- CB-103 dosing in tumour tissue biopsies (where available and accessible) as a measure of NOTCH pathway inhibition.
• To assess changes in NOTCH target genes and downstream PD markers (genes, proteins) in pre- and post- CB-103 dosing in whole blood, plasma samples and hair follicles as a surrogate model to measure NOTCH pathway inhibition.
• To explore the potential influence of certain genotypes (e.g. cytochrome P450 [CYP] enzymes or N-acetyltransferases [NAT]) on the PK of CB-103.
• Exploratory genomic studies may be performed on tumour tissue samples as a part of this study to identify gene aberrations and protein expression patterns that are associated with treatment response to CB-103, disease progression, and/or adverse events. The decision to perform such analyses would be dependent on the outcome data and sample availability.
• Optional exploratory pharmacogenetic assessments may be performed (for consenting patients) on DNA derived from blood samples (liquid biopsy with circulating tumour DNA and/or blood cell-derived DNA) with the objectives of examining whether individual genetic variations in genes relating to drug

metabolism, to specific cancer indications, and/or the drug target pathway confer differential response to CB-103. The decision to perform such analyses would be dependent on the outcome data and sample availability.
• To evaluate the potential role of biomarkers and genetic markers for safety, PD, and anti-tumour activity of CB-103.
• To evaluate the biomarkers planned to be assessed in this study for their use to define the optimal biological dose of CB-103.
• To measure possible immune modulatory effects of NOTCH inhibition by CB-103 by monitoring immune cell subsets from whole blood samples (especially CD8+ T-cells, NK cells and gdT-cells).

Study design

This study is designed as an open label, non-randomised, uncontrolled Phase I/IIA dose escalation study with expansion cohorts of CB-103 administered orally on a once-daily schedule, based on a 28-day treatment cycle. The administration schedule may be adapted during dose escalation (e.g. twice-daily, intermittent dosing schedule) depending on the PK and safety signals that occur.
There will be two parts to this study. The aim of the Phase I part of the study (Part A) with the dose escalation is to determine the MTD/RP2D. An adaptive 2-parameter Bayesian logistic regression model (BLRM) for dose escalation with overdose control (EWOC) will be used in Part A to guide determination of the MTD or the RP2D in patients with advanced or metastatic solid tumours and haematological malignancies (i.e.,non- Hodgkin lymphomas).
Part A will be followed by the expansion Phase IIA, Part B of the study to determine preliminary evidence of anti-tumour activity and to confirm the safety of the CB-103 MTD/RP2D in different expansion arms consisting of patients stratified into various pre selected cancer indications at an advanced or metastatic stage of the disease. All patients in Part B will be required to have evidence of NOTCH signalling pathway activation in their tumour tissues through the presence of either mutations, amplifications/translocations or gene/protein expression alterations related to the NOTCH signalling pathway.
Part A - dose escalation (Phase I)
Part A will be a dose-finding study based on a 2-parameter BLRM to investigate the safety and tolerability of sequentially enrolled dose cohorts of at least 3, up to 6 patients per dose cohort. Depending on the BLRM, additional patients may be enrolled in some dose cohorts. If possible, a patient with a haematological malignancy should be included in each dose cohort with the exception of the first 2 dose cohorts for which this rule is not applicable.
The first two patients of each dose level will be enrolled in a staggered approach with at least 1 day apart between first dosing of these patients. Subsequent patients may be enrolled concurrently, whereby a dose cohort must be completed with regards to the dose-limiting toxicity (DLT) assessment period and be reviewed by the Cohort Review Committee (CRC) established for this study before further recruitment into the next dose cohort. The BLRM will be assessed for those patients satisfying the requirements for inclusion in the

dose-determining set (DDS). After completion of a given dose cohort, or at any time the BLRM is updated, the decision to dose escalate and the actual dose and schedule chosen will depend on the recommendation of the BLRM about the highest admissible dose according to the EWOC principle and medical review of available clinical, pharmacokinetic and laboratory data. The outcome of these analyses and the respective datasets will be reviewed by a CRC consisting of the Investigators, Sponsor Chief Medical Officer (CMO) and representatives and independent functional experts as required. The CRC will make the decision to determine the next dose and schedule for continuation of enrolment into the next higher dose cohort.
Part B - dose expansion (Phase IIA)
Part B will be the expansion phase following the determination of MTD/RP2D in Part A. Patients will be enrolled into one or several expansion arm(s). These arms will consist of patients with pre-selected cancer indications with tumour cells characterised by NOTCH signalling pathway over-activation to confirm safety of the MTD/RP2D of CB-103 and to assess its anti-tumour activity in each of the pre-selected indications. For the expansion arms a Bayesian hierarchical design will be applied for the preliminary efficacy analyses.
Enrolment into Part B of the study will start once the MTD or RP2D in Part A has been determined.

Intervention

The following assessments/procedures will be performed:
• Oral intake of the study drug CB-103: once-daily schedule, based on a 28-day treatment cycle.
• Hospital visits: In Cycle 1 visit the hospital on Days 1, 2, 3, 8, 9, 15 and 22. Afterward you will be asked to visit the hospital at Day 1 and 15 of Cycle 2, 3, 4 and subsequent.
• Keeping record of intake of the study drug in Patient Diary
• Blood collection: Approximately 2.5 to 40 ml of blood will be taken each time.
• Urine Sampling: Every month for pregnancy testing for woman with childbearing potential.
• Vital signs and physical examination during the visits: pulse, blood pressure, height, weight, temperature and respiratory rate will be measured.
• Heart tracing (ECG, Holter or MUGA scan)
• CT, MRI or PET-CT scan after cycle 2, every 8 weeks and after cycle 6 every 12 weeks until End of Treatment or disease progression/overall survival.
• Hair Sampling
• Archival tumour biopsy

Optional Assessments and Sub-studies
• Liquid Biopsy
• Fresh Tumour Biopsy
• Sub-study about influence of food intake or acid reducing agents

Study burden and risks

This is the first clinical study where CB-103 is given to patients; thus, its risks and side effects in humans are not known. Based on what has been observed so far in studies in animals and on the side effects from other similar drugs, the human subject will be monitored closely to detect any potential serious side effects, including the following: :
• Changes to your heart beat and frequency
• High blood pressure
• Cardiac dysfunction including congestive heart failure with signs and symptoms of cardiac dysfunction such as dyspnoea, orthopnoea, increased cough, pulmonary oedema, abnormal heart sound, or reduced cardiac pump function.
• Increased extramedullary haematopoesis (e.g. production of blood cells outside of the bone marrow)
• Enlarged spleen (Splenomegaly)
• Diarrhoea, nausea, vomiting, abdominal pain
• Dilated pupils (Mydriasis)
• Skin rash and redness
• Decreased physical activity and fatigue
• Decreased body weight
• Convulsions
• Oedema

CT scans
CT scans give higher radiation doses than ordinary x-rays do. The main risk of exposure to radiation is that another cancer may occur many years after the exposure. The risk of a cancer forming from the amount of radiation patient receive during these diagnostic tests is considered to be low to moderate for an individual in good health. However, for a patient with cancer condition, the risk of inducing such a cancer from these exposures can be considered to be negligible compared to the benefit of monitoring the benefit/risk to treatment and so patient are very unlikely to experience any health problems due to radiation exposure as a result of these tests.

MRI scan
An MRI scan is a painless and safe procedure. Patients may find it uncomfortable if a patient has claustrophobia (fear of enclosed spaces), but with support from the radiographer, most people find this manageable. Sometimes going into the scanner feet first may be easier, although this is not always possible. However, not everyone can have an MRI scan such as people who have certain types of implants fitted, such as a pacemaker (a battery operated device that helps control an irregular heartbeat).

PET scan
A PET-CT scan is a safe test for most people. But like all medical tests it has some risks. The radiation in the radioactive tracer is very small. Drinking

plenty of fluids after scan will help to flush the drug out of system.

X-Ray
The risk of the radiation causing any problems in the future is very small. The ovaries and testicles are particularly sensitive to radiation and may have lead blocks to shield them if they are in the x-ray field.

Bone Marrow Biopsy and Aspirate
For lymphoma indication, bone marrow biopsy at baseline is needed only if clinically indicated, at the discretion of study doctor.
It is likely that patient will experience some discomfort or pain, redness, swelling and bruising at the site of the needle insertion. There is a very small chance (approximately less than 1/100) of developing a significant infection from this procedure or bleeding from site of the needle insertion. An allergic reaction to the anaesthetic may occur.

Risks associated with fresh tumour biopsy
The risk of a tumour biopsy depends on the size, type and location of your cancer. The risks include discomfort and bruising at the place where the biopsy needle is inserted. Significant bleeding and infection can occur but are uncommon (less than 2 in 100 patients).

Risks associated with drawing blood
Risks associated with drawing blood from your arm include pain and/or bruising, infection, nerve damage excess bleeding, clotting or fainting are also possible. There may be other risks that are unknown and we cannot predict.

Pregnancy risk
It is not known whether or not the treatment would harm an unborn child if given to a pregnant woman.

Contacts

Public
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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. Disease
a. Patients with histologically or cytologically confirmed solid tumours that are surgically unresectable, locally advanced, or metastatic whose disease has progressed on at least one line of systemic therapy and for whom no standard curative therapy exists.
b. The following solid tumour indications are allowed to be enrolled into Part A of this study (dose escalation) based on known involvement of the NOTCH pathway activation in these indications:
• Breast cancer (triple negative breast cancer [TNBC], ER+/-, HER2+/-), gastrointestinal (GI) cancers (colorectal cancer [CRC], cholangiocellular carcinoma [CCC]), sarcomas (osteosarcoma, liposarcoma, rhabdomyosarcoma, fibrosarcoma), desmoid tumours adenoid cystic carcinoma, and malignant glomus tumour.
c. Patients with histologically or cytologically confirmed, advanced haematological malignancies) whose disease has relapsed or progressed upon standard therapy and for whom at that point no standard therapy exists:
• Non-Hodgkin lymphomas (NHL): Follicular lymphoma (FL), diffuse large B-cell lymphoma (DLBCL), Burkitt lymphoma, nodal marginal zone lymphoma (NMZL), splenic marginal zone lymphoma (SMZL), mantle cell lymphoma (MCL), peripheral T-cell lymphoma (PTCL), anaplastic large cell lymphoma (ALCL, ALK-positive and ALK-negative)
Specific criteria per type of lymphoma:
• B-cell non-Hodgkin lymphoma: relapsed/refractory upon at least one line of chemo-immunotherapy, no standard therapy available.
• T-cell non-Hodgkin lymphomas: relapsed/refractory upon at least one line of chemotherapy, no standard curative therapy available.
d. Patients with solid tumours must have at least one measurable lesion (at least 1.0 cm in diameter) according to Response Evaluation Criteria in Solid Tumours (RECIST) v1.1 guideline

for solid tumours (irradiated lesions are only measurable if unequivocal disease progression is demonstrated).
e. Patients with lymphomas must have at least one measurable lesion (at least 1.5 cm in diameter) according to *The Lugano Classification* for lymphomas.
f. Only for patients in Part B (dose expansion): patients must have tumours characterised by activation of the NOTCH signalling pathway (either by mutations, amplification/translocations or gene/protein expression alteration) validated by molecular and/or biochemical biomarkers assessed by using established methods at the central laboratory. All patients should have sufficient archival biopsy tissue not older than 6 months prior to pre-screening (or, if not available, a fresh tumour biopsy must be taken) in order to enable the selection of the patients.
g. Only for patients in Part B (dose expansion): willing to provide a fresh pre-dose and, if feasible, on-treatment and an end of treatment (EOT) tumour biopsy.
h. Patients in Part A (dose escalation) must have sufficient archival tumour tissue samples preferably not older than 6 months prior to screening - or, if not available - a fresh pre-dose tumour biopsy.
2. Demography
a. Men and women >= 18 years old on the day of signing informed consent.
b. Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1.
c. Patients able and willing to swallow capsules.
3. Organ function and laboratory results
Patients must have the following laboratory values (obtained within 14 days of enrolment):
a. Absolute neutrophil count (ANC) >= 1.5 x 109/L for patients with solid tumour indications and >= 1.0 x 109/L for patients with haematological malignancies
b. Haemoglobin (Hgb) >= 10 g/dL (>= 100 g/L)
c. Platelet count >= 75 x 109/L (without platelet transfusion or growth factor support in the preceding 7 days)
d. Total serum bilirubin <= 1.5 x upper limit of normal (ULN)
e. Alkaline phosphatase (ALP) <= 2.5 x ULN; if liver function abnormalities are due to the underlying malignancy and known bone metastases, then ALP must be <= 5 x ULN
f. Serum aspartate aminotransferase (AST/SGOT) and alanine aminotransferase (ALT/SGPT) <= 2.5 x ULN; if liver function abnormalities are due to the underlying malignancy and known hepatic metastases or bone metastases, then AST and ALT must be <= 5 x ULN
g. Serum creatinine <= 1.5 x ULN; or if serum creatinine > 1.5 x ULN, then serum creatinine clearance (CrCl) >= 50 mL/min (estimated by Cockcroft-Gault formula)
h. Potassium levels within normal limits or correctable with supplements
i. Total calcium levels (corrected for serum albumin) within normal limits or correctable with supplements
j. Magnesium levels within normal limits or correctable with supplements
k. Phosphorus levels within normal limits or correctable with supplements
l. Serum albumin concentration >= 30 g/L
m. Serum amylase and serum lipase <= ULN
n. Partial thromboplastin time (PTT) <= 1.5 x ULN and international normalised ratio (INR) <= 1.3 (unless the patient is receiving therapeutic anticoagulants)
4. Contraceptive measures
a. Women of childbearing potential (WOCBP, for definition see protocol Section 6.2) must have a serum pregnancy test performed within a maximum of 7 days before start of study

treatment, and a negative result must be documented before start of study treatment.
b. Women of childbearing potential and men must agree to use at least two highly effective forms of contraception (i.e., two of the following - oral contraception, mechanical contraception including a condom for the partner, or an intrauterine coil) with a failure rate of < 1% and must continue using them throughout the entire clinical trial period and for 90 days post-treatment completion (duration of 3 ovulatory cycles). Contraception has to start from the day of 1st administration of CB-103.
c. Men whose partners could be of child bearing potential must routinely use a condom throughout the entire clinical trial period and for 90 days post-treatment completion (duration of sperm turnover). The partner should also use a reliable form of contraception such as the oral contraceptive pill or an intrauterine device.
d. Azoospermic males and females with sterilisation (e.g. tubal ligation) are exempt from contraceptive requirements.
e. Women capable of becoming pregnant who are continuously not heterosexually active are exempt from contraceptive requirements. However, they must still undergo pregnancy testing as described in inclusion criterion *4a*.
5. Informed consent
a. Ability to understand the patient information and informed consent form (ICF) and comply with the protocol-related procedures.
b. Signed and dated written informed consent obtained prior to performing any study-related procedure, including pre-screening (part B only) and screening.

Exclusion criteria

1. Medical History
a. Patients with symptomatic CNS metastases who are neurologically unstable or require increasing doses of steroids to control their CNS disease.
Note: Patients with controlled CNS metastases may participate in this study. The patient must have completed radiotherapy or surgery for CNS metastases > 2 weeks prior to study entry. Patients must be neurologically stable, having no new neurologic deficits on clinical examination, and no new findings on recent CNS imaging. If patients require steroids for management of CNS metastases, they must have been on a stable dose of steroids for two weeks preceding study entry.
Note: Patients without clinical signs or symptoms of brain involvement are not required to have a computed tomography (CT)/magnetic resonance imaging (MRI) scan of the brain.
b. Hypersensitivity to any of the excipients of the finished drug CB-103
c. Patients with unresolved nausea, vomiting, or diarrhoea of common terminology criteria for adverse events (CTCAE) grade * 1
d. Impairment of GI function or presence of GI disease that may significantly alter the absorption of CB-103 (e.g., ulcerative diseases, uncontrolled nausea, vomiting, diarrhoea, malabsorption syndrome, or small bowel resection)
e. History of second or other primary cancer with the exception of:
• Curatively treated non-melanomatous skin cancer
• Curatively treated cervical cancer or breast carcinoma in situ
• Other primary solid tumour treated with curative intent and no known active disease

present and no treatment administered during the last 2 years
2. Exclusionary concurrent medical conditions
a. Impaired cardiac function or clinically significant cardiac diseases, including any one of the following:
1. Clinically significant cardiac disease including congestive heart failure (New York Heart Association [NYHA] class III or IV), arrhythmia or conduction abnormality requiring medication, or cardiomyopathy
2. Clinically uncontrolled hypertension (blood pressure > 160/110 mmHg)
3. Complete left bundle branch block
4. Right bundle branch block + left anterior hemiblock
5. Mandatory use of a cardiac pacemaker
6. Congenital long QT syndrome
7. History or presence of sustained or symptomatic ventricular tachyarrhythmia
8. Presence of atrial fibrillation
9. Clinically significant resting bradycardia (< 50 bpm)
10. Corrected QT interval using Fridericia formula (QTcF) > 450 ms for males and > 470 ms for females at the screening ECG
11. QRS >= 110 ms
12. History of symptomatic congestive heart failure
13. Left ventricular ejection fraction (LVEF) < 50%. History of absolute decrease in LVEF of >= 15 absolute percentage points, or >= 10 absolute percentage points and crossing from > lower limits of normal (LLN) to < LLN on prior anti-HER2 therapy, even if asymptomatic
14. Angina pectoris <= 6 months prior to starting study drug
15. Acute myocardial infarction (MI) <= 6 months prior to starting study drug
b. General conditions or other clinically significant diseases, including any one of the following:
1. Haemorrhagic, embolic, or thrombotic stroke within 6 months prior to the first planned CB-103 infusion
2. Prior allogeneic bone marrow/haematopoietic stem cell transplant
3. Autologous haematopoietic stem cell transplant <= 6 months prior to starting study drug
4. Known infection with human immunodeficiency virus (HIV); or, hepatitis B or C requiring treatment
5. Any active infection requiring the use of parenteral anti-microbial agents or that is > Grade 2
6. Non-malignant interstitial lung disease or pneumonitis
7. Dyspnoea of any cause requiring supplemental oxygen therapy and dyspnoea at rest due to complications of advanced malignancy and co-morbidities
8. Significant traumatic injury or major surgery (major surgery means opening of a body cavity, e.g., thoracotomy, laparotomy, laparoscopic organ resection, and major orthopaedic procedures, e.g. joint replacement, open reduction and internal fixation) within 14 days of scheduled dosing day 1
9. Other concurrent severe and/or uncontrolled medical conditions (e.g. uncontrolled diabetes, active or uncontrolled infection) that could cause unacceptable safety risks or compromise compliance with the protocol
3. Prior Therapy
a. Cytotoxic chemotherapy within 3 weeks (6 weeks for nitrosoureas and mitomycin C) of the scheduled first dose of CB-103 on day 1.

b. Prior cumulative doxorubicin exposure of >= 450 mg/m2
c. Prior cumulative epirubicin exposure of >= 900 mg/m2
d. Any investigational treatment (including NOTCH signalling inhibitors and prior treatments with CB-103) within 4 weeks of scheduled CB-103 dosing day 1.
e. Proton pump inhibitors (PPIs) and/or H2-blockers within at least 2 weeks of the scheduled first dose of CB-103 on day 1.
f. Concurrent enrolment in another therapeutic clinical trial involving ongoing therapy with any investigational or marketed product or placebo
g. Radiation therapy within 2 weeks of scheduled CB-103 dosing day 1, unless the radiation comprised a limited field to non-visceral structures (e.g. a limb bone metastasis).
h. Immunotherapy (including interferons, interleukins, immune-conjugates, immune checkpoint inhibitors), biological therapies (including monoclonal antibodies, antibody drug conjugates or other engineered proteins), targeted small molecules (including but not limited to kinase inhibitors), hormonal therapies within 3 weeks of scheduled CB-103 dosing day 1.
i. Unresolved toxicity CTCAE grade > 1 from previous anti-cancer therapy or radiotherapy (excluding neurotoxicity, alopecia, ototoxicity, lymphopenia), or incomplete recovery from previous surgery, unless agreed by Sponsor and the Principal Investigator and documented
4. Concomitant medications
a. Drugs which prolong QT interval, either with a known or a conditional/ possible risk to induce Torsades de pointes (list of drugs is given in Appendix 4 of the protocol)
b. Acid reducing agents (i.e., proton pump inhibitors (PPIs) or H2 blockers)
c. Patients receiving warfarin and phenytoin that cannot be discontinued at least one week prior to start of treatment with CB-103 and for the duration of the study
d. Anticoagulants: Patients receiving coumarin-type anticoagulants who cannot discontinue at least one week prior to start of treatment and for the duration of the study. Low molecular weight heparin and direct oral anticoagulants are permitted.
5. Demography
a. Patients who are pregnant or breast feeding.
6. Others
a. Patients who are unable or unwilling to comply with all study requirements for clinical visits, examinations, tests, and procedures.

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	33
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	CB-103
Generic name:	CB-103

Ethics review

Approved WMO Date:	11-07-2017
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	29-11-2017
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	14-02-2018
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	20-02-2018
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	22-08-2018
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	09-10-2018

Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	08-11-2018
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	20-11-2018
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	09-04-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	12-07-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	10-05-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)

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	EUCTR2017-001491-35-NL
ClinicalTrials.gov	NCT03422679
CCMO	NL62228.041.17