CLINICAL STUDY PROTOCOL

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 LOCALLY ADVANCED OR METASTATIC SOLID TUMOURS AND HAEMATOLOGICAL MALIGNANCIES CHARACTERISED BY ALTERATIONS OF THE NOTCH SIGNALLING PATHWAY

PROTOCOL NUMBER:	CB103-C-101
VERSION:	4.3
DATE FINAL:	28 May 2021
STUDY PHASE	I/IIA
EUDRACT NUMBER:	**2017-001491-35**
CLINICALTRIAL.GOV:	NCT03422679
IND NUMBER:	**141987**
TEST COMPOUND:	CB-103
SPONSOR:	Cellestia Biotech AG Hochbergerstrasse 60C 4057 Basel, Switzerland

SPONSOR CONTACT DETAILS

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MEDICAL HOTLINE	Site-specific toll and toll-free telephone numbers for the Medical Hotline can be found in the Investigator Site File

COORDINATING INVESTIGATOR

Name / Title	**Address**
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CRO (Asian countries)	dMed Biopharmaceutical Co., Ltd. Room 301 building 1, 298 Xiangke Road, China (Shanghai) Pilot Free Trade Zone
Bioanalytical Analysis of PK samples	SYNLAB Analytics & Services Switzerland AG Sternenfeldstrasse 14 4127 Birsfelden Switzerland
ECG and Holter ECG	ERT (Cardiac safety and imaging) Waversesteenweg 1945 Chaussée de Wavre 1160 Brussels Belgium
Medical Imaging	ERT (Cardiac safety and imaging) Waversesteenweg 1945 Chaussée de Wavre 1160 Brussels Belgium

For the biomarker analyses refer to the related laboratory manuals listing the labs involved with all contacts details.

SPONSOR APPROVAL SIGNATURE PAGE

Compound Name: CB-103

Protocol Number: CB103-C-101

Protocol Title:

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 Locally Advanced or Metastatic Solid Tumours and Haematological Malignancies Characterised by Alterations of the NOTCH Signalling Pathway

NAME	TITLE	DATE	SIGNATURE
Florian Vogl, MD, PhD	Chief Medical Officer / Protocol Author		
Oliver Schoenborn-Kellenberger	Statistician, Cogitars GmbH, Germany		

CLINICAL RESEARCH ORGANISATION APPROVAL SIGNATURE PAGE

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NAME	TITLE	DATE	SIGNATURE
Victor Angélico	Medical Monitor, Covance		

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I agree to the terms and conditions relating to this study as defined in this protocol, Investigator's Brochure, the Case Report Form (CRF), and any other protocol-related documents. I am aware of my responsibilities as a coordinating investigator under the International Council of Harmonisation (ICH) Good Clinical Practice (GCP) guidelines, and all applicable regulations, laws and the study protocol. I agree to conduct the study according to these guidelines and to appropriately direct and assist the staff under my control, who will be involved in the study.

NAME	DATE	SIGNATURE
Elena Garralda, MD Hospital Vall d'Hebron	_____	_____

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I agree to the terms and conditions relating to this study as defined in this protocol, Investigator's Brochure, the Case Report Form (CRF), and any other protocol-related documents. I fully understand that any changes instituted by the Investigator(s) without previous agreement with the Sponsor would constitute a violation of the protocol, including any ancillary studies or procedures performed on the patients in this study (other than those procedures necessary for the well-being of the patients).

I agree to conduct this study in accordance with the Declaration of Helsinki and its amendments, International Council of Harmonisation (ICH) Good Clinical Practice (GCP) guidelines, and all applicable regulations and laws. In particular, I will obtain approval by an Independent Ethics Committee or Institutional Review Board (IEC/IRB) prior to study start and signed informed consent from all patients included in this study. In case an amendment to the protocol is necessary, I will obtain approval by an IEC/IRB and ensure approval by regulatory authorities (if applicable) has been obtained before the implementation of changes described in the amendment. In addition, I will allow direct access to source documents and study facilities to Sponsor representative(s), particularly monitor(s) and auditor(s),and agree to inspection by regulatory authorities or IEC/IRB representative(s). I will ensure that the study treatment(s) supplied by the Sponsor are being used only as described in this protocol. Furthermore, I confirm herewith that the Sponsor is allowed to enter and utilise my professional contact details and function in an electronic database for internal purposes and for submission to Health Authorities worldwide.

Principal Investigator	**Date**	**Signature**
Name, title	_____	_____

STUDY PROTOCOL SYNOPSIS

TITLE:	**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 locally advanced or metastatic solid tumours and haematological malignancies characterised by alterations of the NOTCH signalling pathway**
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SPONSOR:	Cellestia Biotech AG

OBJECTIVES

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 in adult patients.

Phase I, Part A – Confirmatory Cohort:

- To confirm safety of the RP2D of CB-103 as a single agent in adult patients.

Phase IIA, Part B - Expansion:

- To assess preliminary anti-tumour activity of single agent CB-103 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:**
  - To characterise safety and tolerability of the MTD/RP2D of CB-103 in patients with selected solid tumours and haematological malignancies
  - To assess preliminary anti-tumour activity of single agent CB-103
- **Part B only:**
  - To further characterise safety and tolerability of the MTD/RP2D of CB-103 in patients with selected solid tumours and haematological malignancies, stratified by disease into separate expansion arms.

Exploratory Objectives

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

- To characterise the pharmacokinetic (PK) characteristics of CB-103 in subgroups of patients (e.g., by indication or ethnicity) after single and repeated administration at various dose levels.
- To explore potential correlations between PK and parameters of efficacy (e.g. tumour response, tumour shrinkage, tumour metabolic activity), 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]).
- Positron Emission Tomography (PET) in selected tumours: baseline and on-treatment, ^{18}Fluoro-deoxyglucose positron emission tomography (FDG-PET) in

combination with CT (PET-CT) will be collected to determine changes in glucose metabolism of the tumour lesions in tumour types exhibiting FDG-uptake.

- To investigate plasma levels of metabolite(s) when feasible.
- To explore the CB-103 metabolic profile in biological matrices such as urine and/or stool samples.
- To assess changes in NOTCH target and downstream PD markers (genes, proteins) in solid tumours:
    - pre- and post- CB-103 dosing in **tumour tissue biopsies** as a measure of NOTCH pathway inhibition;
    - pre- and post- CB-103 dosing in **whole blood, plasma samples and hair follicles** (if the appropriate laboratory is available) as a surrogate model to measure NOTCH pathway inhibition.
- To assess changes in NOTCH target genes and downstream PD markers (genes, proteins) in haematological malignancies:
    - pre- and post- CB-103 dosing in **T-lymphocytes from blood and/or bone marrow samples**;
    - pre- and post- CB-103 dosing in **whole blood and plasma samples** (if the appropriate laboratory is available).
- To assess the changes in the percentage of mutated alleles in liquid biopsies pre- and post CB-103 dosing and their relation to the effect of CB-103 treatment.
- To evaluate the cerebrospinal fluid (CSF) exposure of CB-103 in patients with haematological malignancies in whom intra-thecal (IT) prophylaxis is planned by the treating physician.
- 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 analysis may be performed on **tumour tissue samples or on blood and/or bone marrow samples** as a part of this study to identify gene 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.
- Exploratory CB-103 quantification analysis may be performed on **tumour tissue samples**.
- To evaluate the potential role of biomarkers and genetic markers for safety, pharmacodynamic, and anti-tumour activity of CB-103 and to define the optimal biological dose of CB-103.
- To explore and assess changes in the immune system in pre- and post-CB-103 dosing whole blood and plasma.
- Additional exploratory analyses may be performed on available samples from the study, for example to establish a correlation of biomarkers across methods or types of tissue.

Note: during the course of the study, sample collection for and analysis of any of the above-mentioned exploratory objectives may be stopped for all patients or in selected patients' groups depending on the emerging preliminary data; the decision will be documented in a Note to File.

STUDY DESIGN

Description of Study

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 a dose escalation phase and the MTD/RP2D confirmatory cohort 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. 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.

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. 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, with at least 1 day apart from the second patient, 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 patients are dosed in 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 the CRC consisting of the Investigators, Sponsor and CRO representatives, and independent functional experts as required. The CRC will make the decision to determine the next dose level and schedule for the next dose cohort.

Any dose level cohort that has been declared safe after the DLT period, may be expanded by individual patients in order to collect additional pharmacodynamic (PD) and pharmacokinetic (PK) information to support and/or confirm the mechanism of action and explore doses at the currently tolerated dose level or below. These patients will be

counted for the respective cohort at the future CRC meetings and will contribute towards the overall safety, PK, PD and clinical efficacy evaluation.

When the MTD/RP2D is defined, based on decision of the CRC, approximately 45 additional NOTCH-positive patients (MTD/RP2D confirmatory cohort) with recurrent/metastatic adenoid cystic carcinomas (ACC), breast cancer, relapsed/refractory (r/r) T-cell acute lymphoblastic leukaemia (T-ALL) or lymphoma (T-LBL), or any other solid tumour with proven Notch pathway activation will receive the MTD/RP2D dose to ascertain that optimal safety related to efficacy and pharmacodynamics in the tumour and in peripheral blood are achieved.

Part B - 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 and confirmed.

NUMBER OF PATIENTS

Part A: approximately 55 patients; depending on the BLRM, additional patients may be enrolled in some dose cohorts. Based on the decision of the CRC approximately 45 patients in total may be enrolled in the MTD/RP2D confirmatory cohort to confirm safety before opening Part B.

Part B: 100-140 patients plus the eligible patients from the MTD/RP2D confirmatory cohort, resulting in 145-185 patients dosed at the RP2D.

Total study population: 200-240 patients.

TARGET POPULATION

Adult patients with histologically confirmed locally advanced and/or metastatic solid tumours and with r/r T-ALL or T-LBL for whom no standard-of-care therapy exists.

INCLUSION/EXCLUSION CRITERIA

Inclusion criteria

Patients must meet the following criteria for study entry:

1. **Disease**

   a. Histologically or cytologically confirmed solid tumours that are surgically unresectable, locally advanced, or metastatic which have progressed on at least one line of systemic therapy (with the exception of adenoid cystic carcinoma [ACC] patients who are allowed to be systemic treatment-naïve) and for which no established therapeutic alternatives exist.

   or

   b. Relapsed or refractory (r/r) T-cell acute lymphoblastic leukaemia (T-ALL) or lymphoma (T-LBL). Refractory patients are defined as T-ALL/T-LBL patients with ≥ 5% bone marrow blasts and/or concomitant extramedullary involvement, who have not achieved a CR after standard induction/consolidation therapy attempt. Relapsed patients are defined as T-ALL/T-LBL patients who have recurrent disease, i.e. ≥ 5% bone marrow blasts and/or concomitant extramedullary relapse, after having achieved a prior CR.

   c. For **Part A (dose-escalation)** solid tumour indications based on known frequent involvement of the NOTCH pathway activation in these indications, and tumours with an *a priori* known NOTCH1-4 pathway activation are eligible, as defined below:

      - Breast cancer (triple negative breast cancer [TNBC], ER+/-, HER2+/-), gastrointestinal (GI) cancers (resistant to oxaliplatin or irinotecan-based therapy colorectal cancer [CRC], hepatocellular carcinoma [HCC]), osteosarcoma, ACC and malignant glomus tumour.
      - Any other solid cancer (including lymphoma) with a confirmed NOTCH1-4 activating mutation or genetic lesion.

   d. For **Part A (MTD/RP2D confirmatory cohort) and Part B expansion cohorts,** solid and haematological tumour indications with confirmed Notch pathway activation as follows:

      - ACC
      - Metastatic breast cancer (regardless of receptor status of ER/PR, HER2)
      - r/r T-ALL/T-LBL
      - Any other cancer (haematologic or solid) with a confirmed NOTCH pathway activation, after approval by the Sponsor

      Notes:

      - Patients are eligible if Notch pathway activation was determined in the past. If the Notch status is unknown, it will be determined on fresh bodily material.

- The pathogenic character of the detected mutation/genetic alteration needs to be confirmed before the patient can be enrolled. Patients whose tumour mutations/alterations are not unambiguously pathogenic will be included at the Sponsor's discretion. Details on molecular alterations as signs of Notch pathway activation and the specific test method can be found in the laboratory manual.

e. 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).

f. **Patients with solid tumour indications in Part A (dose-escalation):**

- Sufficient archival tumour tissue samples. If the archival tissue is older than 6 months at screening – or, if not available – a fresh pre-dose tumour biopsy is required. If the lesion is not accessible for a fresh tumour biopsy, a liquid biopsy may be used after confirmation with the Sponsor.

g. **Patients with solid tumours in the MTD/RP2D confirmatory cohort of Part A and in Part B:**

- If Notch status is unknown, patients with solid tumours 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.
- All solid tumour patients: tumour lesions accessible to biopsy and patient willing to provide a fresh tumour biopsy at pre-dose, one during treatment, and one at disease progression or when clinically indicated. In individual cases where the lesion is not accessible for a fresh tumour biopsy, a liquid biopsy may be used after confirmation with the Sponsor.

h. Life expectancy of at least 3 months in the opinion of the investigator.

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. Total serum bilirubin ≤ 1.5 x upper limit of normal (ULN)

b. 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

c. 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

d. 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)

e. Potassium levels within normal limits or correctable with supplements

f. Total calcium levels (corrected for serum albumin) within normal limits or correctable with supplements

g. Magnesium levels within normal limits or correctable with supplements

h. Phosphorus levels within normal limits or correctable with supplements

i. Serum albumin concentration ≥ 30 g/L

j. Patients with solid tumours must have:

- Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L
- Haemoglobin (Hgb) ≥ 10 g/dL (≥ 100 g/L)
- Platelet count ≥ 75 x 10^9/L (without platelet transfusion or growth factor support in the preceding 7 days)
- 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, injectable contraceptives, mechanical contraception including a condom for the partner, or an intrauterine coil) and must continue using them throughout the entire clinical trial period and for 90 days post-treatment completion (duration of 3 ovulatory cycles). Contraception must start from the day of 1st administration of CB-103.

c. Men whose partners could be of childbearing 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 A - MTD/RP2D confirmatory cohort - and part B) and screening.

Exclusion criteria

Patients who meet any of the following criteria will be excluded from participation in the study:

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.

Note: T-ALL/T-LBL patients with active CNS disease defined as the presence of CNS disease at diagnosis, and/or presence of CNS involvement-related symptoms, e.g. related to cranial nerve involvement, may not be included.

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 (systolic blood pressure ≥ 160 mmHg or diastolic blood pressure ≥ 100 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-cancer therapy (e.g., anti-HER2 therapy, anthracyclines), 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 treatment
2. For patients with solid tumours: prior bone marrow/haematopoietic stem cell transplant.
   Note: For T-ALL patients prior allogenic bone marrow/haematopoietic stem cell transplant is allowed if they have no current GvHD and patients are off immunosuppressive therapy.

3. Known infection with human immunodeficiency virus (HIV); or hepatitis B or C requiring treatment
4. Any active infection requiring the use of parenteral anti-microbial agents or that is > Grade 2
5. Non-malignant interstitial lung disease or pneumonitis
6. Dyspnoea of any cause requiring supplemental oxygen therapy and dyspnoea at rest due to complications of advanced malignancy and co-morbidities.
7. 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.
8. 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. In patients with solid tumours, cytotoxic chemotherapy within 3 weeks (6 weeks for nitrosoureas and mitomycin C) of the scheduled first dose of CB-103 on day 1.

b. In T-ALL/T-LBL patients, prior anticancer therapy less than 2 weeks prior to starting therapy or 5 half-lives (whichever is longer) with the following exceptions:

1. Up to 5 days of glucocorticoids (10 mg/m^2 dexamethasone or equivalent/day) in combination with up to 3 doses of cyclophosphamide (200 mg/m^2/day) are allowed as standard prephase treatment up to 1 day before start of study treatment
2. Mercaptopurine may be dosed up to 5 days prior to first dose of CB103
3. Vinca alkaloids may be dosed up to 5 days prior to first dose of CB103
4. Prophylactic intrathecal (IT) chemotherapy may be dosed up to 3 days prior to first dose of CB103.

c. Prior cumulative doxorubicin exposure of ≥ 500 mg/m^2

d. Prior cumulative epirubicin exposure of ≥ 900 mg/m^2

e. Any investigational treatment (including NOTCH signalling inhibitors and prior treatments with CB-103) within 4 weeks of scheduled CB-103 dosing 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 other adverse event associated with leukemic involvement), 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 (a list of drugs is given in Appendix 4 of the protocol). However, in case of a life-threatening infection, in the best interest of the patient, concomitant treatment with the study drug and the relevant anti-infectious drug, though this may be included in the list given in Appendix 4, can be continued with closer monitoring.

b. 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.

c. 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.

DURATION OF STUDY

The study will be completed 28 days after the last patient in Part B of the study received the last treatment.

END OF STUDY

The end-of-study is reached when the last patient in Part B of the study has been on study treatment for up to 12 cycles plus the safety follow-up period of 28 days after the last dose of CB-103. In case the study is stopped before any patient was treated for 12 months, the end-of-study is reached 28 days after the last patient in Part B of the study has received his/her last dose of CB-103.

DOSE-LIMITING TOXICITY (DLT)

DLT is defined as an adverse event or abnormal laboratory value assessed as unrelated to disease progression, inter-current illness, or concomitant medications, that occurs ≤ 28 days following the first dose of CB-103 (Cycle 1) and that meets any of the following criteria shown in the table below.

Note: For T-ALL/T-LBL patients enrolled into the confirmatory cohort of Part A or expansion cohort of Part B of the study, haematological toxicity in non-responding patients, or death after progression should not be considered as DLT.

Toxicity	Any of the following criteria
Haematology	≥ CTCAE grade 3 neutropenia (ANC < 1.0 x 10^9/L) lasting for ≥ 7 days[1]
	≥ CTCAE grade 4 neutropenia (ANC < 0.5 x 10^9/L)[1]
	Febrile neutropenia (ANC < 1.0 x 10^9/L, fever ≥ 38.3°C) [1]
	CTCAE grade 3 thrombocytopenia (platelets < 50-25 x 10^9/L) lasting for ≥ 7 days and/or with signs of bleeding[1]
	CTCAE grade 4 thrombocytopenia (platelets < 25 x 10^9/L)[1]
	≥ CTCAE grade 4 anaemia[1]
Cardiac	≥ CTCAE grade 3
	≥ CTCAE grade 3 hypertension for > 14 consecutive days despite optimal anti-hypertension therapy
Renal	Serum creatinine > 2 x ULN
Hepatic	≥ CTCAE grade 3 total bilirubin (>3 x ULN)
	CTCAE grade 2 total bilirubin lasting for ≥ 7 days.
	≥ CTCAE grade 2 total bilirubin and ≥ CTCAE grade 2 ALT or AST
	CTCAE grade 3 ALT or AST lasting for ≥ 7 days
	CTCAE grade 4 ALT or AST
	Hepatic lab parameters fulfilling Hy's Law: AST/ALT 3 x ULN and concomitant 2 x ULN for bilirubin[2]
Pancreatic	≥ CTCAE grade 3 pancreatitis
	CTCAE grade 3 asymptomatic serum lipase lasting for ≥ 7 days
	CTCAE grade 3 symptomatic serum lipase
	CTCAE grade 4 serum lipase
Other adverse events	Any CTCAE grade 5 toxicity
	≥ CTCAE grade 3 blurred vision or any other eye disorder
	≥ CTCAE grade 3 vomiting or nausea for ≥ 72 hours despite optimal anti-emetic therapy[3]
	≥ CTCAE grade 3 diarrhoea for ≥ 72 hours despite optimal anti-diarrhoea treatment[3]

	Any other ≥ CTCAE grade 3 adverse event, except for the exclusions noted below
	Inability to administer CB-103 on ≥ 75% of scheduled treatment days during cycle 1 (i.e., ≥ 21 days for a 28-day daily dosing schedule) due to unresolved adverse event of any grade related to CB-103.
	Delay in 2nd cycle administration due to failure of recovery from a possibly, probably or definitely related adverse event to grade ≤ 1 or baseline by Day 43 (D28 of cycle 1 + 15 days), except for alopecia.
Exceptions to DLT criteria	CTCAE grade 3 or 4 elevations in alkaline phosphatase
	< 96 hours of CTCAE grade 3 fatigue
	Investigations (e.g., laboratory values) CTCAE grade ≥ 3 which are judged not clinically significant by the Investigator[4]

Abbreviations: ALT, alanine aminotransferase; ANC, absolute neutrophil count; AST, aspartate aminotransferase; CTCAE, Common Terminology Criteria for Adverse Events; DLT, dose-limiting toxicity; PRBC, packed red blood cells; ULN, upper limit of normal.

NCI CTCAE v4.03 will be used for all grading.

[1] Patients may receive supportive care (e.g. use of granulocyte-colony stimulating factor [G-CSF], packed red blood cells (PRBCs), platelets) as per local institutional guidelines. However, during the DLT period it is not allowed to administer these supportive measures prophylactically.

[2] Patients fulfilling the criteria for Hy`s law will need to be immediately discontinued from treatment

[3] Optimal therapy for vomiting or diarrhoea will be based on institutional guidelines and based on Section 7.4.7, with consideration of the prohibited medications listed in the protocol.

[4] An abnormal lab value / investigation should be deemed clinically significant (assessed by the Investigator) if either of the following conditions is met:

- The abnormality suggests a disease and/or organ toxicity that is new or has worsened from baseline
- The abnormality is of a degree that requires additional active management, e.g., change of dose, discontinuation of the drug, close observation, more frequent follow-up assessments, or further diagnostic investigation.

Therefore, a clinically significant lab value is one that indicates a new disease process, an exacerbation or worsening of an existing condition, or requires further action(s) to be taken.

During the MTD/RP2D confirmatory cohort of Part A of the study and during Part B, the study will use the CTCAE version 4.03 criteria to capture toxicities and these will be managed, and dose modified as described in Section 7.4.6. The CRC will review at least on a quarterly basis all CTCAEs ≥ grade 3, all SAEs, all clinically significant laboratory abnormalities and all available safety data to confirm the proposed dose for the expansion part is safe and well tolerated. The CRC will recommend, if necessary, to pause enrolment or implement additional safety monitoring while such a review is undertaken.

All decisions made by the CRC will be captured in meeting minutes.

PRIMARY OUTCOME MEASURES

The primary outcome measures for this study are as follows:

Part A (Escalation):

- Dose limiting toxicities (DLT)

Part B (Expansion):

- Best overall response according to the respective tumour assessment criteria for the different cancer indications

SECONDARY OUTCOME MEASURES

The secondary outcome measures for this study are as follows:

- Safety
    a. Adverse events
    b. Safety laboratory
    c. Vital signs
    d. Electrocardiogram
- Preliminary efficacy
    a. Overall response rate
    b. Clinical benefit rate at Month 3, 6, and 9
    c. Duration of response
    d. Progression free survival (PFS) and overall survival (OS)

PHARMACOKINETIC OUTCOME MEASURES (SECONDARY)

The PK outcome measures are:

- Maximum plasma concentration (C_{max}), time to C_{max} (t_{max}), minimum plasma concentration (C_{min}), last measurable plasma concentration (C_{last}), time to last measurable plasma concentration (t_{last}), area under the curve (AUC) during 8 and 24 hours (AUC_{0-8}, AUC_{0-24}), AUC from time 0 extrapolated to infinite time ($AUC_{0-\infty}$), apparent volume of distribution (V_d/F), apparent volume of distribution at steady state (V_{ss}/F), apparent clearance after oral administration (CL/F), elimination half-life ($t_{1/2}$) and accumulation ratio (AR).

PHARMACOKINETIC/ PHARMACODYNAMIC OUTCOME MEASURES (EXPLORATORY)

The PK/PD measures for this study are as follows:

- Association of CB-103 plasma concentrations and/or PK parameters (e.g., AUC, C_{max}) with signs of efficacy, PD parameters and safety.

FURTHER EXPLORATORY OUTCOME MEASURES

Further exploratory outcomes measures for this study are:

- Additional PK, metabolite, PD markers, genomic, protein , and pharmacogenetics analyses (separate analysis plan and report).

BIOMARKER OUTCOME MEASURES (EXPLORATORY)

The biomarker outcomes measures for this study are:

- Summary statistics of PD, mechanistic and tumour profiling biomarkers will be reported by dose group and may be examined for possible correlations with CT/MRI/positron emission tomography (PET)-CT outcomes.

BIOMARKER/GENOTYPING SAMPLE COLLECTION

Remaining blood and/or tumour tissue samples may be used for DNA, RNA and/or protein-based analyses. Details regarding the biomarkers analysed will be provided in a separate Laboratory Manual.

INVESTIGATIONAL MEDICINAL PRODUCT

Test product: CB-103

Placebo: Not applicable

PROCEDURES

Informed consent will be obtained prior to any study-specific procedures. Following eligibility at screening and the confirmation at baseline, patients will be enrolled into the study. The assessments and examinations will be conducted as described in the Schedules of Assessments for Part A (Escalation) and Part B (Expansion).

Assessments as deemed necessary by the Investigator and/or Sponsor/its delegate clinical research organisation (CRO) Covance in particular for safety and any other additional examinations and assessments deemed necessary, can be performed at unscheduled visits at the discretion of the Investigator and Sponsor/delegate CRO Covance.

Patients who complete the study will be followed-up for survival.

STATISTICAL METHODS

PRIMARY ANALYSIS

Part A (Escalation):

- Bayesian Logistic Regression Model for dose escalation to determine MTD or RP2D.

Part B (Expansion):

- Bayesian hierarchical partially exchangeable binomial design to determine preliminary efficacy.

SAFETY ANALYSES

Adverse events, related adverse events, serious adverse events and related serious adverse events, adverse events with NCI CTCAE Grades ≥ 3, related adverse events with NCI CTCAE Grades ≥ 3, adverse events leading to premature discontinuation, interruptions or discontinuation of study drug or dose modification will be analysed descriptively utilising corresponding Medical Dictionary for Regulatory Activities (MedDRA) System Organ Classes (SOCs) and Preferred Terms (PTs).

Safety laboratory results will be graded by NCI CTCAE version 4.03, if no grading exists values will be classified into low/normal/high based on laboratory normal ranges. Each parameter will be presented by descriptive statistics at each visit including change from baseline (screening). Shift tables for CTCAE grades and normal ranges will be presented. All laboratory values will be listed. A separate listing for abnormal lab values (Grade 3 and higher, and low/high values) will be presented.

Vital signs will be summarised by descriptive statistics at each visit including change from baseline; these will be presented, and a listing will be provided.

Centrally-read ECG data will be listed overall and a separate listing for any clinically significant finding in ECG values will be provided. Change from baseline in QT intervals by cohort will be summarised for each visit as well as change from baseline in all other ECG parameters. Also, the worst change from baseline will be summarised. The frequency and percentage of patients with notable ECGs and newly occurring qualitative ECG abnormalities will be tabulated by cohort.

EFFICACY ANALYSES

Overall response rate as defined by achieving:

- In solid tumours, confirmed complete response (CR) and/or partial response (PR) will be presented by percentage rates and 95% confidence intervals (CI). For changes in solid tumour size, waterfall plots will be presented.
- In T-ALL/T-LBL patients, confirmed Complete Remission (CR) and/or Complete Remission with Incomplete Hematologic Recovery (CRi) will be presented by percentage rates and 95% CI.
- For solid tumour indications: clinical benefit rate at Month 3, 6, and 9, as defined by achieving complete response (CR) and/or partial response (PR) and/or stable disease (SD) will be assessed by RECIST 1.1 and presented by percentage rates and 95% CI. Waterfall plots will be presented.
- For T-ALL/T-LBL patients: the ORR is the sum of patients achieving a CR or a CRi divided by the total number of patients with T-ALL/T-LBL treated. Assessment of efficacy will be performed on results of bone marrow biopsies or aspirates, blood and CSF samples, and PET-CT in patients with extramedullary disease, based on the NCCN Guidelines on Adult Acute Lymphoblastic Leukemia (Version 1.2020).

For all response assessments, swimmers plots will be presented. All response assessments will be listed.

The duration of response defined as time from first assessment of PR or CR in solid tumours or CRi in T-ALL/T-LBL to follow-on first assessment of PD or relapse will be summarised by descriptive statistics including median duration of response and respective 95% CI. Duration of response will also be listed.

Time from first treatment received until progressive disease (PD)/OS will be summarised by Kaplan-Meier estimates, median PFS/OS and respective 95% confidence intervals. Patients with no event will be censored at the last available tumour assessment for PFS and at the last timepoint known alive for OS.

PHARMACOKINETIC ANALYSES

CB-103 concentrations will be determined by a validated high-performance liquid chromatography (HPLC) tandem mass spectrometry (LC/MS/MS) method and the following PK parameters of CB-103 including: C_{max}, t_{max}, C_{min}, C_{last}, t_{last}, AUC_{0-8}, AUC_{0-24}, $AUC_{0-\infty}$, V_d/F, V_{ss}/F, CL/F, $t_{1/2}$ and AR. All PK parameters will be calculated from the curves constructed from the individual patients. Non-compartmental analysis will be performed using Phoenix WinNonlin version 6.3 (Pharsight Corporation, Mountain View, CA, USA).

No formal statistical analysis beyond descriptive statistics is planned. For each PK parameter, individual and mean data and summary statistics (including number of patients, arithmetic mean, geometric mean [for time to maximum plasma concentration (t_{max}) and time to last measurable plasma concentration (t_{last}) no geometric mean will be

calculated], standard deviation (StD), confidence value (CV), median, Min and Max) will be presented.

EXPLORATORY ANALYSES

Exploratory PK assessments, plasma levels of metabolite(s), PD markers (genes, proteins) in tumour tissue biopsies and in whole blood, plasma samples and hair follicles, genotypes, protein expression, and circulating tumour DNA in blood samples will be analysed post-hoc by Sponsor or by a delegated Laboratory or investigational site. With the PK timepoints collected, a population PK model will be built and then used to estimate individual AUCs or CL of CB-103. CB-103 AUC, as well as the observed C_{max}, will then be tested for association with signs of efficacy and safety. A separate analysis plan and report for such assessments will be written.

BIOMARKER ANALYSES

Summary statistics of PD, mechanistic and tumour profiling biomarkers will be reported by dose group and may be examined for possible correlations with CT/MRI/PET-CT efficacy endpoints. Additional analyses include comparing PD modulation with exposure.

SAMPLE SIZE JUSTIFICATION

Part A (Escalation)

For all dose levels, from starting dose to the respective dose escalation levels, 3-6 patients will be enrolled and treated with CB-103 according to a staggered inclusion scheme to ensure adequate time for safety observation between inclusions, and before dose escalation. During the study, a minimum of 3 patients evaluable for the DDS will be treated per dose cohort until determination of the MTD or RP2D. Depending on the BLRM, additional patients may be enrolled in some dose cohorts. Approximately 11 dose cohorts are considered for this study with at least 3 patients per dose cohort. It is estimated that approximately 55 patients will be enrolled, not taking into account the drop-outs and additional patients enrolled for some of the dose groups. Based on the decision of the CRC, approximately 45 patients may be enrolled in the MTD/RP2D confirmatory cohort to confirm safety before opening Part B.

Part B (Expansion)

Part B of the study will consist of one or several expansion arm(s) with selected tumour indications. For the analysis of the expansion arms a Bayesian Hierarchical binomial-design will be applied with enrolment of at least 10 patients into each arm. With 10-20 patients enrolled into each expansion arm it is estimated that about 100-140 patients (pending of the number of arms) will need to be recruited. Patients from the MTD/RP2D confirmatory cohort of Part A that qualify for any of the expansion arms will be included into the analyses of Part B and will contribute to the total sample size per arm.

20 patients per indication arm will give sufficient evidence to determine early signs of clinical benefit. Assuming a true response rate of 30% for exchangeable and partially-exchangeable indications (based on response criteria) the lower limit of the credible band for the point estimate would be greater than or equal to 19%.

The following indications for patients with NOTCH activated pathways are considered and grouped into the respective expansion arms:

1. Adenoid cystic carcinoma (ACC)
2. Triple negative breast cancer (TNBC)
3. Breast cancer (ER+/-, HER2+/-)
4. Osteosarcoma, Malignant glomus tumour
5. GI cancers (resistant to oxaliplatin or irinotecan-based therapy colorectal cancer, hepatocellular carcinoma)
6. r/r T-cell Acute Lymphoblastic Leukaemia (T-ALL) or T-cell Lymphoblastic Lymphoma (T-LBL)
7. Any other cancer (haematologic or solid) with confirmed Notch pathway activation (basket arm)

The indications considered for the expansion arms in Part B might be adapted and/or additional arms added by a protocol amendment based on the outcome of Part A and further findings from non-clinical studies with CB-103 and the planned interim analysis; this might increase the planned sample size.

Interim Analyses

Part A (Escalation)

Each dose escalation step is considered to be an interim analysis. The BLRM will be updated with the respective number of patients treated and the number of DLTs observed in the last cohort. The updated model will then give a statistical recommendation for the next escalation step. However, a risk-benefit assessment that includes a comprehensive analysis of safety and available clinical information will be done to decide on the next escalation steps.

Part B (Expansion)

Interim analyses will be triggered each time 10 patients in an arm have completed their first response assessment, this includes patients from the MTD/RP2D confirmatory cohort of Part A that qualify for any of the extension arms. An interim analysis will include all patients enrolled at, or prior to the cut-off (set by the completion of the 10th patient), and will be conducted once all patients have completed sufficient assessments to be categorised under the response endpoint, or have withdrawn from study. All arms that remain open to recruitment, and for which the minimum data efficacy requirements have been met, will be assessed for futility. For the interim and final analyses, a hierarchical model will be used. This model leads to more precise estimates of the indication-specific treatment effects as compared to those from stratified analyses. Details of the model can be found above, and further descriptions are given in Appendix 10 of the protocol. The results of the interim analyses will be non-binding. Safety criteria will also be evaluated to decide on the continuation of the study arms. Since this is a non-comparative multiple arm study, no adjustment for multiple testing is made.

LIST OF PROHIBITED MEDICATIONS

The following medications are strictly prohibited in this study:

Prior concomitant therapy

Patients who have received any of the therapies and medications prior to study entry as outlined in the exclusion criteria under point 3, “Prior Therapy” are not allowed to be enrolled in this study.

Concomitant medications

- **Drugs with a known risk to induce Torsades de Pointes:**

  All QT-prolonging drugs (see Table 1 in Appendix 4) of the protocol) are prohibited for all patients from screening through permanent discontinuation of study treatment.

- **Drugs with a conditional risk to induce Torsades de Pointes:**

  The concomitant use of any QT prolonging medication with a conditional risk of inducing Torsades de Pointes (see Table 2 in Appendix 4) is allowed during the DLT period and throughout the treatment period, ONLY under the exceptions described in Section 7.4.7 for the management of diarrhoea and nausea. These exceptions will have to be discussed upfront with the Sponsor on a case-by-case basis.

- **Drugs with a possible risk to induce Torsades de Pointes:**

  The concomitant use of any QT prolonging medication with a possible risk of inducing Torsades de Pointes (see Table 3 in Appendix 4) is not allowed during the DLT period and should be used with caution and under special attention throughout the treatment period before more safety information about CB-103 is collected.

  However, in case of a life-threatening infection, in the best interest of the patient, concomitant treatment with the study drug and the relevant anti-infectious drug, though this may be included in the list given in Appendix 4, can be continued with closer monitoring.

List of drugs that should be used with caution:

- **Drugs that are metabolised by cytochrome p450 (CYP450)**

  Caution should be exercised when CB-103 is combined with sensitive substrates of CYP enzymes and CYP substrates with a narrow therapeutic index (see examples in Table 1 of Appendix 5 of the protocol).

- **Drugs that are inhibitors or inducers of CYP450**

  Strong inhibitors and inducers of CYP isoenzymes should be avoided during treatment with CB-103 (Table 1 in Appendix 6 of the protocol).

- **Drugs that affect serotonin levels**

  Caution should be exercised when compounds that affect serotonin levels (e.g., SSRIs, serotonin norepinephrine reuptake inhibitors, tricyclic antidepressants, tryptophan, dextromethorphan, meperidine) are combined with CB-103.

- **Anticoagulants**

  Patients receiving coumarin-type anticoagulants who cannot discontinue treatment at least one week prior to the start of treatment with CB-103 and for the duration of the study. Low molecular weight heparin and direct oral anticoagulants are permitted.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ACC	Adenoid cystic carcinoma
ADC	Antibody-drug conjugates
ADME	Absorption, distribution, metabolism, and excretion
AE	Adverse Event
AESI	Adverse events of special interest
AGA	American Gastroenterological Association
AhR	Aryl hydrocarbon receptor
ALCOA	Attributable, Legible, Contemporaneous, Original and Accurate
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
aPTT	Activated partial thromboplastin time
AR	Accumulation ratio
ARA	Acid-reducing agent
AST	Aspartate aminotransferase
ATC	Anatomical, Therapeutic and Chemical
AUC	Area under the curve
$AUC_{0-\infty}$	AUC from time 0 extrapolated to infinite time
AUC_{0-8}	AUC during 8 hours
AUC_{0-24}	AUC during 24 hours
BCP	B-cell precursor
BID	Twice daily
BLRM	Bayesian logistic regression model
BM	Bone marrow
BNP	Brain natriuretic peptide
Bpm	Beats per minute
CCC	Cholangiocellular carcinoma
CI	Confidence interval
CL	Clearance
CL/F	Oral clearance
CLL	Chronic lymphocytic leukaemia
C_{last}	Last measurable plasma concentration

Abbreviation	Definition
C_{max}	Maximum plasma concentration
C_{min}	Minimum plasma concentration
CNS	Central nervous system
CONSORT	Consolidated Standards of Reporting Trials
CPK	Creatine phosphokinase
CR	Complete response/Complete remission
CRC	Cohort Review Committee; colorectal cancer
CRF	Case Report Form
CRi	Complete remission with incomplete haematologic recovery
CrCl	Creatinine clearance
CRO	Clinical research organisation
CRP	C-reactive protein
CSF	Cerebrospinal fluid
CSR	Clinical Study Report
CT	Computed tomography
CTCAE	Common terminology criteria for adverse events
CV	confidence value
CYP	Cytochrome P450
DDI	Drug-drug interaction
DDS	Dose-determining set
DLL1	Delta-like ligand 1
DLL3	Delta-like ligand 3
DLL4	Delta-like ligand 4
DLT	Dose-limiting toxicity
DOR	Duration of response
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDC	Electronic data capture
EDTA	Ethylenediaminetetraacetic acid
EEA	European Economic Area
EMA	European Medicines Agency
EMT	Epithelial-mesenchymal transition

Abbreviation	Definition
EOS	End-of-study
EOT	End of Treatment
ER	Estrogen receptor
EU	European Union
EWOC	Dose escalation with overdose control
FCS	Fetal calf serum
FDA	Food and Drug Administration
F	Bioavailability
FDG-PET	[18F]Fluoro-2-deoxyglucose positron emission tomography
FLC	Free light chain
FPFV	First-patient-first-visit
γ-GT	Gamma-glutamyl-transferase
GBM	Glioblastoma multiforme
GCP	Good Clinical Practice
G-CSF	Granulocyte-colony stimulating factor
GI	Gastrointestinal
GLP	Good Laboratory Praxis
GMP	Good Manufacturing Practice
GOF	Gain of function
GvHD	Graft versus host disease
GSI	Gamma-secretase inhibitors
HCC	Hepatocellular carcinoma
HCT	Haematopoietic Cell Transplantation
HER2	Human epidermal growth factor receptor 2
Hgb	Haemoglobin
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
HNSCC	Head and neck squamous cell carcinoma
HSNTD	Highest non-severely toxic dose
HR	High risk
HRS	Hodgkin and Reed-Sternberg cells
IC_{50}	Concentration of an inhibitor where the response (or binding) is reduced by half
ICF	Informed Consent Form

Abbreviation	Definition
ICH	International Council of Harmonization
IEC	Independent Ethics Committee
IHC	Immunohistochemistry
i.m.	Intramuscular
IMiD	Immunomodulatory agent
IMP	Investigational medicinal product
IMWG	International Myeloma Working Group
IND	Investigational new drug (application)
INR	International normalised ratio
IRB	Institutional Review Board
IT	Intra-thecal
i.v.	Intravenous
LLN	Lower limit of normal
LOF	Loss of function
LVEF	Left ventricular ejection fraction
mAb	Monoclonal antibody
MAO	Monoamine oxidase
MAOI	Monoamine oxidase inhibitor
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial infarction
MRI	Magnetic resonance imaging
NICD1	Notch intracellular domain 1
NSG	NOD Scid Gamma
MTD	Maximum tolerated dose
MUGA	Multigated acquisition
MZB	Marginal zone B
N1, N2, N3, N4	NOTCH1, NOTCH2, NOTCH3, NOTCH4 receptor molecules
NAT	N-acetyltransferase
NCI	National Cancer Institute
NGS	Next generation sequencing
NICD	NOTCH intracellular domain
NIH	National Institutes of Health
NMZL	Nodal Marginal Zone Lymphoma
NOAEL	No-observed-adverse-effect level

Abbreviation	Definition
NOS	Not Otherwise Specified
NSCLC	Non-small cell lung cancer
NT-pro-BNP	N-terminal propeptide brain natriuretic peptide
NYHA	New York Heart Association
OS	Overall survival
PD	Pharmacodynamics
PC	Plasma cell
PDx	Patient derived xenograft
PGx	Pharmacogenomic
PET-CT	Positron emission tomography–computed tomography
PFS	Progression-free survival
Pgp	P-Glycoprotein
PK	Pharmacokinetic
PPI	Proton pump inhibitor
PR	Partial response
PS	Performance status
PRBC	Packed red blood cell
PT	Preferred term
PTT	Partial thromboplastin time
PXR	Pregnane X receptor
QD	Once daily
QRS	QRS complex
QT	QT interval
QTc	QT corrected for heart rate
QTcF	QT corrected for heart rate using the Fridericia's correction factor
r/r	Relapsed or refractory
RBC	Red blood cell
RECIST	Response Evaluation Criteria in Solid Tumours
RP2D	Recommended phase 2 dose
RSI	Reference safety information
SAE	Serious Adverse Event
SAP	Statistical analysis plan
s.c.	Subcutaneous
sCR	Stringent complete response

Abbreviation	Definition
SD	Stable disease
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SNRI	Serotonin norepinephrine reuptake inhibitor
SOC	System Organ Class
SOP	Standard operating procedure
SSRI	Selective serotonin reuptake inhibitor
StD	Standard deviation
$t_{1/2}$	Elimination half-life
T-ALL	T-cell acute lymphoblastic leukaemia
TCA	Tricyclic antidepressants
TCP	T-cell precursor
TdP	Torsades de Pointes
TFH	T Follicular Helper
TID	Three times daily
t_{last}	Time to last measurable plasma concentration
T-LBL	T-cell lymphoblastic lymphoma
t_{max}	Time to maximum plasma concentration
TNBC	Triple negative breast cancer
TPN	Total Parenteral Nutrition
Trop	Troponin
ULN	Upper limit of normal
US	United States
Vd	Volume of distribution
Vd/F	Apparent volume of distribution
VGPR	Very good partial remission
V_{ss}	Volume of distribution at steady state
V_{ss}/F	Apparent volume of distribution at steady state
WBC	White blood cell
WHO	World Health Organization
WOCBP	Women of childbearing potential

1. INTRODUCTION

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 locally advanced or metastatic oncology indications. 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) including a dose escalation part to determine the maximum tolerated dose (MTD) or recommended Phase II dose (RP2D) and a MTD/RP2D confirmatory cohort. Part B (the Phase IIA component of the study) is the expansion part of the study with several expansion arms in patients with selected tumour indications and to explore preliminary clinical efficacy and PD of CB-103 in these indications. While in the dose escalation of Part A no patient enrichment for NOTCH will be implemented, in the MTD/RP2D confirmatory cohort of Part A and in Part B the patients must have tumours characterised by a functionally over-activated NOTCH signalling pathway determined by molecular and/or biochemical biomarkers.

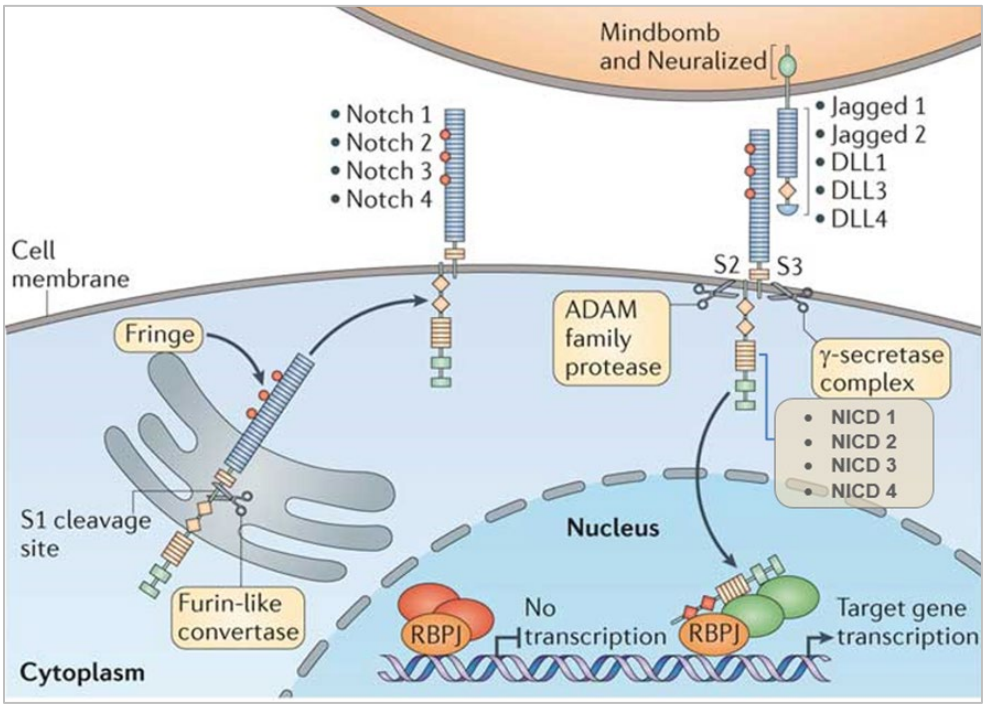
2. BACKGROUND INFORMATION

NOTCH signalling plays a key role in many cellular processes during development. NOTCH is a developmental pathway characterised by cell to cell communication 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 deregulation of the self-renewal process resulting in sustained proliferation, evasion of cell death, loss of differentiation capacity, invasion and metastasis, and resistance 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 cancer, promoting progression, development of metastasis, escaping apoptosis or to even cause resistance against chemotherapy or other targeted therapies.

2.1 NOTCH SIGNALLING PATHWAY

The NOTCH pathway is a cascade that facilitates cell-cell communication during development. NOTCH signalling is initiated upon binding of one of the five NOTCH ligands (Delta-like ligands DLL1, DLL3, DLL4, Jagged ligands Jag1, Jag2) to one of the four NOTCH receptors (NOTCH1, NOTCH2, NOTCH3 and NOTCH4) on adjacent cells (Figure 1; Table 1).

Figure 1 Overview of the NOTCH signalling pathway



Source: Adapted from Radtke et al., 2013.

Table 1 Overview of the NOTCH pathway components and function

NOTCH pathway component	Function
Ligands	
DLL 1	Governing cell fate decisions and cell-to-cell communication
DLL 3	Suppressing cell growth by apoptosis induction
DLL 4	Activating NF-κB signalling to enhance VEGF secretion and promote metastasis
JAG 1	JAG1 activation of NOTCH enhances angiogenesis
JAG 2	Interaction with NOTCH2 to promote cell survival and proliferation
Receptors	
NOTCH1	Transmembrane receptor involved in cell proliferation, invasion, and chemoresistance
NOTCH2	Constitutive NOTCH2 signalling induces hepatic tumours
NOTCH3	Promoting proliferation and migration, and modifying chemotherapy response
NOTCH4	Involved in endocrine therapy resistance and EMT in breast cancer
Example Target Genes	
Hes1	Sequence-specific DNA-binding transcriptional factor involved in cellular proliferation and differentiation
Hey1	Hes-related transcriptional factor involved in neoplastic vasculature development

Source: Adapted from Yuan (Yuan et al., 2015).

Upon this ligand-receptor interaction, proteolytic cleavages on the receptor side with the last cleavage by the γ-secretase activity leads to the liberation of the NOTCH intracellular domain (NICD1, NICD2, NICD3, NICD4). This is a rate-limiting step during NOTCH activation, which can be pharmacologically blocked by small-molecule γ-secretase inhibitors. Once the NICD is liberated, it translocates to the nucleus and binds to the NOTCH-specific transcription complex (Kovall, 2008). The interaction between the transcription factors and NICD potentiates the formation of an active transcription complex to induce transcriptional expression of downstream target genes (HEY1, HES1, NF-kB, MYC, CCND1/3, BCL2, CCR7, human epidermal growth factor receptor 2 [HER2]) (Ntziachristos et al., 2014). NOTCH target genes regulate self-renewal, pivotal cell-fate choices, including differentiation, cell-cycle progression and survival of diverse cell types at various stages of their development. The final phenotypic effect is dependent on the specific signalling context, paralogue, ligand and dosage of the intracellular signal (Suresh and Irvine, 2015).

2.2 NOTCH SIGNALLING IN CANCER

The canonical NOTCH pathway with four NOTCH receptors and five ligands is an evolutionarily conserved cell signalling pathway that plays critical roles in cell-fate determination, differentiation, development, tissue patterning, cell proliferation, and death. Deregulated NOTCH signalling leads to various organ disorders and diseases, such as T-cell leukaemia, Alagille syndrome and a stroke and dementia syndrome known as CADASIL as well as it can play a major role in promoting cancer growth, invasion and metastasis (Andersson and Lendahl, 2014).

The oncogenic role of NOTCH signalling in human malignancy was first unravelled in T-cell acute lymphoblastic leukaemia/lymphoma (T-ALL/T-LBL) (Reynolds et al., 1987; Ellisen et al., 1991) and NOTCH1 gain-of-function mutations were subsequently found in approximately 55% of T-ALL (Aster et al., 2017). Since the discovery of NOTCH1 gene alterations in T-ALL, aberrant NOTCH signalling was subsequently identified in many solid tumours (Ranganathan et al., 2011) and haematological malignancies (Gu et al., 2016).

Aberrant activation of NOTCH signalling leads to deregulation of the self-renewal process resulting in sustained proliferation, escape from apoptosis, loss of differentiation capacity, invasion and metastasis, and may also be the cause of developing therapy resistance to several treatment modalities (chemotherapy, targeted therapy, radiotherapy), all of which are hallmarks of cancer. Over-activation of the NOTCH signalling pathway can lead to cancer development like in T-ALL, or, if it occurs during the course of the disease, to a more aggressive phenotype and more malignant progression (Takebe et al., 2014). Thus, as a consequence these alterations of the NOTCH signalling pathway may result in a worse prognosis for these patients.

NOTCH aberrant regulation of the pathway and its over-activation in cancer cells are caused by multiple and distinct mechanisms (Ntziachristos et al., 2014):

- **Chromosomal translocation** overlapping with NOTCH regions on the chromosomes, leading to fusion of NOTCH related genes and expression of truncated versions of the NOTCH1 or 2 proteins, causing ligand-/receptor-independent constitutive activation of the respective NOTCH pathway.

- **Gain of function (GOF) mutations** in the NOTCH genes leading to a constitutive, ligand-/receptor-independent activation of the respective NOTCH pathway.

- **Loss of function (LOF) mutations** in negative regulators of the NOTCH pathway, like FBXW7 or NUMB.

- **Over-expression of the different NOTCH-specific ligands or receptors**, leading to extended activation of the respective NOTCH pathways 1, 2, 3 or 4.

This variety of genetic changes of the NOTCH pathway leading to over-activation and altered signalling occur in a variety of solid tumour indications and haematological malignancies without a specific pattern and in different frequencies. All these different genetic lesions may influence tumour initiation, but is also important for aspects of promoting tumour growth and progression, including a direct effect on cell cycle regulation, inhibition of apoptosis, deregulation of progression and differentiation programs in cancer cells, promoting angiogenesis, epithelial to mesenchymal transition (EMT)-driven metastatic growth and the formation and maintenance of cancer stem cells (CSC) (Bhola et al., 2016; Wieland et al., 2017). Besides the direct effect of NOTCH over-activation on promoting tumour growth, invasion and metastasis, NOTCH signalling plays a major role in regulating survival and apoptosis pathways. Therefore, NOTCH may play through the regulation of these pathways a very significant role in cancer cells to gain a survival advantage which leads to the development of treatment resistance to chemotherapy, targeted therapies and also radiotherapy. Taken together, all these multiple effects caused by NOTCH over-activation and cross-talking to other signalling pathways reveal the NOTCH pathway as being an attractive and reasonable therapeutic target for novel therapeutic regimens to treat tumour cells directly and to sensitise tumour cells to chemotherapeutic agents and radiotherapy (Ranganathan et al., 2011).

Depending on expression patterns, the NOTCH pathway can function as either oncogenic or tumour suppressive depending on the tissue and cellular context. The functional role of NOTCH in the different indications has been the subject of intensive studies and in general, NOTCH seems tumour-suppressive only in a limited number of malignancies, like in several squamous cancers (Nowell and Radtke, 2017), but activating and oncogenic in most haematological malignancies (Gu et al., 2016) and adenocarcinomas, reflecting its normal functions in those tissues (Previs et al., 2015).

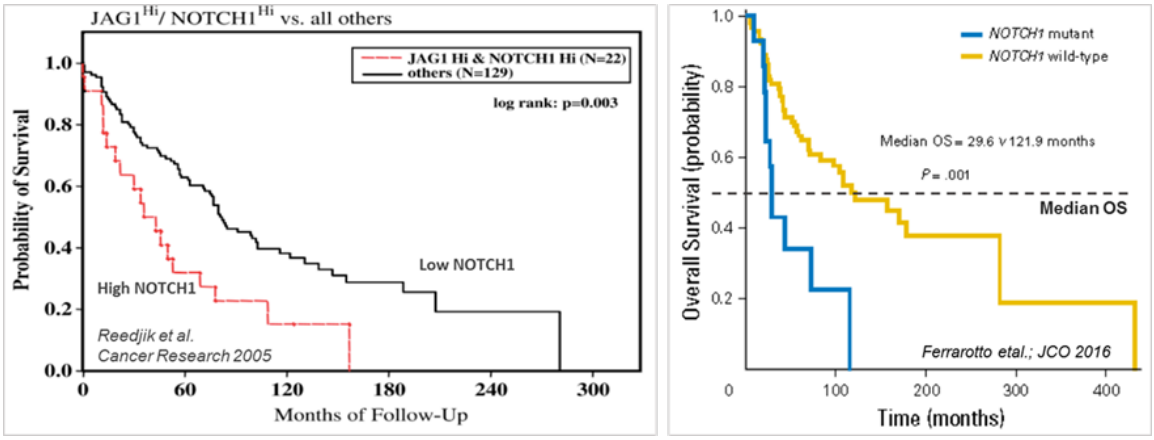
With whole genome sequencing and other sensitive technologies available to detect all the different genetic lesions of the NOTCH pathway at the molecular level, the oncogenic function of NOTCH signalling is well understood and can be detected in various **solid**

tumour indications (subtypes of breast cancer, gastrointestinal (GI) cancers, cholangiocellular carcinoma [CCC], hepatocellular carcinoma [HCC], subtypes of sarcomas, desmoid tumours, adenoid cystic carcinomas [ACC], malignant glomus tumour) (Ranganathan et al., 2011) as well as frequently also in numerous **haematological malignancies** (T-ALL/T-LBL, chronic lymphocytic leukaemia [CLL] and many subtypes of non-Hodgkin lymphomas (Gu et al., 2016)).

Given the importance of NOTCH signalling in human cancers, several therapeutic approaches have been utilised to block NOTCH signalling. Two of these strategies are a) the use of monoclonal antibodies (mAbs) against NOTCH ligands and receptors, and b) the use of small molecule gamma-secretase inhibitors (GSIs). However, these approaches can only be effective if tumour cells express full-length ligand or receptor molecules. On the contrary, in human cancers with constitutive activation of the NOTCH pathway through NOTCH gene fusion due to chromosomal translocations or specific NOTCH mutations, the use of mAbs and GSIs will have very limited clinical benefits (Andersson and Lendahl, 2014). In contrast to the aforementioned inhibitors, the pan-NOTCH inhibitor CB-103 binds to the NOTCH-specific transcription complex in the cell nucleus and unfolds its effects at the transcription level of NOTCH target genes at the most downstream and central location. CB-103 therefore has the potential to address all mechanisms causing NOTCH over-activation. Besides over-expression of ligands and receptors, it can also inhibit the ligand- and receptor-independent, constitutive activation of NOTCH signalling caused by the various genetic aberrations known to activate the pathway.

Over-activation, in particular the constitutive activation of NOTCH signalling (independent of ligand/receptor expression) in these cancer indications 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 (OS) seen in patients with the same tumours not having any aberration or dysregulation of the NOTCH pathway. Several studies have confirmed the negative prognostic importance of NOTCH over-activation in many cancer indications and showed that an aberrant NOTCH pathway in the tumour leads to significantly shorter survival of the patients. High co-expression of NOTCH1 and JAG1 in tumours of breast cancer patients is associated with poor survival with median OS of 40 months in patients with high NOTCH activation compared to 83 months in patients without such NOTCH overexpression (Reedijk et al., 2005). For patients with adenoid cystic carcinomas (ACC), a very aggressive, treatment-refractory tumour of salivary glands, this correlation is even stronger with a median OS of only 29.6 months in patients with tumours bearing NOTCH1 mutations compared to 121.9 months in patients with tumours without any NOTCH activation (Ferrarotto et al., 2017). The respective survival curves for both examples can be seen in Figure 2 and additional examples for the negative prognostic value of NOTCH are provided in the Investigator's Brochure.

Figure 2 Overall survival of patients with breast cancer and adenoid cystic carcinomas with and without over-activation of NOTCH signalling in their tumour cells



Source: Reedijk et al., 2005, Ferrarotto et al., 2017.

Altogether, these examples of the dependency of the patient's life expectancy with the NOTCH status in their tumours confirms the important role of NOTCH signalling in human malignancies, indicating that a strong rationale exists for the development of NOTCH-tailored therapies (Ntziachristos et al., 2014).

2.3 OVERVIEW OF CHOSEN CANCER INDICATIONS

Patients with advanced and metastatic solid tumours often have limited therapeutic options beyond institutional standard of care. For patients whose cancer has become refractory to all available treatments, there is a significant unmet therapeutic need. In some malignancies, the cancer pathology can be driven by, or be largely dependent, on well-defined genetic aberrations in selected cellular signalling pathways like mutations, chromosomal translocations or overexpression of the respective ligands or receptors. The NOTCH signalling pathway is such an example where activating genetic aberrations which occur in many different malignancies, lead to an oncogenic transformation of the tumour and its microenvironment resulting in NOTCH-driven growth, proliferation, invasion and metastasis. The rationale for specific inhibitors of such defined targets is logical, and in the case of cancers which have oncogenic aberrations of the NOTCH pathway, development of specific NOTCH inhibitors is a reasonable and promising therapeutic approach and some of the existing NOTCH inhibitors have already shown clinical activity in early stage clinical development in various indications (Previs et al., 2015).

In order to select the right solid tumour indications for treatment with the pan-NOTCH inhibitor CB-103 within this study, a literature research was performed and CB-103 was studied in various non-clinical *in vitro* and *in vivo* pharmacology studies in models derived from different cancer indications. Criteria for the selection of indications are that activation of the NOTCH pathway by genetic aberrations based on known mutations, translocations or overexpression of ligands/receptors are known to be present and well characterised to be biologically active as oncogenic growth drivers. Any indication where the functional role

of NOTCH is not clear or described in literature as tumour-suppressive will be excluded and will not be considered for this clinical study (Nowell and Radtke, 2017).

2.3.1 Advanced and Metastatic Solid Tumours

Since discovery of NOTCH1 gene alterations in T-ALL, aberrant NOTCH signalling was subsequently identified in many solid tumours (Ranganathan et al., 2011). NOTCH-related somatic mutations and chromosomal translocations have been characterised and are infrequent in the members of the NOTCH family in solid tumours. These specific genetic aberrations of the NOTCH pathway and the functionally oncogenic effect of these lesions have been characterised and are found in several solid tumour indications that include all subtypes of breast cancer (estrogen receptor [ER]+/-), progesterone receptor [PR]+/-, HER2+/-, triple negative breast cancer [TNBC], GI cancers (colorectal cancer, CCC, HCC), subtypes of sarcomas, desmoid tumours, adenoid cystic carcinomas, malignant glomus tumour and non-Hodgkin lymphomas (Egloff and Grandis, 2012). Additionally, deregulated expression of wild-type NOTCH receptors and NOTCH ligands has been found in a growing number of human solid tumours including pancreatic, prostate, breast, lung, GBM, sarcomas, desmoid tumours, adenoid cystic carcinomas, cervical, melanoma, head and neck, and renal cancers (Takebe et al., 2014). Aberrant activation of NOTCH1 signalling was associated with loss of Numb activity, a negative regulator of NOTCH pathway, in about 40% of breast cancers and 30% of lung cancers (Stylianou et al., 2006). High levels of JAG1 or NOTCH1 was seen in about 25% of human breast tumours by in situ hybridisation; and high versus low levels of co-expression of NOTCH1 and JAG1 were associated with reduced overall survival (Reedijk et al., 2005).

The solid tumour indications under investigation in this study must have reported genetic aberrations of the NOTCH pathway, characterised as being biologically active and functionally oncogenic, in driving tumour growth, proliferation, survival, escape from apoptosis, invasion and metastasis. Non-clinical *in vitro* and *in vivo* studies have been performed for some of the selected indications to identify and confirm the occurrence of these aberrations in the tumour cells and to investigate the cytotoxic effects of CB-103 treatment. Indications such as squamous cell carcinomas, pancreatic cancer and HNSCC, with known or suspected NOTCH signalling involvement in tumour suppression, are not under investigation in this study.

Furthermore, selection of indications is also made based on strategical considerations by the Sponsor with regards to the future development plans for CB-103 in these indications.

The following tumour indications are selected to be included in this study:

- Breast cancer (ER+/-, HER2+/-, TNBC), GI cancers (resistant to oxaliplatin or irinotecan-based therapy colorectal cancer, hepatocellular carcinoma), osteosarcoma, adenoid cystic carcinoma (ACC), malignant glomus tumour and T-ALL/T-LBL.

More details on the known genetic aberrations of NOTCH signalling in these indications and their frequency are provided in the Investigator's Brochure and in Appendix 3.

Additionally, NOTCH pathway activation has been reported in other malignancies with lower frequency. Patients whose tumours exhibit Notch pathway activation are eligible for this study even if the tumour is not among the indications mentioned above.

2.3.2 Acute Lymphoblastic Leukaemia / Lymphoma

The incidence of ALL follows a bimodal distribution, with the first peak occurring in childhood and a second peak occurring around the age of 50 (Dores et al., 2012). In Western countries, the annual incidence rate of adult ALL (i.e. patients older than 15) is approximately one per 100,000 (Sant et al., 2010; Howlander et al., 2014). In adult ALL, B-cell ALL accounts for ~75% of cases, while T-cell ALL comprises the remaining cases. In the EU, with the current population of 510,000,000 inhabitants, about 1250 new cases of adult T-ALL are expected every year.

The OS rates in adult ALL is still <45% (Bassan et al., 2011) despite the addition of CNS prophylaxis, late intensification with prolonged maintenance chemotherapy, and an extensive use of allogeneic Haematopoietic Cell Transplantation (HCT) in high-risk (HR) subsets. Paediatric-inspired regimens, initially reserved for adolescents and young adults (Stock et al., 2008; Ribera et al., 2008; Boissel et al., 2003) and later applied to patients up to 50-60 years of age (Huguet et al., 2009; DeAngelo et al., 2015; Storring et al., 2009), have increased the 5-year OS rate to ≥ 50%, and up to 70%-80% in favourable subsets (Curran et al., 2015). Finally, allogeneic HCT is often considered in first complete remission (CR) in adults with HR disease to reduce the risk of relapse (Goldstone et al., 2008), but potential benefits may be offset by transplant-related morbidity and mortality, especially in the elderly (Gupta et al., 2013). Relapse affects one-third or more of the patients and remains an unsolved issue due to extremely poor results with standard salvage chemotherapy. An international study of 1,706 patients with refractory or recurrent (r/r) B-cell precursor (BCP) ALL reported 3-year survival rates of only 10% (Gökbuget et al., 2016). Results are worse in Ph+ ALL (Cortes et al. 2012) and T-cell precursor (TCP) ALL, with some mitigation provided by nelarabine (DeAngelo et al., 2007).

Nelarabine was approved in the US and Europe for the treatment of patients with T-ALL and T-cell lymphoblastic lymphoma (T-LBL) whose disease has not responded to or has relapsed following treatment with at least two chemotherapy regimens. The approval in adult patients was based on an open-label study carried out by the Cancer and Leukaemia Group B and the Southwest Oncology Group, which evaluated the safety and efficacy of nelarabine in 39 adults with T-ALL T-LBL (DeAngelo et al., 2007). Twenty–eight of the 39 adults had relapsed or were refractory to at least two prior inductions. Of the 28 patients who had previously received at least 2 prior induction regimens, 8 (29%) experienced a complete remission (CR) with or without hematopoietic recovery (CRi). In comparison, 4 of 11 (36%) patients who had received only one prior induction regimen demonstrated a CR or a CRi to nelarabine. Time to complete response in both classifications of response

ranged from 2.9 to 11.7 weeks. Of the 28 patients with 2 or more prior inductions, the 1-year survival rate was 25%. The most common non-hematologic toxicity of neralabine is reversible peripheral sensory and motor neuropathy, which limits the combination of the drug with standard combination chemotherapy. As many of the commonly-used agents for ALL therapy, such as vincristine and methotrexate, also have neuropathic toxicities, nelarabine use remains limited.

The oncogenic role of NOTCH signalling in human malignancy was first unravelled in T-ALL/T-LBL: the most frequent actionable mutations are NOTCH1 (Aster et al., 2017) occurring in approximately 55% of T-cell ALL cases, and FBXW7-inactivating gene mutations occurring in approximately 30% of cases (Yet et al., 2016), with the result that approximately 80% of cases have Notch pathway activation by mutations in at least one of these genes.

In T-ALL, NOTCH1 inhibitors and the strictly associated γ-secretase inhibitors were tested in late-stage disease, with some responses of short duration and considerable gut toxicity (Gu et al., 2016). The best study reported one CR and an overall 32% response rate in 25 patients with relapsed disease (Weidler-McKay et al., 2014). Theoretically, targeting NOTCH1-related overexpression of the chemokine receptor CCR7 and its ligand CCL19 could also reduce the risk of CNS disease (Buonamici et al., 2009).

2.4 NOTCH TARGETING THERAPIES

The therapeutic rationale for the use of NOTCH-inhibiting strategies is based on the fact that blocking this pathway can have both direct effects on cancer cells, and can also indirectly hinder tumour growth by reducing blood supply through angiogenesis dysregulation and by disrupting the tumour stem cell niche. Furthermore, the fact that tumour cells often acquire multiple mutations in several different pathways interplaying with NOTCH, such as Hedgehog, WNT, PI3K, mTOR, NF-kb and others, supports the use of combination targeted therapies. Importantly, combination with traditional chemo-radiotherapy also seems promising as their therapeutic effect can also be enhanced by the use of NOTCH inhibitors (Takebe et al., 2015).

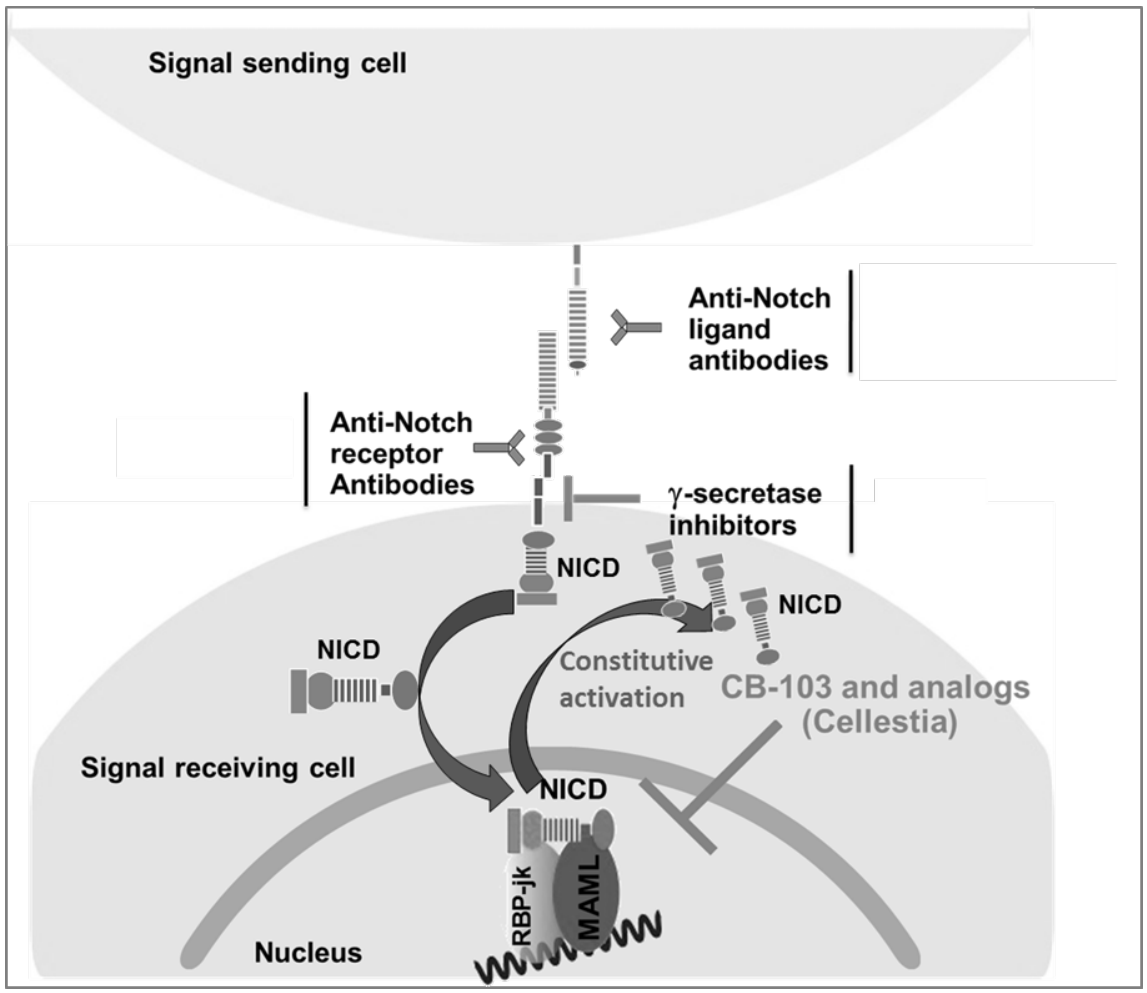
At present, several classes of NOTCH pathway inhibitors are in clinical development, with significant differences in the targets, mechanism of action, and drug class. The two main classes of NOTCH inhibitors are the γ secretase inhibitors (GSIs) and monoclonal antibodies targeting either the NOTCH ligands or receptors (Figure 3):

1. A major class of agents targeting the NOTCH pathway is the **γ secretase inhibitors (GSIs),** which prevent the final proteolytic cleavage of NOTCH receptors that releases the active intracellular fragment. GSIs were initially developed as treatment for Alzheimer's disease and were subsequently the first class of NOTCH inhibitors to reach clinical development in oncology (De Strooper, 2014). However, there are systemic toxicities and off-target effects, as γ secretase has > 80 substrates related to different pathways in addition to the NOTCH

receptors. GSIs potentially inhibit the cleavage of all substrates, which might contribute to their toxicity and/or effectiveness in ways that are not currently understood. Based on the toxicities and moderate efficacy seen in early clinical development several GSI programs were terminated and a few second generation GSIs are continuing in several Phase I/II clinical studies either as monotherapy or in combination with different chemotherapies and targeted therapies (Takebe et al., 2015).

2. Another class of agents under development is the **monoclonal antibodies (mAb)** either against NOTCH receptors (NOTCH1, NOTCH2, NOTCH3) or NOTCH ligands (DLL3, DLL4). Experimental evidence demonstrates that NOTCH inhibition by either mAb against NOTCH1 or NOTCH2 alleviates the toxicities seen with GSIs while simultaneous inhibition of NOTCH1 and 2 leads to severe GI toxicities (Wu et al., 2010). It is hoped that this category of drugs could reduce or spare some of the toxicities associated with GSIs. Besides monoclonal antibodies binding to the different NOTCH receptors, there are also several mAb in early clinical studies binding to different NOTCH ligands with most of them targeting DLL4 and an antibody-drug-conjugate (ADC) binding to DLL3 with subsequent internalisation of the ADC complex and release of the cytotoxic payload within the cells. Most of these programs are in early clinical development (Takebe et al., 2014).

Figure 3 NOTCH signalling pathway and binding sites of γ-secretase inhibitors (GSIs) and monoclonal antibodies targeting the NOTCH ligands or receptors.



Source: Sponsor

Besides the drug classes of monoclonal antibodies and GSIs being currently in early stage clinical development and the clinical experience that the effects of these may be limited by the toxicities observed, other potential therapeutic approaches are currently under pre-clinical investigation including mAbs targeting various NOTCH receptors, mAbs to the γ-secretase complex component nicastrin, and soluble decoy NOTCH receptors that interfere with ligand–receptor interactions (Takebe et al., 2015).

Despite the promising therapeutic potential however, limiting toxicities and on-target side effects associated with the various NOTCH therapies have been observed in pre-clinical and clinical studies. Early discontinuation of patients and drug exposure below the therapeutic range might be the reason for the moderate clinical activity observed so far in clinical studies. For example, the success of GSI-based therapies in Phase I trials have been hampered by their GI toxicity, explained by normal NOTCH signalling directing GI stem cells towards an epithelial fate, with subsequent blockade causing increased

numbers of mucus-secreting goblet cells in the small intestine (Gu et al., 2016). Based on the negative prognostic relevance of NOTCH signalling and knowledge of the oncogenic function of NOTCH in many solid tumours and haematological malignancies, together with the high unmet medical need in those patients with NOTCH-driven tumours, there is still a strong rationale to therapeutically target this pathway with specific NOTCH inhibitors. It will be important to discover novel NOTCH signalling inhibitors with a new mode of action which may lead to an improved safety profile and increased efficacy. Additionally, another key success factor for NOTCH inhibitors will be to consider a biomarker strategy and development of a companion diagnostic to characterise NOTCH pathway aberrations in order to select the most suitable patient population for a particular NOTCH-targeted therapy.

Further information on the different drug classes of NOTCH inhibitors and the current stage of clinical development for selected candidates can be found in the Investigator's Brochure.

2.5 CB-103 – PAN-NOTCH TARGETING DRUG CANDIDATE

CB-103 is an orally bioavailable synthetic small molecule (Molecular weight: 278.78 g/mol) and a first-in-class pan-NOTCH inhibitor. It targets the NOTCH signalling pathway in its most downstream part by binding to the NOTCH-specific transcription complex located in the cell nucleus. CB-103 is an oral drug administered as a capsule. In animals, the compound is rapidly absorbed after administration, distributes rapidly into tissue and diffuses into the nucleus of malignant cells, binds to the transcription complex and inhibits translation and protein expression of NOTCH-related target genes which are responsible for the various functions NOTCH can trigger and modulate in many fundamental processes and in a wide range of tissues.

2.5.1 Mechanism of Action

After entering the tumour cells, CB-103 translocates to the cell nucleus and binds to the NOTCH-specific transcription complex hindering subsequent binding of the NICD and therefore blocking the transcription and translation of the NOTCH target genes. The molecular target and binding site of CB-103 at the NOTCH-specific transcription complex has been identified. Two pharmacodynamics studies were conducted to confirm the mechanism of action and characterise the cellular target of CB-103 at the transcription complex. Further details on these studies can be found in the Investigator's Brochure.

2.5.2 Non-Clinical Pharmacology

A summary of the *in vitro* and *in vivo* pharmacology studies is given in the Investigator's Brochure.

2.5.2.1 Safety Pharmacology

Single oral doses of CB-103 at 10, 30 and 80 mg/kg had no effect on respiratory function in the rat. In addition, CB-103 at 10 mg/kg was devoid of effects on the CNS in the rat.

Single oral doses of CB-103 up to and including 200 mg/kg had no effect on blood pressure and heart rate in the conscious telemetered rat. Likewise, the compound had no effect on blood pressure, heart rate or the PR and RR intervals of the electrocardiogram (ECG) in the conscious dog when administered as a single dose up to 26.3 mg/kg or two doses of 10 mg/kg given 12 hours apart.

CB-103 at 0.8 mg/kg had no effect on the QRS complex (QRS) QT interval corrected for heart rate or (QTc) intervals of the ECG.

The higher doses of CB-103 caused an increase in the QTc in dogs. These increases in QTc were transient with a single time point at 0.5 hour post-dose being statistically significant following treatment with 7.8 mg/kg and values up to 6.0 hours post-dose being statistically significant after the top dose (26.3 mg/kg). Similar effects on the QTc interval were observed when CB-103 was given as two 10 mg/kg doses 12 hours apart. The plasma concentrations associated with these effects are estimated to be >> 3000 ng/mL total CB-103 (free concentration >> 90 ng/mL) and the most likely mechanism for the effect of CB-103 on the QTc interval in the dog is inhibition of the hERG-mediated potassium current (IC_{50} = 38.5 μM=9333 ng/mL) and the inhibition of L-type calcium channel (hCav1.2) at lower concentrations (IC_{50} = 26.88 μM=6516 ng/mL). Compounds with this profile (greater calcium antagonist potency than hERG) have been shown to have a lower pro-arrhythmic potential than 'pure' hERG blockers and therefore CB-103 may have a low risk for Torsades de Pointes arrhythmia in man (Kramer et al., 2013b).

CB-103 at a dose of 0.8 mg/kg had no effect on the QRS interval in the dog. However, the higher doses of 7.8 and 26.3 mg/kg caused a dose-related increase in the QRS interval, with the duration of action being longer at the top dose (~6 hours) than that observed at the mid-dose (~1 hour). These effects were also associated with some morphological changes in the ECG waveform in 2 of 4 dogs after 7.8 mg/kg and in all 4 dogs after 26.3 mg/kg. Prolongation of the QRS interval is indicative of the slowing of conduction through the heart and the most likely mechanism for this effect is inhibition of cardiac sodium channels ($Na_v1.5$ (IC_{50} = 58.9 μM to 60.66 μM)). Cardiac sodium channel blockers can also reduce the force of contraction of the heart and this may explain the small increase in the QA interval observed in dogs treated with CB-103 at doses of 7.8 and 26.3 mg/kg.

Thus, these data suggest that CB-103 has some potential to affect cardiac repolarisation and cardiac conduction and careful monitoring of the ECG will be warranted in human clinical trials.

Gastrointestinal (GI) safety studies revealed for CB-103-treated mice completely normal intestinal tissues and no indication of goblet cell accumulation. At an increased dosing frequency (3 x daily), CB-103 exhibited a mild intestinal toxicity apparent by an increase in goblet cell population in the intestine. In the spleen, CB-103 mediated inhibition of NOTCH2 signalling led to more than 90% reduction in the MZB confirming its *in vivo* activity. Overall in all animal studies performed in different species (mice, rats and dogs) and with different doses and schedules of CB-103, there were no signs of diarrhoea reported suggesting that the typical gastro-intestinal toxicities seen caused by the goblet

cell metaplasia reported for the other classes of NOTCH inhibitors, may not be the key toxicity driver and limiting-factor with regards to exposure for CB-103.

2.5.3 Pharmacokinetics

2.5.3.1 Animal Pharmacokinetics and Drug Metabolism

The absorption, distribution, metabolism, and excretion (ADME) profile of CB-103 has been investigated in *in vitro* and *in vivo* studies and the repeat dose PK in rats and dogs was assessed as part of the toxicokinetic program. The study results are summarised in this section and more detailed information can be found in the Investigator's Brochure.

CB-103 shows excellent drug-like properties based on the pre-clinical *in vitro* and *in vivo* ADME profile. The compound is highly permeable and well absorbed after oral administration with a time at which the maximum serum concentration (C_{max}) is observed (t_{max}) of about 1 hour. CB-103 is not a substrate for P-Glycoprotein (Pgp). Bioavailability after various formulations given to mice and dogs is high or complete. Rats show a lower bioavailability most likely due to a combination of high first past metabolism and potentially incomplete absorption.

Despite its high binding to plasma proteins from various animal species and humans (≥ 97%) CB-103 distributes widely into the body and was detectable in brain, kidney, liver, spleen and skin tissues from rats. The elimination of CB-103 in animals is relatively fast (elimination half-life [$t_{1/2}$]: 2 hours in mice, 3 hours in rats and 7-10 hours in dogs), and no signs of significant accumulation have been observed with daily dosing. The expected $t_{1/2}$ in humans is around 16 hours (see Section 2.5.3.2) Overall, the PK parameters after first and repeated administration were comparable, except for a decrease in exposure over time during the 28-day Good Laboratory Praxis (GLP) toxicity study in dogs at all doses and in both genders. No explanation for this observation has been found, but the exposure coverage at the end of this study was still sufficient to allow a valid assessment of CB-103 toxicity in dogs for the calculation of safety margins.

In general, the PK of CB-103 is dose proportional, with a tendency to higher than dose proportional exposure in dogs in the range of 1 to 10 mg/kg/day. At 50 mg/kg given to dogs absorption of CB-103 is delayed and the C_{max} is lower than expected. In rats an absorption plateau is reached with 200 mg/kg.

All human metabolites formed in hepatocytes are covered by the toxicology species (rats and dogs), but some species differences have been observed with respect to CB-103 metabolism. The predominant metabolic conversion of CB-103 in rodents, monkey and humans seems to be N-acetylation. Oxidative metabolism occurs as well, but seems to play a minor role in humans. Dogs are deficient of the enzymes catalysing N-acetylation (N-acetyltransferase [NAT] isoforms 1 and 2) and have a lower intrinsic clearance (CL) of CB-103. The predominant metabolic route of clearance in the dog is oxidative metabolism combined with glucuronidation.

The involvement of NAT1/NAT2 in the metabolism of CB-103 in humans might be of relevance since NAT polymorphism results in high- and low metabolizing individuals. Metabolic stability of CB-103 in human hepatocytes from individuals genotyped as slow, intermediate and fast NAT metabolizers showed a relationship of metabolic *in vitro* turnover and genotype. Genotyping patients for polymorphisms of metabolising enzymes to understand its impact on the clinical PK of CB-103 is foreseen in the clinical protocol (refer to the Schedule of Assessments). Preliminary results of these pharmacogenetic investigations exploring the potential influence of NAT genotypes on the PK of CB-103 have not revealed any correlation or effect on the pharmacokinetics of CB-103.

2.5.3.2 Prediction of Human PK from Non-Clinical Studies (Allometric Scaling)

Allometric scaling for CB-103 using mouse, rat and dog intravenous (i.v.) PK data was performed to predict the human PK parameters CL, volume of distribution at steady state (V_{ss}) and $t_{1/2}$.

Table 2 summarises the prediction along with the input values for the scaling. No correction for plasma protein binding was performed as the differences across species is minimal (binding approx. 98% in all species).

Table 2 Pharmacokinetic parameters observed in mouse, rat and dog and predicted for humans using allometric scaling

Species	**Mouse**	**Rat**	**Rat**	**Dog**	***Human***
Data Source	CB-103-ADME010	CB-103-ADME011	CB-103-T002	CB-103-T001	*PREDICTED*
Body weight	0.025 kg	0.3 kg	0.38 kg	12 kg	*70 kg*
CL (mL/h/kg)	**3627.5**	**2481.3**	**3940**	**456**	
CL (mL/h)	*90.7*	*744.39*	*1497.2*	*5472*	*23520*
V_{ss} (mL/kg)	**1664.8**	**1125.3**	**897**	**5670**	
V_{ss} (L)	*0.042*	*0.338*	*0.341*	*68.0*	*380*
$T_{1/2}$ (h)	**0.49**	**0.73**	**0.157**	**10.2**	*16.2*
Bioavailability (F)	**100%**	**16.3%**	**15.4%**	**81%**	
Plasma Protein Binding (%)	**98.3**	**98.2**		**98.7**	**97.0**

Data in bold are measured, data in italics are calculated. Parameters for humans are predicted.

For the human predicted values of CL 23520 mL/h (or 23.52 L/h) and of V_{ss} 380 L, the estimated half-life (V_{ss}/CL) is around 16 hours. It is therefore expected that CB-103 needs about 3 to 4 days to reach steady state concentrations. With daily administration, the predicted accumulation ratio (AR) would be 1.5. The first dose level administered in this clinical protocol is 15 mg (fixed dose) and the expected AUC at this dose is 639 µg*h/mL

assuming complete bioavailability of the compound after oral administration. If the bioavailability of CB-103 in humans is less than 100% the exposure with be respectively lower.

2.5.4 Animal Toxicology and Toxicokinetics

The pre-clinical safety and toxicology package presented for CB-103 determined the tolerability of the compound in rodent and non-rodent species over a wide range of doses and exposure levels.

The assessment of the safety of CB-103 in rats and dogs demonstrates a safety profile commensurate with administration to cancer patients. A finding common to both rat and dog toxicology studies with CB-103 was reduced thymus weight with accompanying histological changes. Effects in the thymus, as described in rats and dogs dosed with CB-103, are commonly associated with stress induced by many different stressors, including high systemic exposure to xenobiotics (Everds et al., 2013), therefore these are not a safety risk for humans.

The liver was a target organ in both rats and dogs. In rats, hypertrophy and resultant increased liver weight are indicative of an adaptive response due to the presence of large amounts of a xenobiotic present in the liver. Likewise, the hepatomegaly and histological changes that occurred in the MTD study are considered due to the presence / accumulation of large amounts of compound. Of note, no changes occurred in livers of dogs from the 28-day GLP study, therefore the changes in the livers of rats and dogs given high doses of CB-103 are not a toxicological risk to cancer patients.

In both rats and dogs, dilation of the pupils occurred. In rats this effect was evident at doses of 10 and 30 mg/kg/day (GLP 28-day study). In dogs this was evident at all doses in the GLP 28-day study (1, 3, 10 mg/kg/day) and at 25 mg/kg/day in the non-GLP MTD/fixed-dose study. In rats, retinal atrophy was present in females at the end of the 28-day GLP study and was still present at the end of the recovery period. Retinal atrophy was also present in males at the end of the recovery period whereas it was not present at the end of the dosing period. The exact mechanism of retinal atrophy caused by CB-103 remains unclear, however it is consistent with observations in albino rats exposed to excess light (De Vera Mudry et al, 2013), therefore the retinal degeneration is considered secondary to dilation of the pupils. Importantly, retinal atrophy was not present in dogs and is therefore not expected in humans. No specific eye exams are foreseen in the clinical protocol, but pupil size in patients will be monitored as part of the regular physical examination occurring at every study visit.

Severe toxicity and unscheduled death were only observed at very high doses given repeatedly to rats and dogs leading to exposure levels above 4000 ng/mL (C_{max}) and 30,000 ng*h/mL (AUC_{0-24}). The 28-day GLP toxicity studies in rats and dogs determined 10 mg/kg/day and 2.6 mg/kg/day as the no observed adverse effect level (NOAEL), respectively with minimal signs of toxicity and exposure levels of approx. 300-500 ng/mL (C_{max}) and approx.1300-3400 ng*h/mL (AUC_{0-24}). The findings at the next higher dose

levels in both species were still mild and reversible. The observations in rats at 30 mg/kg/day included transient clinical signs (ploughing, salivation, decreased activity and pale/dark eyes), decreased body weight gain, changes in haematology, clinical chemistry parameters and increased liver and spleen weights correlating with erythropoiesis in the spleen and hypertrophy on the liver. The observations at 8.6 mg/kg/day in dogs included dilated pupils, pale skin and gums, rimmed eyelids and lacrimation, decreased activity, apparent pain, changes in thymus and spleen and an increased reticulocyte count. Therefore, 30 mg/kg/day in rats and 8.6 mg/kg/day in dogs are considered the highest non-severely toxic doses (HSNTD) with exposure levels of approx. 1200-3100 ng/mL (C_{max}) and 6000-9000 h.ng/mL (AUC_{0-24}). The starting dose in humans (15 mg) targets an AUC_{0-24} of 600 h.ng/mL after repeated administration (Section 2.5.3.2), which equals 1/10th of the HSNTD in the most sensitive species (rat AUC_{0-24} on Day 28 at 30 mg/kg/day 5980 h*ng/mL in male rats).

CB-103 is not mutagenic in the *S. typhimurium* tester strains (TA1537 or TA98) or *E. coli* reverse mutation assay strain WP2uvrA. The positive results from the S9-mix showing mutagenic response with the tester strains TA1535 and TA100 of *S. typhimurium* in the presence of S9-mix suggest that metabolites of CB-103 generated in the presence of S9-mix might be mutagenic. However, no additional studies were performed as these were not required according to the “ICH S9 Nonclinical evaluation for anticancer pharmaceuticals Guideline” to support clinical trials for therapeutics intended to treat patients with advanced cancer.

2.5.5 Biomarker Development

Biomarkers are objectively measured and evaluated indicators of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention. Multiple potential biomarkers relevant to the NOTCH signalling pathway and mechanism of action of CB-103 have been incorporated into this study to explore the relationship between the expression or presence of appropriate markers and clinical outcome. In addition, the PD effects of CB-103, including their usefulness in determining the recommended phase 2 dose based on considerations for optimal biological dosing of CB-103 will be explored. The success of the overall biomarker strategy will be dependent on obtaining sufficient tumour material at pre- and post-treatment with CB-103 at a selected time point after the initiation of CB-103 dosing.

2.5.5.1 Patient Profiling Biomarkers

Various biomarker approaches to detect genetic aberrations of NOTCH signalling and to characterise the functional level of NOTCH activation have shown to be of value with regards to the prognostic value that these NOTCH aberrations have in terms of poorer survival seen in patients of different tumour indications, as well as to be used to select the right patient population for treatment with a NOTCH inhibitor (Takebe et al., 2015). As there are different genetic alterations of the NOTCH pathway, known to cause NOTCH over- and constitutive activation and that their functional role may be different in different

cancer indications, there will be a need to develop and apply several methods to detect and characterise these in tumour samples.

NOTCH1-mutant ACC tumors have demonstrated significantly higher levels of Notch1 pathway activation than wild-type tumors on the basis of Notch1 intracellular domain staining. NOTCH1 mutations define a distinct disease phenotype characterized by solid histology, liver and bone metastasis, poor prognosis, and potential responsiveness to Notch1 inhibitors (Ferrarotto et al 2016).

The use of NOTCH-specific biomarkers and different methods used for their detection for patient selection will be explored in Part A (escalation) in a retrospective fashion, whereas it will be prospectively applied for patient selection in Part B (expansion) of the study. Characterisation of functional NOTCH activation in tumour samples will be based on detection of the different genetic aberrations of the NOTCH signalling pathway found in various cancer indications and/or the characterisation of the activation level of NOTCH signalling at the protein and/or RNA level.

Genetic mutations of the NOTCH pathway known to cause over-activation of NOTCH signalling (such as single nucleotides variations, InDels, structural variations (rearrangements), copy number variations) will be assessed by next-generation sequencing (NGS). NICD1 IHC and/or gene expression analysis can also be used to assess NOTCH pathway activation.

Details on the collection, handling and processing of the required specimens for the diagnostic (patient selection) and exploratory biomarker studies will be provided in a separate Laboratory Manual.

2.5.5.2 Pharmacodynamic Markers of NOTCH Inhibition

The available published data show that NOTCH inhibitors produce demonstrable PD effects, such as the reduction of NOTCH pathway components (e.g. NOTCH NICD) and the down-regulation of various NOTCH target genes in both tumours and surrogate tissues.

For GSI treatment reports have shown that measurement of NOTCH1 NICD by immunohistochemical (IHC) staining (Kluk et al., 2013) and HES-1 and HES-4 as NOTCH target genes represent the most promising predictive biomarkers of response to NOTCH-targeted therapies in TNBC and ACC (Stoeck et al., 2014).

In this clinical study, NOTCH inhibition will be assessed in whole blood and plasma samples, in hair follicles and available tumour specimens (pre- and post-treatment) by evaluating several PD markers of target modulation and mode of action such as the reduction of certain NOTCH-related components of the pathway, as well as the modulation of key NOTCH-specific and -related genes.

Technologies as NGS and nCounter Nanostring gene expression analysis will be used to detect the different genetic lesions of the NOTCH pathway, and the expression of the functional target genes at the molecular level. IHC or Western Blot may be used to assess expression levels of NOTCH pathway related proteins. The oncogenic function of NOTCH

signalling is well understood and can be detected in various solid tumour indications and frequently in numerous haematological malignancies.

Details on collection, handling and processing of the required specimens for the PD biomarker analysis will be provided in a separate Laboratory Manual.

2.5.5.3 Pharmacodynamic Markers of Cellular Effects

The response biomarkers for NOTCH inhibitors primarily include tumour or cellular effect markers that indicate changes in tumour cell growth or viability that may be necessary for inducing a clinical response. Cellular signalling through the oncogenic NOTCH target proteins is critical for cell proliferation and survival, which is obtained through the positive regulation of cell cycle, transcription, translation, and the repression of apoptotic machinery. Inhibition of NOTCH signalling will result in a reduced expression of the target proteins and as a result, a decrease in cellular proliferation and/or an increase of apoptosis is expected, and both of these effects can be quantitated as early response markers. Specifically, it is planned to measure apoptosis markers and Ki67, a cellular proliferation marker, by IHC in pre- and post-treatment tumour biopsy samples and hair follicles, or T-lymphocytes from blood and/or bone marrow samples in T-ALL/T-LBL.

Details on the collection, handling and processing of the required specimens for the biomarkers' analysis will be provided in a separate Laboratory Manual.

2.5.6 Clinical Experience

This is the first clinical study on the safety and efficacy of CB-103 oral capsules for the treatment of patients with locally advanced or metastatic solid tumour and haematological malignancies to date.

As of 20 August 2020, 41 patients (median age 55 years, range 25 to 76 years) with solid tumours have been treated with CB-103 in the dose escalation part of the clinical study at oral doses of 15 mg-600 mg QD. Preliminary safety data indicates that CB-103 is well tolerated with 73.3% of adverse events (AEs) being mild (Grade 1) or 21% moderate (Grade 2) in severity, and 5.7% Grade 3. All AEs were evenly distributed over the dose cohorts with no evidence of dose relation. Cumulatively, a total of 352 AEs has occurred in 41 patients since study initiation, of which 132 AEs (37.2%) in 31 patients were considered related to the study drug. The treatment-related treatment-emergent AEs (TEAEs) most commonly reported ($\geqslant$10% of patients) were nausea (24%), diarrhea (20%), dyspepsia (15%), fatigue (12%), and vision blurred (12%).

The majority of treatment-related TEAEs resolved or were resolving at the time of data cut-off without requiring medications or discontinuation of CB-103 dosing. The study includes intense ECG monitoring. There was one related AE of tachycardia Grade 1 (in cohort 2; 30mg QD). Overall, there was no signal of cardiotoxicity and no QTc prolongations have been reported to date.

No events of skin phototoxicity or eye mydriasis have been reported to date in this study. Of the 352 AEs reported, 12 (3.4%) were considered serious adverse events (SAEs) and included abdominal pain, anorexia, atrial flutter, cardiac failure congestive, drug-induced liver injury, duodenal haemorrhage, dyspnoea, general physical condition decreased, respiratory tract infection, spinal cord compression, transaminase increase, and tumour pain. Of these, one SAE was considered related to study drug (drug-induced liver injury), which was reported in a patient with metastatic adenoid cystic carcinoma with extensive liver involvement, treated at an intermediate dose level.

One patient in cohort 8 (600mg) experienced one dose limiting toxicity (DLT). This was an elevation of the gamma-glutamyl transferase (GGT), grade 3, that was asymptomatic and deemed not clinically significant by the investigator. There has been one unrelated SAE with fatal outcome due to respiratory tract infection in cohort 1 (15 mg). No deaths due to drug-related AEs have been reported to date.

CB-103 is rapidly absorbed after oral administration and reaches Cmax within 1 to 2 hours of dosing. Plasma exposure increases with increasing doses. There were no signs of saturated absorption in the dose range tested. The elimination half-life is approximately 20 hours and CB-103 accumulates about 2-fold with repeated daily administration. Steady state concentrations are reached within one week of dosing.

Hair follicles used as surrogate tissue were obtained at pre-defined time points to measure changes in NOTCH target genes expression by CB-103 treatment. In patients in the ongoing phase 1 study, average target gene downregulation on Cycle 2 day 1, 1h post-dose compared to baseline prior to treatment with CB-103 showed a strong dose-dependent down-regulation of several NOTCH target genes, reaching values higher than 70% inhibition at the highest CB-103 dose tested in this series (250mg). Additionally, a sustained time-dependent down-regulation of NOTCH target genes was observed, reaching up to a 90% inhibition after 4 weeks of daily administration of CB-103 at 250mg dose.

Clinically, best response was durable stable disease (SD) with no or only mild AE at doses showing target engagement. Ten patients with ACC had radiologically confirmed SD, of whom 4 patients had a Notch activating mutation or fusion. The Notch status of the other patients is under investigation. Disease control rate (DCR) of 19 ACC patients at 3 months was 68% (DCR defined as number of patients with CR, PR, or SD divided by the number of patients treated).

Based on the safety profile, the Cohort Review Committee declared the dose of 600mg given once daily QD as a safe dose. The MTD was not reached. The Bayesian statistical model allows further dose escalation to 800mg. Because the visual symptoms caused considerable discomfort to some patients, the 600mg dose was declared as provisional RP2D for further exploration in the dose confirmatory cohort. In parallel, a twice daily schedule of CB-103 is being explored.

Emerging clinical data and any safety findings from this study will be summarized in the Investigator Brochure for CB-103.

2.5.6.1 Risk Mitigation Strategies

For this first-in-human study, strategies to mitigate risks have been considered as per the Guideline on strategies to identify and mitigate risks for FIH and early clinical trials with investigational medicinal products (EMEA/CHMP/SWP/28367/07). Based on the findings from the GLP Safety Pharmacology and Toxicology studies, a thorough cardiac monitoring with frequent ECG, periodical Holter monitoring and echocardiogram (ECHO)/multigated acquisition (MUGA) scans will be performed to detect any early cardiac effects of CB-103 in patients and a continuous central reading for the ECGs will be implemented in Part A (dose escalation) and also in Part B of this study (depending on the results from Part A). Additionally, adverse events will be strictly monitored within each part of the study. Sufficient data from Part A will be collected in order to ensure safety of selected dose/exposure for Part B. For any unanticipated pharmacological responses detected, a revised dose escalation will be required.

2.5.6.2 Drug-Drug Interaction Potential

Based on available *in vitro* data with CB-103 the following points regarding potential drug-drug interactions (DDI) have been considered.

Absorption DDI

A majority of the novel orally administered, molecularly targeted anticancer therapies are weak bases that exhibit pH-dependent solubility, and suppression of gastric acidity with acid-reducing agents (ARAs) could potentially influence their absorption (Budha et al., 2012). ARAs are the most commonly prescribed medications in North America and Western Europe and the prevalence of their use among cancer patients is high. Smelick et al (Smelick et al., 2013) reported that among all cancer patients, the total prevalence proportion of ARA use (no. of cancer patients receiving an ARA/total no. of cancer patients) was 20% and 33% from the MarketScan and VA databases, respectively. Proton pump inhibitors (PPIs) were the most commonly prescribed agent, comprising 79% and 65% of all cancer patients receiving a prescription for an ARA (no. of cancer patients receiving a PPI /no. of cancer patients receiving an ARA) for the MarketScan and VA databases, respectively.

CB-103 is a weak base and its solubility is pH dependent. The solubility is 0.77 mg/mL at pH 1.6 and drops steeply to 0.26 mg/mL at pH 2.9 and 0.11 mg/mL at pH 3.3. At pH values of 3.9 and higher the compound is very poorly soluble (approx. 0.06 mg/mL). It is therefore possible that the concomitant administration of ARAs may reduce the absorption of the drug and lead to lower drug exposure.

In a PK sub-study to this protocol, where ranitidine was given to a group of patients prior to dosing with CB-103, there was no difference in plasma concentrations of CB-103 compared to patients who did not take ranitidine.

Metabolism DDI

Effect of CB-103 on other drugs: *In vitro* testing of Cytochrome P450 (CYP) inhibition with pooled probe substrates in human liver microsomes by CB-103 (10 µM) showed a low potential to directly inhibit CYP1A2, 2C9, 2C19, 2D6 or 3A4. Furthermore, *in vitro* experiments showed no indication for CYP induction by interactions with the pregnane X receptor (PXR) or aryl hydrocarbon receptor (AhR). It appears therefore, that the potential for CB-103 to cause significant drug-drug interaction via inhibiting or inducing CYP isoenzymes is low. However, since the *in vitro* data are preliminary at this stage and since the results of experiments to investigate time dependent inhibition of CYP isoenzymes by CB-103 are still pending, caution should be exercised when CB-103 is combined with substrates of CYP enzymes that have a narrow therapeutic index.

Effect of other drugs on CB-103: The metabolism of CB-103 in humans is still under investigation. *In vitro* data using human recombinant CYP enzymes have shown that CB-103 is a substrate for CYP1A1 and 2C19 and can also be metabolized by 2B6, 2C9, 2E1 and 4A4. However, CB-103 is metabolically very stable in human liver microsomes, indicating that even though CB-103 is a substrate for several CYP isoenzymes, the overall contribution of CYP-mediated metabolism to CB-103 elimination in humans could potentially play a minor role. Metabolism of CB-103 in human hepatocytes is much faster than in microsomes and seems to be driven by N-acetylation via N-acetyl transferase (NAT). As the prediction of clinically relevant drug-drug interactions affecting CB-103 plasma concentration is difficult at this stage, it is advised that strong inhibitors and inducers of CYP isoenzymes and NAT1/2 should be avoided during treatment with CB-103.

Monoamine Oxidase

CB-103 can inhibit MAO-A and B at high concentrations (IC_{50} 9.8 and 4.3 µM), but clinically relevant drug-drug interactions are unlikely at therapeutic concentrations of CB-103 (1 µM) due to the high plasma protein binding of the compound. Nevertheless, as interactions of monoamine oxidase inhibitors with compounds that affect serotonin levels (e.g. SSRIs, serotonin norepinephrine reuptake inhibitors, tricyclic antidepressants, tryptophan, dextromethorphan, meperidine) can increase the risk of serotonin syndrome (caused by excessive activation of serotonin receptors in the central nervous system) caution should be exercised when these drugs are combined with CB-103. Clinical manifestations represent a concentration-dependent spectrum of toxicity ranging from barely noticeable to seizures, coma and death. Early recognition and treatment are therefore essential.

3. STUDY RATIONALE AND PURPOSE

3.1 STUDY RATIONALE

The primary purpose of this Phase I/IIA study is to establish the safety profile and to determine and subsequently confirm the MTD or RP2D of CB-103 when administered orally on a continuous daily dosing schedule in adult patients with locally advanced or metastatic solid tumour and haematological malignancies. If MTD cannot be reached, the RP2D will be determined based on the dose level which can be taken by the patient with an acceptable risk-benefit.

The recruitment of patients into several expansion arms in Part B of the study will allow to further characterise the safety, preliminary efficacy and multiple dose PK of CB-103 at the MTD/R2PD and schedule determined in Part A of the study. In this expansion part of the study, the tumours are required to have confirmed genetic alterations or over-activation of the NOTCH signalling pathway. Several cancer indications are investigated in this study in order to confirm the safety and tolerability of the MTD/RP2D and to assess preliminary efficacy, as outlined below.

NOTCH pathway activated tumours under investigation:

- Breast cancer (TNBC, estrogen receptor [ER]+/-, HER2+/-), gastro-intestinal cancers (resistant to oxaliplatin or irinotecan-based therapy colorectal cancer, hepatocellular carcinoma), osteosarcoma, ACC, malignant glomus tumour, and T-ALL/T-LBL.

For some of the indications mentioned above there are only specific subtypes selected for the study. The respective subtypes of these indications are presented in Appendix 3.

Additionally, NOTCH pathway activation has been reported in other tumours with lower frequency. Patients whose tumours exhibit Notch pathway activation are eligible for this study even if the tumour is not among the indications mentioned above.

3.2 POTENTIAL RISKS AND BENEFITS

The Risk/Benefit assessment is based on (i) numerous pre-clinical models demonstrating the anti-tumour activity of CB-103, (ii) several non-clinical repeat dose toxicity studies conducted in rats and dogs, with GLP-compliant studies with dosing up to 28 days conducted in each species and (iii) and on the available documentation of the safety of other NOTCH inhibitors currently in early clinical development with different modes of actions taken into account.

Unmet clinical need: For many patients with advanced solid tumour or hematologic malignancies where the available and approved curative treatments have failed and the disease progresses and becomes treatment resistant and refractory, there is no further therapeutic option available and this represents a patient population with high unmet clinical need. In this context, many studies report a negative correlation of NOTCH

signalling activation and survival in patients with tumour cells characterised by genetic aberrations or over-activation of NOTCH signalling. These patients have a worse prognosis and significantly shorter survival than patients with a NOTCH wild-type tumour.

Potential benefits: Based on nonclinical studies and the known clinical efficacy deficiencies of other NOTCH inhibitors in clinical testing as well as the strong negative prognostic impact of NOTCH over- and constitutive activation, it is thought that CB-103 could provide benefit and an improvement to the treatment of NOTCH-positive solid tumour and haematological malignancies. In addition to the impact of aberrant NOTCH signalling on malignant proliferation and growth, the well-defined target of CB-103 and its new mode of action to block NOTCH signalling most downstream of the pathway at the level of the transcription complex and its proven ability to kill tumour cells in different *in vitro* and *in vivo* cancer models, as well as *ex vivo* to directly kill primary patient-derived leukaemia cells, supports the rationale and hypothesis that CB-103 will show efficacy in various solid tumour and haematological malignancies.

Potential risks: As outlined in Section 2.4, other NOTCH inhibitors with different modes of action compared to the central binding of CB-103 to the NOTCH-specific transcription complex, namely the GSIs and mAB targeting NOTCH receptors or ligands, have shown clinical efficacy in early stages of clinical development. However, due to the occurrence of toxicities reported in several clinical studies many patients had to discontinue treatment before the full benefit of anti-NOTCH treatment was achieved. The dose-limiting toxicities seen with GSIs are gastrointestinal with partially severe episodes of diarrhoea (goblet cell accumulation) leading to early and permanent treatment discontinuation. Besides the gastrointestinal toxicities, observed also with several of the mABs, there were also some cardiotoxicities reported from clinical studies with this class of drugs. In particular, with the anti-DLL-4 antibody Demcizumab, some patients were identified with cardiac insufficiencies leading also to early and permanent treatment discontinuation and correction of the dose and schedule of these drugs had to be made for these programs. These toxicities have not been observed in the non-clinical studies of CB-103 at the doses and schedules used and therefore the Sponsor believes that the safety profile to be established for CB-103 in humans might be better than those observed with the other NOTCH inhibitors which are currently in phase I and II clinical testing.

The safety and toxicology of CB-103 has been adequately evaluated in rat and dog during the non-clinical development following the current regulatory requirements for the support of the proposed Phase I/IIA clinical trial. Several non-GLP and two GLP-compliant 28-day MTD *in vivo* single and repeated dose toxicology studies, have been performed in one rodent (rat) and one non-rodent (dog) species following oral administration for the treatment duration up to 28 days. In these studies, no major signs of toxicity were observed and the dose-limiting factors in rats were adverse event findings in lungs, eyes (dilated pupils), liver and spleen (increased extramedullary erythropoiesis). In dogs, the dose-limiting factor was the slight transient changes in heart rate and QTc. The ECG changes seen in dogs together with the non-clinical finding that CB-103 can block the hERG and

ion channel at high doses with a high peak concentration, suggest that CB-103 may have some potential to affect cardiac repolarisation and cardiac conduction. The clinical consequence of this finding is currently unknown as the translatability of ECG changes from dogs to humans is not known. As part of risk management, a robust, multiple ECG monitoring aligned with PK sampling - including periodical Holter monitoring, with concentration-response analysis and a central review performed by a cardiac expert - will be implemented in the study. Furthermore ECHO/MUGA scans will be performed at selected time points in the study to also investigate any effect of CB-103 on heart contractility. Patients should be monitored for clinical signs of heart abnormalities, and consideration be given to withdrawal from the study of any patients who develop signs of cardiac abnormalities taking into consideration overall benefit and risks for the patients.

Based on pre-clinical data with CB-103 and on information known from other drugs inhibiting the NOTCH pathway the following events might appear after CB-103 oral administration (see also Investigator's Brochure):

- ECG alterations
- Hypertensive events
- Cardiac dysfunction (New York Heart Association [NYHA] Class II-IV) including congestive heart failure with signs and symptoms of cardiac dysfunction such as dyspnoea, orthopnoea, increased cough, pulmonary oedema, S3 gallop, or reduced ventricular ejection fraction, that can be associated with fatal outcome.
- Increased extramedullary haematopoiesis (e.g. erythropoiesis)
- Splenomegaly
- Gastro-intestinal toxicities (diarrhoea, nausea, vomiting, abdominal pain)
- Mydriasis (dilated pupils)
- Phototoxicity
- Skin rash and redness
- Decreased physical activity and fatigue
- Decreased body weight
- Convulsions
- Oedema

The severity and seriousness of adverse events cannot be defined yet as this will be the first clinical study with CB-103. With respect to additional unknown risks, as per normal practice for Phase I, FIH clinical trials, the patients will be closely monitored in order to detect any additional, study drug-related adverse events.

The phototoxicity was deemed a hypothetical risk solely based on the UV spectrum peak absorption of the drug substance (CB-103 HCl) in the wavelength of 290 - 700 nm; phototoxicity was not observed in any pre-clinical studies with CB-103.

The potential risk of phototoxicity and occurrence of mydriasis are two distinct potential risks to be considered separately as the occurrence of both in the eye is rather rare, but the below precautionary measures will also cover this risk of coincidence.

In order to avoid potential drug-induced phototoxicity and to protect the patient from any harm caused by the occurrence of dilated pupils the measures below should be followed and the patients should be informed accordingly:

- Limit prolonged sun exposure
- Wear protective clothes
- Wear sunglasses when exposed to bright sun
- Use sun cream with high sun protection factor on skin when exposed to bright sun
- Immediately notify the study doctor about any eye symptoms or blurred vision
- Refrain from activities that may cause the risk of an accident, in the event of any eye symptom or vision impairment (e.g. driving car, bike, operating machines).

In order to detect any potential cardiac effects of CB-103 already early on, an intense, continuous ECG monitoring with central management and read by a specialised CRO to assess cardiac safety as well as Holter ECG monitoring to detect any arrhythmias and echocardiogram/multi-gated acquisition (ECHO/MUGA) scans to assess LVEF will be assessed at baseline and at selected time points throughout the study to ensure the patients' health and safety at all times during the treatment period.

CB-103 will be administered orally as single agent.

In summary, the risks for patients in the FIH clinical trial are expected to be acceptable as they are largely predictable, monitorable and treatable in an appropriately equipped hospital environment.

Conclusion: Taking these potential benefits and risks into consideration, the Sponsor is of the opinion that the potential benefit of CB-103 for patients with locally advanced or metastatic solid tumours and haematological malignancies outweighs the potential risk.

3.3 CONDUCT OF STUDY

This clinical study will be conducted in compliance with this protocol, the guidelines of the World Medical Association Declaration of Helsinki, the ICH, Harmonised Tripartite Guidelines for GCP (R2), the European Directive 2001/20/EC, designated standard operating procedures (SOPs), and with local laws and regulations relevant to the use of new therapeutic agents in the country of conduct.

4. STUDY OBJECTIVES AND ENDPOINTS

4.1 STUDY OBJECTIVES

4.1.1 Primary Objectives

Phase I, Part A - Dose Escalation:

- To determine the MTD or RP2D of CB-103 as a single agent in adult patients.

Phase I, Part A – Confirmatory Cohort:

- To confirm safety of the RP2D of CB-103 as a single agent in adult patients.

Phase IIA, Part B - Expansion:

- To assess preliminary anti-tumour activity of single agent CB-103 in the different expansion arms across the different indications.

4.1.2 Secondary Objectives

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

- To characterise the PK characteristics of CB-103 in patients after single and repeated administration at various dose levels.
- **Part A only:**
  - To characterise safety and tolerability of the MTD/RP2D of CB-103 in patients with selected solid tumours and hematological malignancies.
  - To assess preliminary anti-tumour activity of single agent CB-103.
- **Part B only:**
  - To further characterise safety and tolerability of the MTD/RP2D of CB-103 in patients with selected solid tumours and haematological malignancies, stratified by disease into separate expansion arms.

4.1.3 Exploratory Objectives

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

- To characterise the pharmacokinetic (PK) characteristics of CB-103 in subgroups of patients (e.g., by indication or ethnicity) after single and repeated administration at various dose levels.
- To explore potential correlations between PK and parameters of efficacy (e.g. tumour response, tumour shrinkage, tumour metabolic activity), PD markers (genes and proteins) and safety (e.g. occurrence of adverse events, relationship of CB-103 concentration versus 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]).

- Positron Emission Tomography (PET) in selected tumours: baseline and on-treatment, ^{18}Fluoro-deoxyglucose positron emission tomography (FDG-PET) in combination with CT (PET-CT) will be collected to determine changes in glucose metabolism of the tumour lesions in tumour types exhibiting FDG-uptake.
- To investigate plasma levels of metabolite(s) when feasible.
- To explore the CB-103 metabolic profile in biological matrices such as urine and/or stool samples.
- To assess changes in NOTCH target and downstream PD markers (genes, proteins) in solid tumours:
  - pre- and post- CB-103 dosing in **tumour tissue biopsies** as a measure of NOTCH pathway inhibition;
  - pre- and post- CB-103 dosing in **whole blood, plasma samples and hair follicles** (if the appropriate laboratory is available) as a surrogate model to measure NOTCH pathway inhibition.
- To assess changes in NOTCH target genes and downstream PD markers (genes, proteins) in haematological malignancies:
  - pre- and post- CB-103 dosing in **T-lymphocytes from blood and/or bone marrow samples**;
  - pre- and post- CB-103 dosing in **whole blood and plasma samples** (if the appropriate laboratory is available).
- To assess the changes in the percentage of mutated alleles in liquid biopsies pre- and post CB-103 dosing and their relation to the effect of CB-103 treatment.
- To evaluate the cerebrospinal fluid (CSF) exposure of CB-103 in patients with haematological malignancies, in whom intra-thecal (IT) prophylaxis is planned by the treating physician.
- To explore the potential influence of certain genotypes (e.g. CYP enzymes or NAT) on the PK of CB-103.
- Exploratory analysis may be performed on **tumour tissue samples or on blood and/or bone marrow samples** as a part of this study to identify gene 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.
- Exploratory CB-103 quantification analysis may be performed on **tumour tissue samples**.
- To evaluate the potential role of biomarkers and genetic markers for safety, PD, and anti-tumour activity of CB-103 and to define the optimal biological dose of CB-103.
- To explore and assess changes in the immune system in pre- and post-CB-103 dosing whole blood and plasma.
- Additional exploratory analyses may be performed on available samples from the study, for example to establish a correlation of biomarkers across methods or types of tissue.

Note: during the course of the study, sample collection for and analysis of any of the above-mentioned exploratory objectives may be stopped for all patients or in selected patients' groups depending on the emerging preliminary data; the decision will be documented in a Note to File.

4.2 STUDY ENDPOINTS

4.2.1 Primary Endpoints

The primary endpoint for Phase I, Part A (dose-escalation) of this study is as follows:

- The number of patients experiencing dose-limiting toxicity (DLT) during the first 28-day cycle of CB-103 treatment

The primary endpoint for Phase I, Part A (confirmatory) of this study is as follows:

- The incidence rate, severity and relationship to CB-103 of adverse drug reactions and serious drug reactions according to common terminology criteria for adverse events (CTCAE) V4.03, safety laboratory, vital signs, ECG and ECHO/MUGA assessments.

The primary endpoint for Phase IIA, Part B of this study is as follows:

- To assess tumour response rates in each expansion arm as best overall response rate (in solid tumours complete response [CR] + partial response [PR]) assessed by Response Evaluation Criteria in Solid Tumours (RECIST 1.1); in T-ALL/T-LBL patients, confirmed CR and Complete Remission with Incomplete Hematologic Recovery (CRi) assessed by the criteria according to NCCN Guidelines on Adult Acute Lymphoblastic Leukaemia (Version 1.2020).

4.2.2 Secondary Endpoints

The secondary endpoints for both Part A and B of this study are as follows, unless otherwise specified:

- The incidence rate, severity and relationship to CB-103 of adverse drug reactions and serious drug reactions according to common terminology criteria for adverse events (CTCAE) V4.03, safety laboratory, vital signs, ECG and ECHO/MUGA assessments in each dose group and expansion arm.
- CB-103 plasma concentrations, PK parameters: C_{max}, t_{max}, C_{min}, C_{last}, t_{last}, area under the curve (AUC) during 8 and 24 hours (AUC_{0-8}, AUC_{0-24}), AUC from time 0 extrapolated to infinite time ($AUC_{0-\infty}$), apparent volume of distribution (V_d/F), apparent volume of distribution at steady (V_{ss}/F), apparent clearance after oral administration (CL/F), $t_{1/2}$ and AR.
- **Part A only:** to assess tumour response rates
  - For solid tumour indications: to assess best overall response rate (CR + PR), assessed by RECIST 1.1 (Eisenhauer et al., 2009).
  - For haematologic malignancies: to assess the best overall response rate (CR or CRi) per NCCN guidelines.
- To assess clinical benefit rate

- For solid tumour indications: clinical benefit rate (CR + PR + SD), assessed by RECIST 1.1. (Eisenhauer et al., 2009).

- Duration of response (DOR), time to response, progression-free survival (PFS), OS.

4.2.3 Exploratory Endpoints

The exploratory endpoints for both Part A and B of this study are as follows:

- To assess plasma levels and PK parameters (C_{max}, t_{max}, C_{min}, C_{last}, t_{last}, AUC_{0-8}, AUC_{0-24}, $AUC_{0-\infty}$, $t_{1/2}$ and AR) of metabolite(s) when feasible.
- To evaluate the relationship between CB-103 plasma concentrations and/or PK parameters (e.g., C_{max} and AUC_{0-24}) and safety, efficacy and PD parameters.
- To assess NOTCH, NOTCH-related genes, and NOTCH target genes expression changes in pre- and post-treatment tumour tissue samples, whole blood / plasma samples and hair follicles in solid tumours and in T-lymphocytes from blood and/or bone marrow samples, whole blood and plasma in T-ALL/T-LBL, and assess their relation to clinical activity of CB-103.
- To assess the cerebrospinal fluid (CSF) exposure of CB-103 in haematological malignancies, in patients in whom IT prophylaxis is planned by the treating physician.
- To assess certain genotypes (e.g. cytochrome P450 enzymes or NAT) and assess relation to PK outcome data.
- To assess NOTCH1-4 NICD expression assessed by IHC staining or by Western Blot in pre- and post-treatment in solid tumour tissue samples and to assess their relation to clinical activity of CB-103.
- To assess NOTCH mutations by genomic mutation analysis in tumour tissue samples in solid tumours and in T-lymphocytes from blood and/or bone marrow samples, whole blood and plasma in T-ALL/T-LBL, and to assess their relation to clinical activity of CB-103 treatment.
- To assess the changes in the percentage of mutated alleles in liquid biopsies pre- and post CB-103 dosing and their relation to the effect of CB-103 treatment.
- To evaluate the intra-tumoral quantification of CB-103 in solid tumour tissue samples.
- To profile tumour tissue samples in solid tumours and T-lymphocytes from blood and/or bone marrow samples in T-ALL/T-LBL by single cell RNA-seq and/or other gene expression and genetic profiling techniques.
- To explore and assess changes in the immune system in pre- and post-CB-103 dosing whole blood and plasma (e.g., measure expression of cytokines/chemokines by RNA expression analysis, quantify pro-inflammatory and anti-inflammatory cytokines and chemokines, phenotype different types of immune cells (T cells, B cells, dendritic cells and macrophages, etc.) using flow cytometry).
- To assess change from baseline cardiac intervals versus increasing plasma CB-103 concentrations.

- To assess the metabolic profile of CB-103 in biological matrices such as urine and/or stool samples based on metabolic expressions of CB-103 in urine and/or stool samples

5. STUDY DESIGN

5.1 DESCRIPTION OF STUDY

5.1.1 Overview of 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 followed by an MTD/RP2D confirmatory cohort is to determine the MTD/RP2D. An adaptive 2-parameter BLRM for EWOC will be used in Part A to guide determination of the MTD or the RP2D.

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.

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. 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, with at least 1 day apart from the second patient, whereby a dose cohort must be completed with regards to the DLT assessment period and be reviewed by the Cohort Review Committee (CRC) established for this study before further patients are dosed in 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 the CRC consisting of the Investigators, Sponsor and CRO representatives, and independent functional experts as required (see Section 5.1.4.1). The CRC will make the decision to determine the next dose level and schedule for the next dose cohort.

Any dose level cohort that has been declared safe after the DLT period, may be expanded by individual patients in order to collect additional pharmacodynamic (PD) and pharmacokinetic (PK) information to support and/or confirm the mechanism of action and

explore doses at the currently tolerated dose level or below. These patients will be counted for the respective cohort at the future CRC meetings and will contribute towards the overall safety, PK, PD and clinical efficacy evaluation.

When the MTD/RP2D is defined, based on the decision of the CRC, approximately 45 additional NOTCH-positive patients with recurrent/metastatic ACC, breast cancer, r/r T-ALL/T-LBL, or any other solid tumour with proven Notch pathway activation will receive the MTD/RP2D dose to ascertain that optimal safety related to efficacy and pharmacodynamics in the tumour and in peripheral blood are achieved.

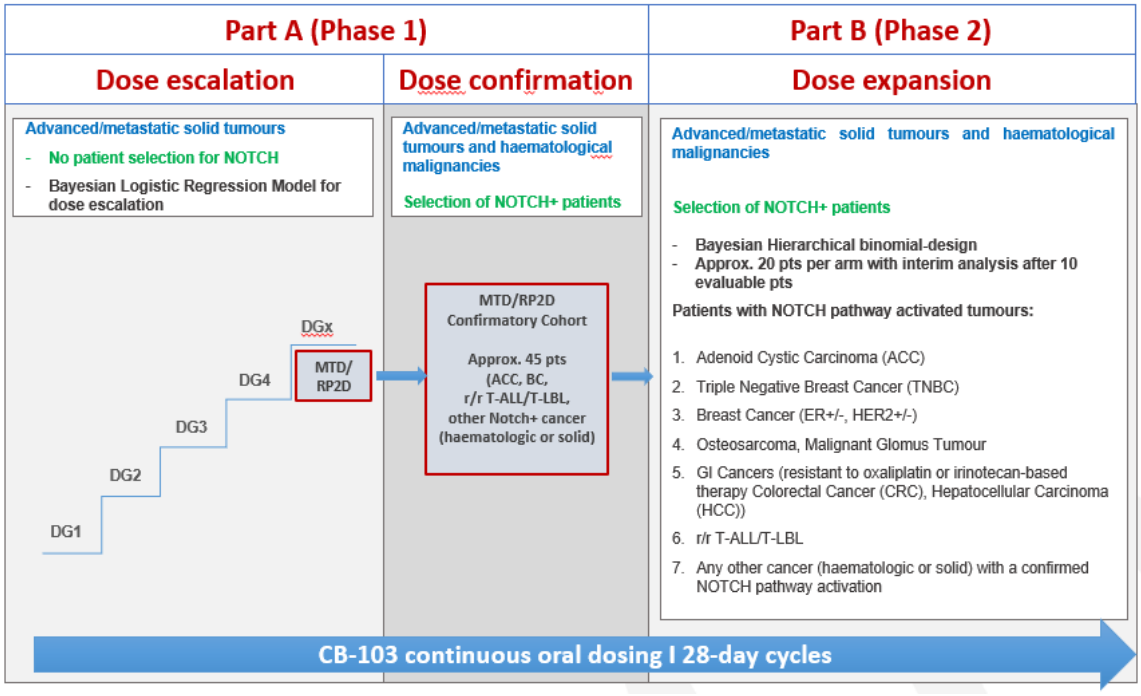
Part B - Expansion (Phase IIA)

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 arms. These arms will consist of patients with pre-selected cancer indications with tumour cells characterised by NOTCH over-activation to confirm safety of the MTD/RP2D of CB-103 and to explore 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.

The study design is depicted in Figure 4.

Figure 4 Overview of study design



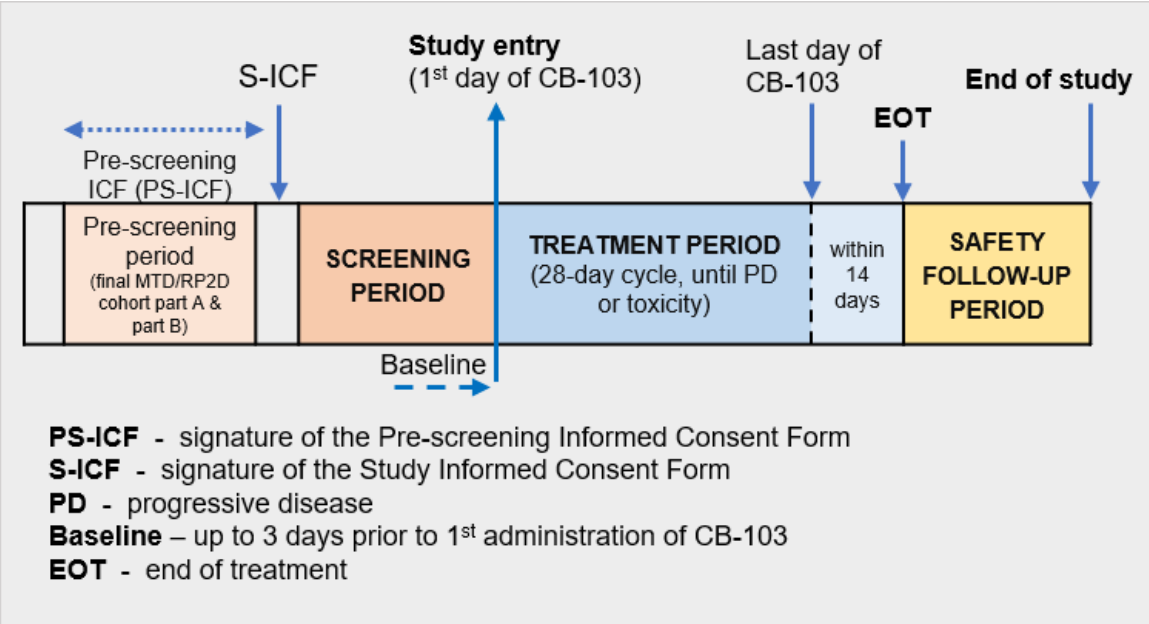
Abbreviations: ACC, adenoid cystic carcinoma; DG, dose group; MTD, maximum tolerated dose; pts, patients; ER, estrogen receptor; CRC, colorectal cancer; HCC, hepatocellular carcinoma; HER2, human epidermal growth factor receptor 2; PR, progesterone receptor; r/r, relapsed/refractory; RP2D, recommended phase 2 dose; TNBC, triple negative breast cancer.

5.1.1.1 Study Periods

The study is split into three periods in Part A and into 4 periods in Part B (Figure 5):

- Pre-screening period (Part A MTD/RP2D confirmatory cohort & Part B)
- Screening period (including baseline assessments)
- Treatment period (including an End-of-Treatment [EOT] visit)
- Safety follow-up period

Figure 5 Study periods



Pre-screening period (Part A MTD/RP2D confirmatory cohort & Part B), for patients whose Notch pathway activation status is not known

The pre-screening period starts once the patient has signed the “pre-screening” informed consent form (ICF) and ends once the patient has signed the “study” ICF.

In Part A (MTD/RP2D confirmatory cohort) & Part B, if the Notch status of the cancer has not been ascertained previously, investigational sites will need to pre-screen patients for either NOTCH pathway activating mutations, amplifications/translocations or gene/protein expression alterations. The investigational site must obtain the signature of the patient on the pre-screening consent form. If there is no archived tumour sample available or if available, but older than 6 months, then a fresh tumour biopsy has to be obtained. The patient’s tumour samples can be sent for characterisation of NOTCH pathway-activation to the central laboratory if the analysis cannot be done locally. The result of the analysis will be communicated within approximately 7 working days to the respective investigational site.

Screening period

The 28-day screening period includes the baseline and starts once a patient has provided written informed consent to participate in the study; it ends on the day prior to the planned 1st administration of CB-103 (day -28 to day -1).

Because of the low overall incidence of cancers with an activated NOTCH signalling pathway (Ntziachristos et al., 2014), enrolment of patients in Part A (dose-escalation) will not include mandatory screening for NOTCH pathway over-activation in tumour tissue.

However, in line with the site's standard-of-care, the investigational sites are encouraged to evaluate their patients prior to study entry with regard to the NOTCH activation level in tumours (either mutations, amplifications/translocations or gene/protein expression alterations) and to consider enrolling patients preferably with a signal of NOTCH over-activation. The selection of patients for Part A (dose-escalation) may be done in favour of those who show evidence of over-activation and genetic aberrations of the NOTCH signalling pathway.

Patients enrolling in the Part A MTD/RP2D confirmatory cohort and in Part B (dose expansion) have to have tumours with demonstrated NOTCH pathway activation. NOTCH status will be determined as outlined in the Inclusion Criteria by using established methods.

Baseline period

Baseline assessments are performed from three days prior to, until the day prior to the planned 1st administration of CB-103 (day -3 to day -1).

Treatment period

Solid tumours (six-twelve cycles): the treatment period commences on the first day of the first cycle of CB-103 treatment (1st administration of CB-103) and ends on the last day of dosing (within the 6 cycles period for Part A or 12 cycles period for Part B).

T-ALL/T-LBL: initial treatment with CB-103 single agent is given for 28 days (one cycle). Patients are assessed for disease response on day 29 (±3 days); however, if the day 29 marrow is hypocellular (cellularity ≤ 15%), then treatment with CB-103 may continue and a repeat bone marrow biopsy is obtained one week later (day 36) to assess response.

Patients achieving a CR are eligible to receive 2 additional courses of CB-103 as consolidation therapy at the same dose and schedule as outlined above. Treatment may be discontinued if the patient is scheduled for HCT, otherwise additional courses of CB-103 until relapse may be given after discussion with the Sponsor.

If residual leukaemia/lymphoma is documented at the point of marrow recovery (cellularity ≥ 15%) after the first induction cycle, then a second course of CB-103 is administered.

End of Treatment (EOT)

The EOT visit occurs within 14 days after the last administration of CB-103. All participating patients must complete this visit even if they have had to prematurely discontinue treatment with CB-103.

Safety follow-up period

All patients will have a safety follow-up for adverse events and serious adverse events 28 days after the last dose of CB-103 after which the end-of-study is reached. The safety follow-up visit must be performed by all patients who have received at least one administration of CB-103. All adverse events and/or serious adverse events occurring

during this period will be recorded in the Adverse Event electronic Case Report Form (eCRF).

5.1.2 Study Duration

The overall study will be completed 28 days after the last patient in Part B of the study received the last treatment.

5.1.3 End of Study

The end-of-study overall is reached when the last patient in Part B has been on study treatment for up to 12 cycles (or after completion of the treatment period in T-ALL/T-LBL patients as defined above) plus the safety follow-up period of 28 days. In case the study is stopped before any patient was treated for 12 months, the end-of-study is reached 28 days after the last patient in Part B of the study has received his/her last dose of CB-103.

If the last patient in Part B of the study remains on treatment for more than 12 cycles for the purposes of generating the Clinical Study Report (CSR), the end of the study will be defined as the point where the last patient enrolled in Part B has had the opportunity to be dosed for up to 12 cycles after 1st CB-103 administration and has completed the safety follow-up/ end-of-study (EOS) visit. Patients on treatment at that time may be eligible to continue treatment with CB-103. The Sponsor reserves the unilateral right, at its sole discretion, to determine whether to supply CB-103, and by what mechanism, after the end of study is reached or termination of the trial and before it is commercially available.

With respect to the Part A of the study, a separate CSR will be prepared and the cut-off for the data to be included in this report will be set after the safety follow-up visit is performed by all patients in Part A of the study, that will occur 28 days after the last dose of CB-103 and the last patient in Part A has been on treatment for a maximum of 6 cycles. An addendum (or addenda) to the CSRs of Part A and Part B may be generated to report the remaining data from patients continuing to be followed up for progression and survival outcome beyond the cycle 6 or cycle 12, respectively.

The study procedures to carry out beyond 6 cycles (Part A) or 12 cycles (Part B) are indicated in the schedule of assessments. Data from these patients will be summarised and reported in a separate, abbreviated CSR.

5.1.4 Committees

5.1.4.1 Cohort Review Committee

Prior to enrolment of patients into Part A (escalation) of the study, a cohort review committee (CRC) will be established, consisting of the Principal Investigators of at least those sites where the patients are enrolled, Sponsor CMO/designee and representatives, CRO representatives (e.g. medical monitor, statistician) and independent experts as required (e.g. cardiology expert). The CRC will oversee safety, cohort evaluation, dose escalation and the evaluation of MTD/RP2D for the study. A formal charter which will

establish the rules, meeting frequency and scope of responsibilities of the CRC will be prepared prior to the start of the study.

For the review of a dose level by the CRC, there will be at least 3, up to 6 patients evaluable for DLT. The CRC will review data from one complete treatment cycle (28 days) for at least 3 patients in the respective dose cohort to authorise dose escalation.

5.2 INVESTIGATIONAL SITES

This is a multi-centre study to be conducted globally in several countries. Additional site(s) may be included for back-up purposes and may be activated if needed.

Administrative and Contact Information, and List of Investigators are provided separately.

6. STUDY POPULATION

This study will include adult male and female patients ≥ 18 years. Patients must meet all of the inclusion criteria and none of the exclusion criteria in order to qualify for the study.

Adult patients with locally advanced solid tumour or haematological malignancies (surgically unresectable locally advanced or metastatic solid tumours or haematological malignancies) whose disease has progressed on at least one line of systemic therapy and for whom no standard curative therapy exists will be enrolled into Part A (Phase I dose-escalation). All participants must have histological or cytological evidence for the diagnosis of the respective cancer indication. CB-103 has been shown to cross the blood-brain-barrier in animals. All patients must be in an advanced or metastatic stage of disease after available curative therapies have failed to confer acceptable clinical benefit/risk to their advanced or metastatic cancer. Patients may be enrolled into the study and treated with CB-103 at an earlier line of treatment if they have a tumour with confirmed NOTCH pathway activation assessed by at least one diagnostic method, justifying the treatment with a NOTCH pathway inhibitor in an earlier line of treatment. This will be at the discretion of the Investigator.

When the MTD/RP2D is defined, based on decision of the CRC, the MTD/RP2D confirmatory cohort will open to include approximately 45 additional NOTCH-positive patients with recurrent/metastatic adenoid cystic carcinomas (ACC), breast cancer, r/r T-ALL/T-LBL, or any other solid tumour with proven Notch pathway activation, who will receive the MTD/RP2D dose to ascertain that optimal safety related to efficacy and pharmacodynamics in the tumour and in peripheral blood are achieved.

For the expansion arms in Part B of the study, the following are the preliminary indications for patients with NOTCH activated pathways planned:

1. Adenoid cystic carcinoma (ACC)
2. Triple negative breast cancer (TNBC)
3. Breast cancer (ER+/-, HER2+/-)
4. Osteosarcomas, Malignant glomus tumour
5. GI cancers (resistant to oxaliplatin or irinotecan-based therapy colorectal cancer, hepatocellular carcinoma)
6. r/r T-ALL/T-LBL
7. Any other cancer (haematologic or solid) with confirmed Notch pathway activation (basket arm)

The preliminary indications considered for the expansion arms may be adapted and modified based on the results of Part A of this study as well as from the outcome of future *in vivo* pharmacology studies with CB-103. All the adaptations will result in a protocol amendment.

6.1 RECRUITMENT PROCEDURES

Patients will be recruited primarily from investigational site/country clinical databases; however, in some cases, potential patients may be identified prior to consenting to take part in this study using pre-screening enrolment logs, Independent Ethics Committee (IEC)/Institutional Review Board (IRB) approved newspaper/radio advertisements and mailing lists.

6.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

1. **Disease**

   a. Histologically or cytologically confirmed solid tumours that are surgically unresectable, locally advanced, or metastatic, which have progressed on at least one line of systemic therapy (with the exception of ACC patients who are allowed to be systemic treatment-naïve) and for which no established therapeutic alternatives exist.

   or

   b. Relapsed or refractory (r/r) T-ALL or T-LBL. Refractory patients are defined as T-ALL/T-LBL patients with ≥ 5% bone marrow blasts and/or concomitant extramedullary involvement, who have not achieved a CR after standard induction/consolidation therapy attempt. Relapsed patients are defined as T-ALL/T-LBL patients who have recurrent disease, i.e. ≥ 5% bone marrow blasts and/or concomitant extramedullary relapse, after having achieved a prior CR.

   c. For **Part A (dose-escalation)** solid tumour indications based on known frequent involvement of the NOTCH pathway activation in these indications, and tumours with an *a priori* known NOTCH1-4 pathway activation are also eligible, as defined below:

      - Breast cancer (TNBC, ER+/-, HER2+/-), GI cancers (resistant to oxaliplatin or irinotecan-based therapy colorectal cancer, hepatocellular carcinoma), osteosarcoma, ACC and malignant glomus tumour.
      - Any other solid cancer (including lymphoma) with a confirmed NOTCH1-4 activating mutation or genetic lesion.

   d. For **Part A (MTD/RP2D confirmatory cohort) and Part B expansion cohorts**, solid and haematological tumour indications with confirmed Notch pathway activation as follows:

      - ACC
      - Metastatic breast cancer (regardless of receptor status of ER/PR, HER2)
      - r/r T-ALL/T-LBL
      - Any other cancer (haematologic or solid) with a confirmed NOTCH pathway activation, after approval by the Sponsor

Notes:

- Patients are eligible if Notch pathway activation was determined in the past. If the Notch status is unknown, it will be determined on fresh bodily material.
- The pathogenic character of the detected mutation/genetic alteration needs to be confirmed before the patient can be enrolled. Patients whose tumour mutations/alterations are not unambiguously pathogenic will be included at the Sponsor's discretion. Details on molecular alterations as signs of Notch pathway activation and the specific test method can be found in the laboratory manual.

e. Patients with solid tumours must have at least one measurable lesion (at least 1.0 cm in diameter) according to RECIST v1.1 guideline for solid tumours (irradiated lesions are only measurable if unequivocal disease progression is demonstrated).

f. **Patients with solid tumour indications in Part A** (**dose-escalation):**

- Sufficient archival tumour tissue samples. If the archival tissue is older than 6 months at screening – or, if not available – a fresh pre-dose tumour biopsy is required. If the lesion is not accessible for a fresh tumour biopsy, a liquid biopsy may be used after confirmation with the Sponsor.

g. **Patients with solid tumours in the MTD/RP2D confirmatory cohort of Part A and in Part B:**

- If the Notch status is unknown, patients with solid tumours 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.

  All solid tumour patients: tumour lesions accessible to biopsy and patient willing to provide a fresh tumour biopsy at pre-dose, one during treatment, and one at disease progression or when clinically indicated. In individual cases where the lesion is not accessible for a fresh tumour biopsy, a liquid biopsy may be used after confirmation with the Sponsor.

h. Life expectancy of at least 3 months in the opinion of the investigator.

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. Total serum bilirubin ≤ 1.5 x upper limit of normal (ULN)

b. 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

c. 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, then AST and ALT must be ≤ 5 x ULN

d. 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)

e. Potassium levels within normal limits or correctable with supplements

f. Total calcium levels (corrected for serum albumin) within normal limits or correctable with supplements

g. Magnesium levels within normal limits or correctable with supplements

h. Phosphorus levels within normal limits or correctable with supplements

i. Serum albumin concentration ≥ 30 g/L

j. Patients with solid tumours must have:

- Absolute neutrophil count (ANC) $\geqslant$ 1.5 x 10^9/L
- Haemoglobin (Hgb) $\geqslant$ 10 g/dL ($\geqslant$ 100 g/L)
- Platelet count $\geqslant$ 75 x 10^9/L (without platelet transfusion or growth factor support in the preceding 7 days)
- 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 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, injectable contraceptives, mechanical contraception including a condom for the partner, or an intrauterine coil) and must continue using them throughout the entire clinical trial period and for 90 days post-treatment completion (duration of

3 ovulatory cycles). Contraception must start from the day of 1st administration of CB-103.

c. Men whose partners could be of childbearing 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 A - MTD/RP2D confirmatory cohort - and part B) and screening.

6.1.2 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.

Note: T-ALL/T-LBL patients with active CNS disease defined as the presence of CNS disease at diagnosis, and/or presence of CNS involvement-related symptoms, e.g. related to cranial nerve involvement, may not be included.

b. Hypersensitivity to any of the excipients of the finished drug CB-103.

c. Patients with unresolved nausea, vomiting, or diarrhoea of 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 (NYHA class III or IV), arrhythmia or conduction abnormality requiring medication, or cardiomyopathy
2. Clinically uncontrolled hypertension (systolic blood pressure ≥160 mmHg or diastolic blood pressure ≥100 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 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-cancer therapy (e.g. anti-HER2 therapy, anthracyclines), 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 treatment
2. For patients with solid tumours: prior bone marrow/haematopoietic stem cell transplant.
   Note: For T-ALL patients prior allogenic bone marrow/haematopoietic stem cell transplant is allowed if they have no current GvHD and patients are off immunosuppressive therapy.
3. Known infection with human immunodeficiency virus (HIV); or hepatitis B or C requiring treatment
4. Any active infection requiring the use of parenteral anti-microbial agents or that is > Grade 2
5. Non-malignant interstitial lung disease or pneumonitis
6. Dyspnoea of any cause requiring supplemental oxygen therapy and dyspnoea at rest due to complications of advanced malignancy and co-morbidities
7. 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.

8. 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. In patients with solid tumours, cytotoxic chemotherapy within 3 weeks (6 weeks for nitrosoureas and mitomycin C) of the scheduled first dose of CB-103 on day 1.

b. In T-ALL/T-LBL patients, prior anti-cancer therapy less than 2 weeks prior to starting therapy or 5 half-lives (whichever is longer) with the following exceptions:

1. Up to 5 days of glucocorticoids (10 mg/m^2 dexamethasone or equivalent/day) in combination with up to 3 doses of cyclophosphamide (200 mg/m^2/day) are allowed as standard prephase treatment up to 1 day before start of study treatment
2. Mercaptopurine may be dosed up to 5 days prior to first dose of CB103
3. Vinca alkaloids may be dosed up to 5 days prior to first dose of CB103
4. Prophylactic IT chemotherapy may be dosed up to 3 days prior to first dose of CB103.

c. Prior cumulative doxorubicin exposure of ≥ 500 mg/m^2

d. Prior cumulative epirubicin exposure of ≥ 900 mg/m^2

e. Any investigational treatment (including NOTCH signalling inhibitors and prior treatments with CB-103) within 4 weeks of scheduled CB-103 dosing 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 other adverse event associated with leukemic involvement), or incomplete recovery from

previous surgery, unless agreed by the 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 (a list of drugs is given in Appendix 4 of the protocol). However, in case of a life-threatening infection, in the best interest of the patient, concomitant treatment with the study drug and the relevant anti-infectious drug, though this may be included in the list given in Appendix 4, can be continued with closer monitoring.

b. 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.

c. 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.

6.2 CRITERIA FOR WOMEN OF CHILDBEARING POTENTIAL

A woman is considered to be of childbearing potential (WOCBP) unless she meets at least one of the following criteria:

- Previous bilateral salpingectomy, bilateral salpingo-oophorectomy or hysterectomy.
- Premature ovarian failure confirmed by a specialist.
- XY genotype, Turner syndrome, uterine agenesis.
- Postmenopausal, defined as 12 consecutive months with no menses without an alternative medical cause (ICH M3 definition).

6.3 NUMBERING OF PATIENTS AND INVESTIGATIONAL SITES

Each patient in the study is uniquely identified by a 6-digit patient number which is a combination of his/her 3-digit centre number and 3-digit patient number.

The site number is assigned by the Sponsor (or its delegate) to the investigational site.

The patient number will be assigned when the case book is created in the eCRF after the informed consent is obtained.

7. STUDY TREATMENT

7.1 FORMULATION

The Investigational Medicinal Product (IMP) CB-103 will be provided in the form of capsules for oral treatment. More detailed information on the oral formulation of CB-103 can be found in the Investigator's Brochure.

Capsules with different drug strengths will be provided, e.g. 5, 10, 20, 50 and 100 mg each. All drug supplies should be stored in a secure, temperature-controlled area, which can be accessed only by the pharmacist, the Investigator, or another duly designated person. The investigational sites will be supplied with study drug according to the sites' needs. Patients should be given a sufficient supply to last until their next study visit. Detailed storage conditions will be provided on the medication label and on the Pharmacy Manual.

The respective CB-103 doses will be given as fixed dose in milligrams (mg).

7.2 PACKAGING, LABELING AND HANDLING

IMP packaging will be overseen by the Sponsor Clinical Trial Supplies department or delegate and will bear a label with the identification required by local law, the protocol number, drug identification and dosage.

The packaging and labelling of the study medication will be performed in compliance with Good Manufacturing Practices (GMP) and any other or local applicable regulations. The qualified individual responsible for dispensing the study drug will prepare the correct drug product according to the individual specific dose allocated to the individual patient. This individual will also record study drug batch number received by each patient during the study.

Upon arrival of investigational products at the investigational site, site personnel should check for damage and verify proper identity, quantity, integrity of seals and temperature conditions, and report any deviations or product complaints to the Monitor upon discovery.

7.3 IMP STORAGE AND DISPENSING

The Investigator is responsible for safe and proper handling and storage of the study drug at the investigational site and for ensuring that the study drug is administered only to patients enrolled in the study and in accordance with the protocol.

IMP must be kept in a locked temperature-controlled area, which can be accessed only by the pharmacist, the Investigator, or another duly designated person. The investigational sites will be supplied with study drug according to the sites' needs. Patients should be given sufficient supply to last until their next study visit.

Further details on storage conditions and instructions are provided in the Pharmacy Manual and the Investigator's Brochure.

7.3.1 IMP Accountability

All IMP (CB-103) required for completion of this study will be provided by the Sponsor. The investigational site will acknowledge receipt of IMP and confirm the shipment condition and contents. Any damaged shipments will be replaced.

The Investigator is responsible for the control of drugs under investigation. Adequate records of drug dispensed, used, dosages administered, returned, and intervals between visits will be maintained during the study.

IMP accountability will be performed on a regular basis by the study staff and will be checked by the study monitor during site visits and at the completion of the study. Returned IMP should be stored separately from IMP that needs to be dispensed. All records and drug supplies must be available for inspection by the study monitor at every monitoring visit.

IMPs will either be disposed of at the investigational site according to the investigational site's institutional standard operating procedure or returned to the Sponsor with the appropriate documentation. The investigational site's method of IMP destruction must be agreed upon by the Sponsor. Local or institutional regulations may require immediate destruction of used IMP for safety reasons. In these cases, it may be acceptable for investigational site staff to destroy dispensed investigational product before a monitoring inspection provided that source document verification is performed on the remaining inventory and reconciled against the documentation of quantity shipped, dispensed, returned, destroyed and provided that adequate storage and integrity of the drug has been confirmed.

The investigational site must obtain written authorisation from the Sponsor before any IMP is destroyed, and IMP destruction must be documented on the appropriate form.

Written documentation of IMP destruction must contain the following:

- Identity of investigational product[s] destroyed.
- Quantity of investigational product[s] destroyed.
- Date of destruction.
- Method of destruction.
- Name and signature of responsible person [or company] who destroyed investigational product[s].

Accurate records of all IMPs received at, dispensed from, returned to, and disposed of by the investigational site should be recorded on the Drug Inventory Log.

7.4 DOSAGE AND TREATMENT SCHEDULE

CB-103 will be administered orally as a continuous once daily (QD) dosing during the treatment period of Part A (escalation) and Part B (expansion) until disease progression, unacceptable toxicity or until the Investigator's decision or the patient's refusal. As soon as clinical safety and PK data become available, it is possible that an alternate dosing (e.g. twice daily [BID], intermittent) may be implemented.

For the purpose of scheduling and evaluations, a treatment cycle is defined as 28 days throughout the whole study. For Part A (escalation), the DLT period is defined as the 1st cycle of CB-103 dosing with a duration of 28 days. Eleven provisional dose levels are defined for the dose escalation (see Table 3 in Section 7.4.2), as well as one dose level with a 30% lower dose than the 1st dose level if the first dose level is not well tolerated.

Patients will be instructed to swallow the CB-103 capsules whole with a glass of water (approx. 200 mL) on an empty stomach at least 1 hour before breakfast. Capsules should not be chewed prior to swallowing. Capsules that are broken, cracked, or otherwise damaged should not be ingested.

- In case of the once-daily dosing schedule, when self-administering the drug at home, the patients will be instructed to self-administer CB-103 in the morning, on an empty stomach at least 1 hour before taking breakfast and at approximately the same time each day without treatment breaks, until they experience unacceptable toxicity, disease progression or withdrawal from the study.
- In case a BID dosing schedule is implemented, when self-administering the drug at home, the first capsule should be taken on an empty stomach at least 1 hour before breakfast. The second capsule should be taken within 8 to 12 hours of the first intake and at least 1 hour before or 2 hours after the evening meal.
- On the day of the study visits the patients should come to the site fasted and will be instructed to not take the dose of CB-103 at home since it will be administered at the site.

Regardless of the dosing schedule, the timing of CB-103 intake and the timing of meals should be recorded in the patient diary. The information on the actual dosing times will be transferred into the eCRF.

The Investigator should instruct the patient to record daily administration of the IMP in their patient diaries (paper format). If a patient misses a daily dose and notices this the next day after the scheduled day, they must be instructed not to "make it up" or double the next days' dose. If a patient vomits any time after taking a dose, they must be instructed not to "make it up", but to resume subsequent doses the next day as prescribed. The information on dosing and any missing doses should be noted by the patient in the diary.

All dosages prescribed and dispensed to the patient and all dose changes during the study must be recorded on the concerned eCRF forms (PK Sampling form and Study Drug

Adjustment form). Guidelines for dosage modification and treatment interruption or discontinuation are provided in the following section.

7.4.1 Justification of Starting Dose in Dose Level 1

Phase I, Part A – dose escalation

The starting, FIH dose for CB-103 at dose level 1 of the dose escalation, will be 15 mg (fixed dose) and will be administered on a continuous daily schedule. The starting dose is selected based on the results from the non-GLP and GLP-compliant safety pharmacology and toxicology studies in rats and dogs, as well as, the standard criteria for an anticancer drug were applied. The key toxicokinetic parameters from the 28-day GLP studies in rats and dogs used to derive the safety margins are given in Section 2.5.4.

The starting dose of 15 mg is expected to achieve an exposure (AUC_{0-24}) in humans of approximately 600 µg*h/mL (see Section 2.5.3, assuming, almost complete bioavailability in humans). This is comparable to $1/10^{th}$ of the exposure at the highest non-severely toxic dose (HNSTD) in rats (AUC_{0-24} in males at 30 mg/kg/day on day 28: 5980 µg*h/mL). Rats are more sensitive to CB-103 than dogs and the expected exposure in humans at the starting dose is below $1/10^{th}$ of the exposure at the HNSTD in dogs (AUC_{0-24} at 8.6 mg/kg/day, day 28: 8970 µg*h/mL in males and 13100 µg*h/mL in females). The signs of toxicity at the HNSTD in the 28 day GLP toxicology studies are mild and reversible and a safety factor of 10 is considered reasonably safe. The expected average plasma concentration after 15 mg repeated administration is approximately 25 ng/mL and therapeutic plasma levels (IC_{50} 1 µM = 242 ng/mL) can therefore be achieved in a limited number of dose escalation steps.

The predicted plasma levels and AUC_{0-24} values in humans assumes almost complete bioavailability. If CB-103 is not completely bioavailable in humans, the concentration will be lower and the safety margins even larger. For more details on the PK of CB-103 and selection of the starting doses please refer to the Investigator's Brochure.

7.4.2 Dose Escalation and Maximum Exposure

The design of this FIH study – with the inclusion of the BLRM – allows flexible dose escalation based on observation of DLTs, review of the entire safety data and pharmacokinetics in patients, and it aims to achieve CB-103 plasma concentrations in the range of the IC_{50} (1 µM = 242 ng/mL) as quickly as possible to increase the chances of benefit for the patients.

The provisional dose escalation levels are given in the table below.

Table 3 Provisional dose escalation levels

Dose level	Proposed dose (mg) [b]	Increment from previous dose (%)
-1[a]	10 mg	(30% decrease)
1	15 mg	**Starting dose[c]**
2	30 mg	100 %
3	60 mg	100 %
4	120 mg	100 %
5	180 mg	50 %
6	240 mg	33 %
7	320 mg	25 %
8	400 mg[d]	25 %

[a] Dose level -1 represents a dose that may be evaluated if dose level 1 is poorly tolerated. No dose de-escalation below this level is planned for this study. If dose-level -1 is poorly tolerated the study may be terminated.

[b] It is possible for some dose levels to be skipped or additional dose levels to be added during the course of the study.

[c] If the first PK assessments in humans suggest a major deviation from the expected AUC at the starting dose, the dose of CB-103 in the next dose level might be adapted accordingly.

[d] CB-103 doses higher than 400 mg may be allowed depending on the observed safety, PK and PD, and based on the recommendation of the two-parameter BLRM.

Initially, a daily dosing schedule will be used since the expected half-life in humans is sufficiently long to ensure coverage with CB-103 for 24 hours. As soon as clinical safety and PK/PD data become available it may be preferable to change the administration of CB-103 (e.g. BID or intermittent schedule). The change of the dosing schedule will be discussed by the CRC and decided by the Sponsor, with the new dose and dosing schedule applied to the next patient cohort. The decision to change the dose and/or dose schedule will be based on the totality of safety, PK, biomarker, preliminary efficacy and other data available to be reviewed and discussed by the CRC and Sponsor. Evaluation of safety, PK, preliminary efficacy, PD and biomarker data at the new dose schedule selected (BID or intermittent dosing) will be performed.

7.4.3 Criteria for Dose Escalation and Determination of the Maximum Tolerated Dose

Phase I, Part A – Escalation

Definition of MTD and RP2D

For any given schedule, the MTD is the highest dose of CB-103 if the following criteria are fulfilled: the posterior probability of the true DLT rate in the target interval [0.16 – 0.33] of the MTD is above 0.50 and 6 patients have been treated at the MTD/RP2D confirmatory cohort of the treated patients in the first 28 days of CB-103 treatment under that schedule. If the MTD cannot be reached in the dose escalation part of the study and the therapeutic dose range of CB-103 with the IC_{50} being reached, the RP2D will be determined at a dose below or equal to the MTD, based on the PD, PK, safety and potential efficacy data, upon review of all study data by the CRC and Sponsor. Adverse events and laboratory abnormalities considered to be DLTs are defined in Section 7.4.4 on DLT Assessments.

Estimation of MTD / RP2D

A two-parameter BLRM employing the EWOC principle will be used during the escalation phase for selection of doses to investigate and for estimation of the MTD. The general plan is that cohorts of patients will receive escalating doses of CB-103 until the MTD is reached. Each cohort will consist of newly enrolled patients.

Estimation of the MTD during the escalation phase of the study will be based upon the estimation of the probability of DLT in cycle 1 in patients in the DDS. If MTD cannot be reached in the dose escalation part, the RP2D will be determined based on the review of DLTs, adverse events/serious adverse events, laboratory, PK and PD data and selected as the dose resulting in the best therapeutic window for CB-103.

At all decision time points, the adaptive BLRM permits alterations in the dose increments based on the observed toxicities. It will be possible for some dose levels to be skipped or additional, intermediate dose levels or dosing schedules to be added during the course of the study.

Dose escalation will in general not exceed a 100% increase from the current dose being studied with the exemption of the dose escalation following the starting dose of 15 mg CB-103 where the next dose of CB-103 in the next dose level might be adapted if the exposure of CB-103 (AUC_{0-24}) is much lower than the expected value of approximately 600 µg*h/mL which was determined to be safe from the non-clinical GLP safety and toxicology studies in rats and dogs. If clinically relevant toxicity CTCAE ≥ grade 2 is observed and suspected to be related to CB-103 in > 1 patient within the current cohort, the escalation to the next cohort will be restricted to ≤ 50% of the current dose. Cohorts may be expanded at any dose level below the highest dose deemed unacceptable in order to better understand safety, tolerability, PK or PD.

Dose decisions during escalation are however not limited to the provisional dose levels provided in Table 3. Based on the recommendation of the BLRM regarding the highest

dose that may not be exceeded at any decision point during escalation and the maximum increase in dose allowed by the protocol, intermediate doses may be administered to subsequent new cohorts of patients. This includes doses lower than the starting dose or an intermediate dose between the current and next (lower or higher) provisional dose and different schedules. To further characterise the safety (e.g. specific suspected treatment-related adverse events) or PK/PD of CB-103 a dose that is considered acceptably safe, i.e., shown to be lower than any potential MTD, may be expanded.

Dose escalation may be terminated at any time based on emerging safety concerns without establishing the MTD.

The DLT period starts from the administration of the first oral dose until 28 days after the first oral dosing (1st cycle of CB-103). Intermediate dose levels of CB-103 may be explored, e.g. in case of MTD.

During the MTD/RP2D confirmatory cohort, if in specific subgroups (e.g., by indication or ethnicity) a higher rate of toxicities occurs or the PK profile of CB-103 is different, dose adjustments in such subgroups may be decided.

Phase IIA, Part B - Expansion

The enrolment into the Part B expansion cohorts for the selected cancer indications will begin after the MTD/RP2D is determined in Part A and reviewed by the CRC. CB-103 will be administered orally at the MTD/RP2D with the dosing schedule being determined in Part A (QD, BID or intermittent).

7.4.4 Dose-Limiting Toxicity (DLT)

DLT is defined as an adverse event or abnormal laboratory value assessed as unrelated to disease progression, inter-current illness, or concomitant medications, that occurs ≤ 28 days following the first dose of CB-103 (Cycle 1) and that meets any of the following criteria shown in the table below. Clinically relevant toxicities will be evaluated according to the National Cancer Institute (NCI)/National Institutes of Health (NIH) CTCAE version 4.03.

For the purpose of dose-escalation decisions, only DLTs occurring during the first cycle of treatment will be necessarily considered in the binary logistic regression model.

Refer to the study synopsis “Dose limiting Toxicity” section for the DLTs criteria.

7.4.5 Dose Modifications, Dose Delays and Treatment Discontinuation

Every effort should be made to administer CB-103 at the planned dose and schedule. In the event of treatment-related toxicities and DLT with CB-103, dose or schedule adjustments are required and have to be undertaken by the Investigator in the best interest of the patient to continue therapy. In the event of multiple toxicities, the dose modification should be based on the worst toxicity observed (according to the NCI CTCAE, v4.03). Any adjustment to the CB-103 dose should be documented in the eCRF.

Dose adjustments and interruptions criteria are described in the following sections. Depending on the type, severity and timing of the events, the Investigator will determine and decide on dose reductions and resumption of treatment. The following rules have to be followed:

- After Cycle 1 / Day 1, a continuous treatment interruption of more than 14 days will result in discontinuation of the patient from the study. Interruption of treatment not related to CB-103 may not require discontinuation; in such a case treatment continuation must be discussed with the Sponsor.
- Patients with a continuous treatment delay for more than 7 days during cycle 1 in Part A of the study (DLT period) that is not due to a drug-related AE, will be considered non-evaluable for DLT and will need to be replaced accordingly.
- Doses of CB-103 held or missed will not be made up (i.e., cycles will not be prolonged beyond the 28th calendar day in order to make up any missed doses).
- If doses of CB-103 are missed or forgotten to be taken for more than three sequential dosing events and if this happens more than once, this will result in discontinuation of the patient from the study. Dose delays as outlined above to recover from adverse events are allowed.
- If a treatment interruption continues beyond Day 28 of the current cycle, then the day when treatment is restarted will be counted as Day 1 of the next cycle.
- During cycle 1 in Part A (DLT period), any dose adjustments must be discussed with and approved by the Sponsor.
- One dose reduction is allowed per patient. In case the patient shows clinical benefit a 2nd dose reduction might be allowed, but this needs to be agreed upon on a case-by-case basis with the Sponsor. Section 7.4.6.1 describes the CB-103 dose modifications for the haematologic and non-haematologic toxicities not clearly attributed to disease.

If a patient concurrently experiences both haematological and non-haematological toxicities, then dose modifications for CB-103 should follow the most conservative approach, as outlined in Section 7.4.6.1.1, depending on the specific hematologic and non-hematologic toxicities.

Patients who discontinue from the study for a treatment-related adverse event or an abnormal laboratory value, must be followed up until fully recovered, according to the judgement of the Investigator.

Intra-patient dose escalation

Intra-patient dose escalations for CB-103 must be approved by the Sponsor and will be only allowed on a case-by-case basis, upon evaluation and discussion between the Investigator and the Sponsor. The following criteria have to be fulfilled for a patient under consideration:

- Intra-patient dose escalation can occur only when the next higher dose has been cleared by the CRC. Additional safety data collected will not be included in DLT assessment and discussions for dose escalation.
- Intra-patient dose escalation will be implemented on the first day of the cycle.

7.4.6 Follow-up for Dose-Limiting Toxicities

Patients whose treatment is interrupted or permanently discontinued due to an adverse event or clinically significant laboratory value, must be followed at least once a week for 4 weeks, and subsequently at 4-week intervals, until resolution or stabilisation of the event, whichever comes first.

7.4.6.1 Follow-up Evaluations and Dosing Modifications for Toxicities

The follow-up evaluations for toxicities apply during or beyond cycle 1 in Part A, and throughout Part B of the study.

The following sections outline the specific dose modifications for CB-103 for haematologic and non-haematologic toxicities and should be followed by the Investigator accordingly.

7.4.6.1.1 Haematologic Toxicities for Solid Tumour Patients

If $\geq$ CTCAE grade 3 neutropenia or $\geq$ CTCAE grade 3 thrombocytopenia have been demonstrated, testing for these parameters must be repeated at least twice a week until resolution to $\leq$ CTCAE grade 1 neutropenia or $\leq$ CTCAE grade 1 thrombocytopenia, to allow for re-treatment and then at least weekly until either resolution or until stabilisation.

Table 4 Dose modifications for haematologic toxicities

Dose Modifications for CB-103	
Worst Toxicity CTCAE Grade[1] unless otherwise specified (Value)	**At any time during a cycle of CB-103 (including intended day of dosing)**
Haematologic toxicities:	
Neutropenia (ANC)	
Grade 1 (ANC < LLN - 1.5 x 10^9/L) & Grade 2 (ANC < 1.5 - 1.0 x 10^9/L)	Maintain dose level
Grade 3 (ANC < 1.0 - 0.5 x 10^9/L)	Omit dose administration until resolved to ≤ grade 1, • If resolved in ≤ 7 days, then maintain dose level • If resolved in > 7 days, then ↓ 1 dose level
Grade 4 (ANC < 0.5 x 10^9/L)	Omit dose administration until resolved to ≤ grade 1, then ↓ 1 dose level
Grade 3 Febrile neutropenia (ANC < 1.0 x 10^9/L with a single temperature of >38.3°C or a sustained temperature of ≥38°C for more than one hour)	Omit dose administration until resolved, then ↓ 1 dose level
Thrombocytopenia	
Grade 1 (PLT < LLN - 75 x 10^9/L)	Maintain dose level
Grade 2 (PLT < 75 - 50 x 10^9/L) & Grade 3 (PLT < 50-25 x 10^9/L)	Omit administration dose until resolved to ≤ grade 1, then: • If resolved in ≤ 7 days, then maintain dose level • If resolved in > 7 days, then ↓ 1 dose level
Grade 4 (PLT < 25 x 10^9/L)	Omit administration dose until resolved, then ↓ 1 dose level

[1] Common Terminology Criteria for Adverse Events (CTCAE Version 4.03)

7.4.6.1.2 Renal Toxicities

If serum creatinine ≥ 2 x ULN has been demonstrated, this parameter must be repeated at least twice a week until resolution to ≤ CTCAE grade 1, to allow for initiation of re-treatment and then at least weekly until either resolution or until stabilisation.

If proteinuria or haematuria ≥ CTCAE grade 2 or serum creatinine ≥ 2.0 x ULN has been demonstrated, a 24-hour urine collection must be obtained for total protein and total creatinine must be repeated at least weekly until either resolution to baseline value to allow for initiation of re-treatment, or until stabilisation. Whenever a measured CrCl is obtained, a serum creatinine value should be obtained within ≤ 72 hours of the urine collection.

Table 5 Dose modifications for renal toxicities

Dose Modifications for CB-103	
Worst Toxicity **CTCAE Grade[1] unless otherwise specified (Value)**	**At any time during a cycle of CB-103 (including intended day of dosing)**
Renal toxicities:	
Serum creatinine	
(< 2 x ULN)	Maintain dose level
(2 - 3 x ULN)	Omit dose administration until resolved to ≤ grade 1, • If resolved in ≤ 7 days, then maintain dose level • If resolved in > 7 days, then ↓ 1 dose level
Grade 3 (> 3.0 - 6.0 x ULN) & Grade 4 (> 6.0 x ULN)	Omit dose administration and discontinue patient from study treatment

[1] Common Terminology Criteria for Adverse Events (CTCAE Version 4.03)

7.4.6.1.3 Hepatic Toxicities

If bilirubin ≥ CTCAE grade 2 or AST/ALT ≥ CTCAE grade 3 has been demonstrated, these parameters must be repeated at least twice a week until resolution to ≤ CTCAE grade 1 (or baseline if liver metastases were present at baseline), to allow for initiation of re-treatment and then at least weekly until either resolution or until stabilisation.

Patients with total bilirubin > ULN (any duration) should have fractionation of bilirubin into total/direct or indirect/direct components and any additional work-up as clinically indicated by these results. Follow-up of hyperbilirubinaemia should proceed as per the guidelines above, irrespective of the results of fractionation.

Table 6 Dose modifications for hepatic toxicities

Dose Modifications for CB-103	
Worst Toxicity **CTCAE Grade[1] unless otherwise specified (Value)**	**At any time during a cycle of CB-103 (including intended day of dosing)**
Hepatic toxicities:	
Bilirubin	
Grade 1 (< 1.5 x ULN)	Maintain dose level
Grade 2 (1.5 - 3 x ULN)	Omit dose administration until resolved to ≤ grade 1, • If resolved in ≤ 7 days, then maintain dose level • If resolved in > 7 days, then ↓ 1 dose level
Grade 3 (> 3.0 - 10.0 x ULN)	Omit dose administration until resolved to ≤ grade 1, then ↓ 1 dose level
Grade 4 (> 10.0 x ULN)	Omit dose administration and discontinue patient from study treatment
AST or ALT	
Grade 1 (> ULN – 3.0 x ULN) & Grade 2 (>3.0 - 5.0 x ULN) without increase in total bilirubin >2 x ULN	Maintain dose level
Grade 3 (> 5.0 - 20.0 x ULN) without increase in total bilirubin >2 x ULN	Omit dose administration until resolved to ≤ grade 1 (or ≤ grade 2 in case of liver metastasis), then • If resolved in ≤ 7 days, then maintain dose level • If resolved in > 7 days, then ↓ 1 dose level
Grade 4 (> 20.0 x ULN) without increase in total bilirubin >2 x ULN	Omit dose administration until resolved to ≤ grade 1, then ↓ 1 dose level

[1] Common Terminology Criteria for Adverse Events (CTCAE Version 4.03)

7.4.6.1.4 Ocular/Vision-related Toxicities

For toxicities related to visual symptoms related to CB-103, refer to the following table.

Table 7 Dose modifications for ocular/vision-related toxicities

Dose Modifications for CB-103	
Worst Toxicity CTCAE Grade[1] unless otherwise specified (Value)	**At any time during a cycle of CB-103 (including intended day of dosing)**
Visual symptoms	
Grade 1	Maintain dose level
Grade 2	Omit dose administration until resolved to ≤ grade 1 (or baseline), then continue treatment with CB-103 at the current dose level If visual symptoms ≥ Grade 2 recur upon re-exposure to CB-103 and if is intolerable by patient, discontinue patient from study
Grade 3	Omit dose administration and discontinue patient from study
Grade 4	Omit dose administration and discontinue patient from study

[1] Common Terminology Criteria for Adverse Events (CTCAE Version 4.03)

7.4.6.1.5 Cardiac Toxicities

As in non-clinical studies with CB-103, QT prolongation was observed at higher doses and ECG changes in patients may be observed, therefore, intensive cardiac monitoring is implemented into this study with central management and review of multiple ECGs and Holter ECGs at selected timepoints. Furthermore ECHO/MUGA scans and cardiac markers will be assessed at selected time points. For toxicities related to QTc prolongation, refer to Table 8 below. For all other cardiac toxicities, please follow the non-laboratory recommendations seen in Section 7.4.6.1.7.

Table 8 Dose modifications for cardiac toxicities

Dose Modifications for CB-103	
Worst Toxicity CTCAE Grade[1] unless otherwise specified (Value)	**At any time during a cycle of CB-103 (including intended day of dosing)**
Cardiac - Prolonged QTcF interval[2]	
During Cycle 1:	
Absolute QTcF< 480 ms	Maintain dose level and ECG monitoring as per visit schedule.

Dose Modifications for CB-103	
Worst Toxicity **CTCAE Grade[1] unless otherwise specified (Value)**	**At any time during a cycle of CB-103 (including intended day of dosing)**
Cardiac - Prolonged QTcF interval[2]	
QTcF ≥ 480 ms and < 500 ms	Maintain dose level. ECG monitoring assessments should be increased as indicated (e.g. hourly until no QTcF ≥ 480 ms).
During any Cycle:	
Grade 3 or QTcF ≥ 500 ms as identified by the Investigator on the ECG.	Omit dose administration. Monitor patient with frequent ECGs as indicated (e.g. hourly) until the QTcF has returned to ≤ 480 ms. Further monitoring as clinically indicated. Exclude other causes of QTc prolongation such has hypokalaemia, hypo-magnesaemia and blood oxygenation status. Once QTcF prolongation has resolved, and if the QTcF prolongation was confirmed by central reading, patients may be re-treated at one lower dose level at the Investigator's discretion. ECG monitoring must continue throughout the treatment period as follows: • ECG monitoring assessments should be performed for 2 additional cycles at higher frequency as clinically indicated • If the ECGs obtained in the first additional cycle after dose reduction are without any QTcF prolongation, then ECG monitoring in subsequent cycles will be continued as per the visit schedule. • If the patient had an absolute QTcF ≥ 480 ms and < 500 ms, then ECG monitoring at a higher frequency will be continued for all subsequent cycles. • Patients who experience absolute QTcF ≥ 500 ms after one dose reduction will be discontinued from study. **Note:** • If QTcF ≥ 500 ms result is observed in a patient during the study treatment, this event will be considered as a DLT. If Torsades de Pointes are observed in a patient, the patient will be discontinued from the study. • Whenever QTcF ≥ 500 ms result is observed, a plasma sample for determination of CB-103 concentration should be obtained and the time of sample collection noted.

[1] Common Terminology Criteria for Adverse Events (CTCAE Version 4.03)
[2] Exclude other causes of QTcF prolongation such has hypokalaemia, hypomagnesaemia and blood oxygenation status. Patients who develop hypokalaemia or hypomagnesaemia during the study should receive electrolyte replacement as soon as possible and should not receive further CB-103 dosing until the respective electrolytes are documented to be within normal limits.

7.4.6.1.6 Gastro-Intestinal Toxicities (Diarrhoea, Nausea)

In non-clinical studies in different species (dog, rat, mouse), CB-103 administered at different doses and administration schedules did not show any gastro-intestinal toxicities, e.g. diarrhoea, weight loss. However, as other NOTCH inhibitors (GSIs, mABs) have shown diarrhoea as their major DLT, there might be a risk for CB-103 to also develop gastro-intestinal toxicities. In the event that diarrhoea is observed in clinical trial patients, the following algorithm for CB-103 dose modifications should be followed. Furthermore, Sections 7.4.7.2 to 7.4.7.4 provide a management plan for the occurrence of diarrhoea with a description of measures and treatment suggestions.

Table 9 Dose modifications for gastro-intestinal toxicities

Dose Modifications for CB-103	
Worst Toxicity **CTCAE Grade[1] unless otherwise specified (Value)**	**At any time during a cycle of CB-103 (including intended day of dosing)**
Gastro-intestinal toxicities	
Grade 1	Maintain dose level
Grade 2 (see Sections 7.4.7.2 to 7.4.7.4 for treatment algorithm)	Omit dose administration until recovery to Grade ≤ 1 or baseline then continue at current dose level if grade 2 toxicity persisted for ≤ than 7 days. If grade 2 toxicity persisted for more than 7 days decrease dose by 1 dose level after resolution to Grade 0 or baseline
Grade 3 (see Section 7.4.7.2 to 7.4.7.4 for treatment algorithm)	Omit dose administration until recovery to Grade ≤ 1 or baseline then decrease the next scheduled dose by 1 dose level
Grade 4 (see Section 7.4.7.2 to 7.4.7.4 for treatment algorithm)	Omit dose administration until recovery to Grade ≤ 1 or baseline then decrease the next scheduled dose by 1 dose level In the event Grade 4 toxicity lasts > 24 hours despite maximal medical attention discontinue treatment. If grade 4 toxicity lasts < 24 hours reduce dose by 1 dose level at next cycle If toxicity recurs discontinue treatment.
All grades	At the first sign of abdominal cramping, loose stools, or onset of diarrhoea, the patient should be treated according to Sections 7.4.7.2 to 7.4.7.4 according to the recommended treatment algorithm. Omit dose administration of CB-103 for ≥ CTCAE grade 2 diarrhoea only if diarrhoea could not be controlled despite the use of optimal anti-diarrhoea treatments.

[1] Common Terminology Criteria for Adverse Events (CTCAE Version 4.03)

7.4.6.1.7 Non-Laboratory Toxicities

Patients who experience non-laboratory toxicities related to CB-103 must be evaluated at least once a week following demonstration of the toxicity until resolution of the toxicity to allow for re-treatment, stabilisation of the toxicity, or study treatment completion.

Table 10 Dose modifications for non-laboratory toxicities

Dose Modifications for CB-103 post cycle 1	
Worst Toxicity CTCAE Grade[1] unless otherwise specified (Value)	**At any time during a cycle of CB-103 (including intended day of dosing)**
Non-laboratory adverse events	
Grade 1 or 2	Maintain dose level
Grade 3	Omit dose administration until resolved to ≤ grade 1, then ↓ 1 dose level
Grade 4	Omit dose administration and discontinue patient from study

[1] Common Terminology Criteria for Adverse Events (CTCAE Version 4.03)

7.4.7 Diarrhoea and Nausea Management Plan

Although no signs of gastro-intestinal toxicities (e.g., diarrhoea) were observed in the non-clinical safety and toxicology studies in different species (dog, rat, mouse) treated with CB-103 at different doses and administration schedules, the occurrence of diarrhoea cannot be excluded.

There is **no *a priori* prophylaxis** for nausea, vomiting, and/or diarrhoea. Any of these symptoms constitute DLT only if they reach Grade ≥3 severity in Cycle 1 despite the following adequate supportive care measures:

- Nausea and/or emesis:
  - Metoclopramide +/- meclozine
  - Dexamethasone 2 mg p.o. in case of Grade 3 nausea/emesis
- Diarrhoea:
  - Loperamide 4 mg p.o. as needed

CAUTION:

- Serotonin-antagonists for the 5-HT_3-receptor (e.g., ondansetron, granisetron) must NOT be used.
- Metoclopramide and loperamide are drugs associated with Torsades de Pointes (TdP) BUT only under certain conditions OR by creating conditions that facilitate or induce TdP. Therefore, (i) the patient must be advised accordingly, (ii) the usage of other concomitant QT-prolonging drugs must be carefully considered, (iii) the

use of metoclopramide or loperamide should be closely monitored and (iv) the patient's electrolyte status followed and promptly corrected.

- ECGs that may be taken during the concomitant administration of metoclopramide or loperamide must be repeated if they remain abnormal after a wash-out period from these agents.
- The intake of these agents should be kept as separated as possible from CB-103 intake (at least up to 4 hours before and from 2 hours after CB-103 intake).

Table 11 NCI CTCAE version 4.03 grading of diarrhoea, nausea and vomiting for patients without colostomy

Toxicity	0	1	2	3	4
Diarrhoea[1]	None	Increase of < 4 stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of 4 - 6 stools per day over baseline; moderate increase in ostomy output compared to baseline	Increase of ≥7 stools per day over baseline; incontinence; hospitalisation indicated; severe increase in ostomy output compared to baseline; limiting self-care ADL	Life-threatening consequences; urgent intervention indicated
Nausea	None	Loss of appetite without alteration in eating habits	Oral intake decreased without significant weight loss, dehydration or malnutrition; inadequate oral caloric or fluid intake; tube feeding, TPN, or hospitalization	Inadequate oral caloric or fluid intake; tube feeding, TPN, or hospitalization indicated	-
Vomiting	None	1 - 2 episodes (separated by 5 minutes) in 24 hrs	3 - 5 episodes (separated by 5 minutes) in 24 hrs	≥ 6 episodes (separated by 5 minutes) in 24 hrs; tube feeding, TPN or hospitalization indicated	Life-threatening consequences; urgent intervention indicated

[1] Definition: A disorder characterised by frequent and watery bowel movements.
Web address: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

7.4.7.1 First Report of Diarrhoea

- Obtain history of onset and duration of diarrhoea
- Description of number of stools and stool composition (e.g. watery, blood, mucus in stool)
- Assess patient for fever, abdominal pain, cramps, distension, bloating, nausea, vomiting, dizziness, weakness (i.e., rule out risk for sepsis, bowel obstruction, dehydration)
- Medication profile (i.e., to identify any diarrhoeagenic agents)
- Dietary profile (i.e., to identify diarrhoea-enhancing foods)

Proactively look for occurrence of diarrhoea after start of CB-103 treatment. Call patients at home, if necessary, to detect diarrhoea early during the first 8 weeks. If no problems occur, instruct the patient to call when a problem does arise.

7.4.7.2 Management of Diarrhoea

General measures:

- Stop all lactose-containing products, alcohol
- Stop laxatives, bulk fibre (e.g., Metamucil®, Procter & Gamble), and stool softeners (docusate sodium; Colace, Roberts)
- Drink 8 to 10 large glasses of clear liquids per day (e.g., water, Pedialyte® (Ross), Gatorade (Quaker), broth)
- Eat frequent small meals (e.g., bananas, rice, apple sauce, Ensure®, toast)
- Stop high-osmolar food supplements such as Ensure Plus and Jevity Plus (with fibre)

It is recommended that patients be provided loperamide tablets. It is mandatory that patients are instructed on the use of loperamide at cycle 1 in order to manage signs or symptoms of diarrhoea at home. Patients should be instructed to start oral loperamide (initial administration of 4 mg, then 2 mg every 4 hours (maximum of 16 mg/day) at the first sign of loose stool or symptoms of abdominal pain. These instructions should be provided at each cycle and the investigational site should ensure that the patient understood the instruction. At the beginning of each cycle, each patient should be specifically questioned regarding any experience of diarrhoea or diarrhoea related symptoms. If symptoms were experienced, then the investigational site should question the patient regarding the actions taken for these symptoms.

7.4.7.3 Treatment of Diarrhoea Grade 1 or 2

Diarrhoea grade 1 or 2 will be treated with standard loperamide (initially at first administration 4 mg, then 2 mg every 4 hours [maximum of 16 mg/day] or after each unformed stool).

12-24 hours later:

Diarrhoea resolved

- Continue instructions for dietary modification
- Gradually add solid foods to diet
- Discontinue loperamide after 12-hours diarrhoea-free interval

Diarrhoea unresolved

Persisting diarrhoea grade 1 or 2 will be treated with addition of opium tincture, dihydrocodeine tartrate tablets/injections and start early on with corticosteroids which is the recommended treatment for the development of goblet cell metaplasia seen with other NOTCH inhibitors. Treatment should be accompanied by monitoring the patient's condition (to rule out dehydration, sepsis, ileus), medical check and selected workup if patient does not need hospitalisation (see Section 7.4.7.5 for diarrhoea work-up). Observe patient for response to antidiarrheal treatment and may also consider treatment with high dose corticosteroids.

Persisting diarrhoea grade 3 or 4 may be treated with hospitalisation, high dose loperamide (initially 4 mg, then 2 mg every 2 hours), addition of opium tincture or dihydrocodeine tartrate tablets/injections and with high dose corticosteroids to potentially inhibit the development of the goblet cell metaplasia seen with other NOTCH inhibitors. Furthermore, start of i.v. fluids, parenteral nutrition and antibiotics as needed with monitoring of patients' condition (to rule out dehydration, sepsis, ileus), medical check and workup (perform appropriate additional testing) should be started immediately. Observe patient for response.

After 12-24 hours:

Diarrhoea resolved

- Continue instructions for dietary modification
- Gradually add solid foods to diet
- Discontinue loperamide and/or other treatment after 12-hours diarrhoea-free interval

Diarrhoea unresolved

- If diarrhoea still persisting (NCI CTC grades 1 and 2), after 2 x 24 hours with high dose loperamide, opiates and corticosteroids then admit to hospital and employ measures as for grade 3 and 4 until diarrhoea resolved.
- If diarrhoea still persisting and progressed to NCI grades 3 and 4, employ measures described below.

7.4.7.4 Treatment of Diarrhoea Grade 3 or 4

Severe diarrhoea grade 3 or 4 may be treated with hospitalisation, high dose loperamide (initially 4 mg, then 2 mg every 2 hours, addition of opium tincture or dihydrocodeine tartrate tablets/injections as well as early start of administration of corticosteroids as being the recommended treatment for goblet cell metaplasia observed in patients treated with other NOTCH inhibitors. Furthermore, start of i.v. fluids, parenteral nutrition and antibiotics as needed with monitoring of patients' condition (to rule out dehydration, sepsis, ileus), medical check and workup (see Section 7.4.7.5 for diarrhoea work-up). Observe patient for response.

After 12-24 hours:

- If diarrhoea persisting administer high dose corticosteroids and consider subcutaneous (s.c.) Sandostatin/octreotide (100-500 µg three times daily [TID])
- Continue i.v. fluids, parenteral nutrition and antibiotics as needed
- If diarrhoea grade 3 or 4 still persists patients should receive besides corticosteroids opium tincture or dihydrocodeine tartrate injections s.c. or intramuscular (i.m.)
- If diarrhoea grade 3 or 4 is still persisting s.c. Sandostatin/octreotide (500-1000 µg TID) should be administered.
- To control and/or resolve diarrhoea, next cycle of treatment should be delayed by 1 or 2 weeks. Treatment should be continued only when diarrhoea resolved.

7.4.7.5 Diarrhoea Workup

Perform appropriate tests (American Gastroenterological Association [AGA] Technical Review on the Evaluation and Management of Chronic Diarrhoea; Fine and Schiller, 1999).

Spot stool analysis

- Collect stool separating it from urine (special containers, analysis immediately, exceptionally freeze samples)
- Blood
- Faecal leukocytes (Wright's staining and microscopy) or
- *C. difficile* toxin

- Faecal cultures such as *Shigella* and pathogenic *E. coli* - enterotoxigenic, enterohaemorrhagic etc., possibly *Aeromonas*, *Pleisiomonas* (if suspected exposure to contaminated water)

Endoscopic examinations

Endoscopic examinations may be considered only if absolutely necessary. The bowel is likely to be fragile with evidence of colitis and thus great care and caution must be exercised in undertaking these invasive procedures.

- Gastroscopy to obtain jejunal fluid - re. bacterial overgrowth for cultures and biopsy of proximal jejunum to assess extent of inflammatory jejunitis
- Sigmoidoscopy - reassessment of colitis

7.4.8 Sample Size in Part A and Part B

The sample size of Part A of the study depends on the number of patients to be enrolled in each dose level during the dose escalation with at least 3 and up to 6 patients enrolled per dose cohort. Depending on the BLRM, additional patients may be enrolled in some dose cohorts.

The sample size of Part B will depend on the number of patients being enrolled in each expansion arm. For each expansion arm it is planned to have at least 10 patients enrolled and to continue enrolment in each arm to at least 20 patients based on an interim futility analysis. The table below shows the current calculation of sample size for Part A and Part B of the study.

Table 12 Sample size in Part A and Part B of this study

Escalation Part A	Dose Levels 1-11	MTD/RP2D confirmatory cohort	Expansion Part B	Total Study
N (patients)	55 pts*****	45 pts*	100-140 pts	200-240 pts**

***** Depending on the BLRM, additional patients may be enrolled in some dose cohorts. Based on the decision of the CRC approximately 45 patients in total may be enrolled in the MTD/RP2D confirmatory cohort to confirm safety before opening Part B.
****** Includes the eligible patients from the MTD/RP2D confirmatory cohort

7.5 CONCOMITANT THERAPY

7.5.1 Permitted Concomitant Therapy

Concomitant therapy includes any medication, e.g., prescription drugs, over-the-counter drugs (OTCs), approved dietary and herbal supplements, nutritional supplements and any non-medication interventions (e.g., individual psychotherapy, smoking cessation therapy, physical therapy and rehabilitative therapy) used by a patient within 14 days of the planned 1st dose administration of CB-103. All concomitant medications taken within 14 days prior to planned first dose administration, as well as all new and ongoing concomitant therapy(ies) must be reported to the Investigator and recorded on the eCRF along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

Any diagnostic procedure and all medication administered to manage adverse events during the study will be according to standard of care and at the discretion of the Investigator and must be recorded on the Adverse Event eCRF with the exception of prohibited medications included in Section 7.5.2 below.

Patients who use oral or injectable contraceptives, hormone-replacement therapy, or other maintenance therapy should continue their use, which should be recorded. Dosing should always be used in the dose-range according to the approved local prescribing information.

Stable doses of medications administered for chronic diseases (e.g. hypertension) are allowed. The use of low molecular weight heparin (as an anticoagulant) is permitted.

7.5.2 Prohibited Concomitant Therapy

Refer to the “LIST OF PROHIBITED MEDICATIONS" in the synopsis.

8. VISIT SCHEDULE AND STUDY ASSESSMENTS

8.1 DESCRIPTION OF STUDY ASSESSMENTS

All examinations listed below will be performed according to the Schedule of Assessments outlined in Appendix 1 and Appendix 2.

Phase I, Part A – Escalation:

- All patients from each dose cohort in Part A will stay overnight at the hospital for 1 night following their first CB-103 administration (C1D1) to allow for 24-hour PK sampling and ECG monitoring. During this time the patients will be closely monitored for safety. The overnight stays may not be required if reduced ECG and PK sampling is implemented.

  In case CB-103 is given BID, one more overnight hospital stays at Day 8 in cycle 1 may be necessary to allow late samples collection.

- Patients will then undergo daily visits for 2 days following the overnight monitoring on Day 1 at the hospital, and will get their CB-103 doses administered in the hospital. Patients will stay at the hospital for at least 3 hours following each administration to allow safety reporting.

- Weekly visits to monitor safety and perform ECG monitoring and PK sampling are planned during the rest of the treatment period for the 1st cycle of CB-103 (28 days).

- Every 2 weeks visits to monitor safety and perform PK sampling are planned from cycle 2 until the completion of cycle 6.

- EOT visit within 14 days after the last dose of CB-103 (within the 6 cycles period).

- Safety follow-up visit (End-of-Study) for each patient within 28 days after the last dose of CB-103.

- Survival follow-up (e.g. per telephone) for 1 year is planned every three months after the End-of-study visit or after the last treatment cycle (if outside of the 6 cycles period).

- Further visits might be considered, depending on the health status of the patient, as determined by the treating Investigator of the respective investigational site.

- More frequent laboratory safety tests (e.g., to closely monitor the liver function), are possible and can be performed outside the study site for those patients leaving far away, if necessary. The laboratory reference ranges from the local laboratories must be collected, and filed in the laboratory report together with the patients' medical records. Care should be taken that any outliers possibly produced by the local laboratory findings are investigated at the study site.

Note: for those patients who may have the option to continue treatment after cycle 6, the subsequent visits are planned every 4 weeks if no medical issue or complication occurred in the previous cycles.

Phase I, Part A - MTD/RP2D confirmatory cohort and Phase IIA, Part B – Expansion:

For patients with solid tumours who are not hospitalized:

- Patients will undergo daily visits for 3 days and will get their CB-103 doses administered in the hospital. Patients will stay for at least 3 hours following each administration of CB-103 to allow safety reporting with the exception of the first day where the patients should stay for up to 8 hours post-dose.

  In case CB-103 is given BID, one more overnight hospital stays at Day 8 in cycle 1 may be necessary to allow late samples collection.
- Weekly visits to monitor safety and perform ECG monitoring and PK sampling are planned during the rest of the treatment period for the 1st cycle of CB-103 (28 days).
- Every 2 weeks visits to monitor safety and perform PK sampling are planned from cycle 2 until the completion of cycle 6.
- After cycle 6, subsequent visits are planned every 4 weeks if no medical issue or complication occurred in the previous cycles.
- End-of-Treatment (EOT) visit within 14 days after the last dose of CB-103 (within the 12 cycles period).
- Safety follow-up visit (End-of-Study) for each patient within 28 days after the last dose of CB-103.
- Survival follow-up (e.g. per telephone) for 1 year is planned every three months after the End-of-Study or after the last treatment cycle (if outside of the 12 cycles period), and every six months thereafter for the 2nd year.
- Further visits might be considered, depending on the health status of the patient, as determined by the treating Investigator of the respective investigational site.
- More frequent laboratory safety tests (e.g., to closely monitor the liver function), are possible and can be performed outside the study site for those patients living far away, if necessary. The laboratory reference ranges from the local laboratories must be collected and filed in the laboratory report together with the patients' medical records. Care should be taken that any outliers possibly produced by the local laboratory findings are investigated at the study site.

For hospitalized patients with T-ALL/T-LBL:

- Patient with T-ALL/T-LBL will undergo the same visit and monitoring schedule as outpatients with solid tumours.

Note: for those patients who may have the option to continue treatment after cycle 12, the subsequent visits are planned every 8 weeks if no medical issue or complication occurred in the previous cycles.

8.1.1 Eligibility Screening

Patients are allowed to enter the study based on confirmation of the eligibility criteria (refer to inclusion and exclusion criteria in Section 6.1.1 and Section 6.1.2) at screening/baseline.

The procedures for eligibility check, patient identification number assignments and coordination among the investigational site involved will be provided in a separate document prior to study start.

8.1.2 Information to be Collected on Screening Failures

Screen failures are defined as patients who consent to participate in the clinical trial but are not subsequently treated in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure patients. Minimal information will be entered into the clinical database and includes demography, screen failure reasons, eligibility criteria, and any serious adverse event which occurred after ICF signature during the screening period.

8.1.3 Medical History and Demographic Data

Medical history includes clinically significant diseases, surgeries, reproductive status, smoking history, use of alcohol and drugs of abuse, all medications (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements).

Demographic data will include year of birth, sex and self-reported race/ethnicity (collecting this information is essential in order to be able to evaluate the results of this study, for example, in the case of PK outliers or important between-patient differences in terms of treatment effect).

Evaluation of the inclusion and exclusion criteria will be performed at the screening visit.

8.1.4 Disease History

The patients' disease history from the time of diagnosis (including surgeries, radiographic tumour progression, any biomarker information [e.g. tumour mutations like KRAS, BRAF and NRAS]) and details regarding anti-neoplastic treatments they have received in the past) will be collected at screening. The exact parameters to be collected will be outlined on the respective screening eCRF pages.

8.2 SAFETY ASSESSMENTS

Safety assessments will consist of monitoring by Investigators and recording all adverse events, serious adverse events, and the regular monitoring of laboratory evaluations, physical examination, vital signs, weight, performance status evaluation, ECGs (standard

triplicates and Holter ECG) and repeat cardiac assessments, cardiac markers, ECHO or MUGA scan (if clinically required). Detailed description of the safety monitoring based on adverse events, serious adverse events, cardiac and laboratory monitoring as well as the requirements for the reporting of safety findings for the study and a description of the process for regulatory reporting is provided in Section 9, Safety Monitoring.

8.2.1 Adverse Events

An adverse event for the purposes of this protocol is the appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s), or medical condition(s) occurring after signing the informed consent even if the event is not considered to be related to the study drug(s). Please refer to Section 7.1 to Section 7.4 for the protocol-specific definitions of study drug and study treatment.

Adverse events will be assessed according to CTCAE version 4.03. If CTCAE grading does not exist for an adverse event, the severity of mild, moderate, severe, life threatening and death, or grades 1 - 5, will be used. Adverse event monitoring should be continued for at least 4 weeks following the last dose of study treatment.

Adverse events (but not serious adverse events) occurring before starting study treatment but after signing the ICF are recorded on the Medical History/Current Medical Conditions eCRF. Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant or require therapy (e.g., any haematologic abnormality that requires transfusion or cytokine treatment); and should be recorded on the Adverse Events eCRF under the signs, symptoms or diagnosis associated with them. In addition, isolated abnormal laboratory values that are considered clinically significant (e.g., cause study discontinuation or constitutes in and of itself a Serious Adverse Event) should be recorded on the Adverse Events eCRF. Serious adverse events occurring after signing the ICF are recorded on the Adverse Event eCRF.

The occurrence of adverse events should be sought by non-directive questioning of the patient at each visit during the study. Adverse events also may be detected when they are volunteered by the patient during or between visits or through physical examination, laboratory test, or other assessments. As far as possible, each adverse event should be evaluated to determine:

1. The severity grade (CTCAE grade 1-5)
2. Its relationship to the study drug (suspected/not suspected)
3. Its duration (start and end dates or if continuing at final exam)
4. Action taken (no action taken; study drug dosage adjusted/temporarily interrupted; study drug permanently discontinued due to this adverse event; concomitant medication taken; non-drug therapy given; hospitalisation/prolonged hospitalisation)

5. Whether it is serious (For a description of serious adverse events, please refer to Section 9.1.2)

Adverse events will be graded (wherever possible) using the **NCI CTCAE version 4.03**. It can be viewed electronically or downloaded and printed by visiting the following website: https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

For consistency in adverse event grading, **NCI CTCAE, version 4.03** must be used throughout the trial regardless of any subsequent versions of the CTC that may become available.

All adverse events should be treated appropriately. Such treatment may include changes in study drug treatment including possible interruption or discontinuation, starting or stopping concomitant treatments, changes in the frequency or nature of assessments, hospitalisation, or any other medically required intervention. Once an adverse event is detected, it should be followed until its resolution, an assessment should be made at each visit (or more frequently, if necessary) of any changes in its severity, its suspected relationship to the study drug(s), any of the interventions required to treat it, and its outcome.

Information from non-clinical studies with the investigational drug CB-103 about common side effects seen in the species treated with CB-103 on various doses and dosing schedules (e.g. dog, rat, mouse) has been taken into account to evaluate the potential adverse events which can be expected in patients in this FIH study and a list of these potential adverse events can be found in the Investigator's Brochure or will be communicated between updates to the Investigator's Brochure in the form of Investigator Notifications. This information will be included in the patient informed consent and should be discussed with the patient during the study as needed.

Adverse event monitoring should be continued in the safety follow-up period for ≥ 28 days following the last dose of study drug. In this period of time following last dose of CB-103 all cancer medications/therapies given to the patient as subsequent therapy must be recorded in the eCRF Concomitant Medications page.

8.2.2 Physical Examination, Weight, Height and Vital Signs

All examinations (physical examination, weight, height and vital signs) will be performed according to the standards at each institution. Physical examinations will be conducted as depicted in Appendix 1 and Appendix 2.

In most cases, for all patient visits during the study, the examinations can be performed within 24 hours prior to the visit day. Information about the physical examination, weight, height, vital signs and any additional specific examinations performed at the investigational site or by a clinical expert must be present in the source documentation at the investigational site. Significant findings present prior to the start of study drug must be included in the relevant Medical History/ eCRF. Significant findings made after the start of

study drug which meet the definition of an adverse event must be recorded on the Adverse Event eCRF.

8.2.2.1 Weight and Height

Body weight and height will be measured as outlined below with the time-points specified in the Schedule of Assessments (see Appendix 1 and Appendix 2).

Weight will be measured at baseline, on Day 1 of each treatment cycle (with exemption of Cycle 1 Day 1 where baseline assessment is sufficient), at any unscheduled visit, at EOT and Safety Follow-up visits. Body weight will be measured to the nearest kilogram.

Height need only be recorded once, at screening visit.

8.2.2.2 Physical Examinations

Physical examinations will be performed at the indicated patient visit (see Appendix 1 and Appendix 2), even if administration of study medication is being withheld. More frequent examinations may be performed at the Investigator's discretion, if medically indicated. If these baseline examinations are performed within 72 hours prior to the first administration of CB-103, they need not be repeated on Day 1 of Cycle 1, except for patients with T-ALL/T-LBL who need to repeat the physical examination at C1D1.

A complete physical examination should be performed according to the standards at each institution and must include an evaluation of the head, eyes (including pupil size and reflex status), ears, nose, throat, neck and lymph nodes, and the cardiovascular, dermatological, musculoskeletal, respiratory, GI, genitourinary, and neurological systems.

Any abnormality identified at baseline should be recorded on the General Medical History eCRF.

Eye examinations will be performed by an ophthalmologist during screening, at EOT, and in case of abnormalities at the safety follow-up visit.

An extended eye examination including invasive ophthalmologic assessments should be performed by an ophthalmologist during the treatment period, in case significant abnormalities are experienced by the patient or seen by the study doctor at the regular eye evaluation as part of the physical examinations.

The following standard ophthalmological assessments performed by an ophthalmologist are recommended:

1. Visual acuity test
2. Intraocular pressure test
3. Slit-lamp test
4. Dilated fundus test
5. Colour-vision (Ishihara-plate) test

Additional assessments or tests may be conducted by an ophthalmologist as clinically indicated. Invasive ophthalmologic assessments such as electroretinography (ERG) may

be conducted if feasible, at the discretion of the site and may be conducted at the time when visual symptom(s) are reported (if any).

For any significant abnormalities seen at the eye examination, all assessed parameters and findings should be documented in the respective eCRF pages and source documents.

At clinical visits (or as clinically indicated), limited, symptom-directed physical examinations should be performed. Changes from baseline abnormalities should be recorded in the patient's medical file. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

8.2.2.3 Vital Signs

Vital signs (oral temperature, respiratory rate, sitting blood pressure, and sitting pulse/ heart rate) will be obtained while the patient is in a semi-supine/supine position after the patient has been resting for approximately 5 minutes. Vital signs should be measured prior to blood draw or at least 10 minutes after the last blood draw.

Blood pressure and heart rate should be obtained in a quiet room at a comfortable temperature, with the patient's arm unconstrained by clothing or other material. The patient should be asked to remove all clothing that covers the location of cuff placement. All measurements will be obtained from the same arm and, with the appropriate cuff size, using a well-calibrated automatic instrument with a digital readout, throughout the study (the "ideal" cuff should have a bladder length that is 80% and a width that is at least 40% of arm circumference [a length-to-width ratio of 2:1]). The individual should be comfortably in a semi-supine/supine position.

Blood pressure, heart rate, and body temperature (oral) will be recorded at the time-points specified in the Schedule of Assessments (see Appendix 1 and Appendix 2). Vital signs should be assessed on the scheduled day, even if study medication is being withheld. More frequent examinations may be performed at the Investigator's discretion, if medically indicated.

8.2.2.4 ECOG Performance Status

The ECOG performance status will be assessed at screening within 14 days before planned first dose administration. In addition, an ECOG performance status will be done at baseline and at the indicated visits as per the Schedule of Assessments. With the baseline assessment performed, the assessment does not need to be repeated on the day of the first administration (Day 1 / Cycle 1) (Part A and Part B).

Performance status will be scored using the ECOG performance status scale index (see Table 13).

Table 13 ECOG performance status scale

Score	Performance Status
0	Fully active, able to carry out all normal activity without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry out any self-care. Totally confined to bed or chair.
5	Dead

8.2.3 Cardiac Assessments

The following cardiovascular assessments will be performed in Part A and Part B of the study as outlined in the Schedule of Assessments (see Appendix 1 and Appendix 2):

- Blood pressure and heart rate (as part of vital signs performed at every visit, see Section 8.2.2.3 and Section 8.2.3.1)
- Digital 12-lead ECG (in triplicate) and selected time points for 24 hour Holter ECGs
- Evaluation of cardiac markers as part of the laboratory safety assessments
- ECHO or MUGA for LVEF assessment will be done at the investigational sites at pre-defined time points during the study

As ECG changes were observed in the non-clinical safety and toxicology studies in rats and dogs at the C_{max} concentration of CB-103 and CB-103 might therefore have an influence on the QT interval and bear a risk of cardiotoxicity, intense, continuous cardiac monitoring including central management of ECGs and central review of all ECG data by cardiac experts will be included in the study for Part A (escalation) and depending on results of Part A also in Part B (expansion) as medically required.

8.2.3.1 Blood Pressure and Heart Rate

As part of the assessment of vital signs, blood pressure and heart rate are determined as outlined in Section 8.2.2.3.

8.2.3.2 Electrocardiograms (ECG) and Holter Safety Monitoring

12-lead ECG monitoring in triplicate will be conducted as part of the screening process to evaluate eligibility of the patient and subsequently used as standard procedure during the whole study. 3-lead Holter ECG monitoring with 24 hour ECG profiles will be performed at baseline and used as baseline assessment and subsequently at selected time points as method to detect arrhythmias (for the exact time points refer to Table 14, Table 15, Appendix 1 and Appendix 2).

12-lead ECG monitoring in triplicates and Holter ECG Monitoring (24 hours) will be conducted in Part A component according to the following schedule:

Table 14 Part A ECG schedule (once daily dosing regimen of CB-103)

Cycle	Day	12-lead ECG (E) / Holter (H) ECG	Timing and details
-	Screening	E	Triplicate ECGs will be recorded to evaluate for potential exclusion criteria.
Within 7 days prior to 1st dose	Baseline	H	24 hours Holter recording will be recorded as baseline assessment.
1	1, 8	E, H	24 hours Holter ECG will be hooked up prior to dosing on Day 1 and 8 and returned the day after. 12-lead ECG should be obtained (in triplicate approx.1-2 minutes apart) at the same time when the PK samples are taken: • Day 1: pre-dose (-30' and -60'), 0.5, 1, 2, 4, 6, 8 hours post-dose, 12 hours post-dose and 24 hours post-dose • Day 8: pre-dose (up to 60 minutes), 0.5, 1, 2, 4, 6 and 8 hours post-dose and 24 hours post-dose
	15, 22		12-lead ECG should be obtained (in triplicate approx. 1-2 minutes apart) at the same time when the PK sample is taken: • pre-dose (up to 60 minutes) and 1 hour post-dose
2	1	E, H	24 hours Holter ECG will be hooked up prior to dosing on Day 1 and returned the day after. 12-lead ECG should be obtained (in triplicate approx.1-2 minutes apart) at the same time when the PK sample is taken: • pre-dose (up to 60 minutes), 0.5, 1, 2, 4, 6, and 8 hours post-dose
2	15	E	12-lead ECG should be obtained (in triplicate approx.1-2 minutes apart) at the same time when the PK sample is taken (i.e., pre-dose, up to 60 minutes).
3,4,5,6	1	E	A 12-lead ECG should be obtained (in triplicate approx.1-2 minutes apart) at the same time when the PK sample is taken.
EOT	Within 14 days after last dose	E, H	24 hours Holter ECG and returned the day after. 12-lead ECG should be obtained (in triplicate approx.1-2 minutes apart).
After cycle 6	1	E	A 12-lead ECG should be obtained (in triplicate approx.1-2 minutes apart).

Note 1: ECG and PK blood samples need to be obtained at the same time-points and the ECG should be performed just prior to the drawing of the blood.
Note 2: Holter recording should start 1 to 2 hours before the CB-103 intake.

In Part B component of the study (Phase IIA, expansion), 12-lead ECGs in triplicates and Holter ECG Monitoring (24 hours) should be performed according to the following schedule and may be adapted based on the results of the ECG monitoring in Part A of the study

Table 15 Part B (Phase IIA, expansion) ECG schedule (once daily dosing regimen of CB-103)

Cycle	Day	12-lead ECG (E) / Holter (H) ECG	Timing and details
-	Screening	E	Triplicate ECGs will be recorded to evaluate for potential exclusion criteria.
Within 7 days prior to 1st dose	Baseline	H	24 hours Holter recording will be recorded as baseline assessment.
1	1, 8,15, 22	E	12-lead ECG should be obtained (in triplicate approx.1-2 minutes apart) at the pre-dose time point.
2 till 12	1	E	12-lead ECG should be obtained (in triplicate approx.1-2 minutes apart) at the pre-dose time point.
EOT	Within 14 days after last dose	E	A 12-lead ECG should be obtained (in triplicate approx.1-2 minutes apart).
After cycle 12	1	E	A 12-lead ECG should be obtained (in triplicate approx.1-2 minutes apart).

Note: ECG should be performed just prior to the drawing of the blood.

Digital ECGs should be transmitted to the central ECG CRO designated by Sponsor on the day that they are acquired. Paper copies of the ECGs should be timely reviewed by the Investigator for the purpose of general safety. The central ECG CRO should send alerts to the Investigator and Covance if any ECGs are detected with QTcF values of ≥ 500 ms.

Timing of ECGs may be modified based upon emerging PK data (as some ECGs are matched with the PK data). **When matched with PK sampling all efforts should be made to perform the ECG before each PK sample drawing such that the PK sample is collected at the nominal time.**

A 15-minute window for ECG collection is allowed around each nominal ECG time point except for the 24 hour ECG time point, where a 1 hour window is allowed.

The 12-lead ECG recordings must be obtained in triplicate (i.e., three high quality ECGs without artifacts/lead misplacement, recorded approx.1-2 minutes apart) in Part A and Part B of the study. The average of the three readings will be used to determine ECG intervals (e.g., PR, QRS, QT). Digital 12-lead ECG devices will be provided to each investigational site by the central ECG laboratory for the duration of the study. Digital ECG recording must be performed for all patients according to the study protocol schedule (see Appendix 1 and Appendix 2). ECGs will be reviewed, signed and dated by the Investigator or designee and ECG print-outs must be filed with the source documentation. The data records will be sent to the CRO responsible for central cardiac reading. The conditions should be as close as possible to pre-dose time-points. Details for the ECG collection and transmission will be provided in the ECG manual provided by the ECG core laboratory.

For safety monitoring purposes, the Investigator or designee must review, sign, and date all ECG tracings in a timely fashion. Paper or electronic copies will be kept as part of the patient's permanent study file at the investigational site.

ECG characteristics, including heart rate, QRS duration, and PR, QTcF and QT interval, will be recorded on the eCRF.

For both Part A and Part B, changes to the ECG scheme may be implemented based on emerging data. Any adjustments will be recorded in the study file and the total number of ECGs taken from an individual patient within a cycle will not be exceeded.

ECG Schedule for BID Twice Daily Dosing Regimen of CB-103

In case of oral BID dosing regimen of CB-103 the ECG schedule during cycle 1 will be adjusted concomitantly to the adjusted PK sampling.

The ECG schedule at screening and baseline and from cycle 2 and onwards is identical to the one described above for the once-daily dosing of CB-103. However, the time points are related to the 1st IMP intake unless otherwise indicated.

Table 16 Part A (Phase I) ECG schedule – BID regimen

Cycle	Day	12-lead (E) / Holter (H) ECG	Timing and details
-	Screening	E	Triplicate ECGs will be recorded to evaluate for potential exclusion criteria.
Within 7 days prior to 1st dose	Baseline	H	24 hours Holter recording will be recorded as baseline assessment.
1	1, 8	E, H	24 hours Holter ECG will be hooked up **prior to 1st IMP** dosing on Day 1 and 8 and returned the day after. 12-lead ECG should be obtained (in triplicate approx.1-2 minutes apart) at the same time when the PK samples are taken: • Day 1: pre-dose **1st IMP intake** (-30' and -60'), 0.5, 1, 2 and 4 hours post-dose • Day 1: pre-dose **2nd IMP intake** (-30' and -60'), 0.5, 1, 2 and 4 hours post-dose • **Day 2: pre-dose 1st IMP intake (up to 60 minutes prior to dose)** • Day 8: pre-dose **1st IMP intake** (-30' and -60'), 0.5, 1, 2 and 4 hours post-dose • Day 8: pre-dose **2nd IMP intake** (-30' and -60'), 0.5, 1, 2 and 4 hours post-dose • **Day 9: pre-dose 1st IMP intake (up to 60 minutes prior to dose)**
1	15	E	12-lead ECG should be obtained (in triplicate approx.1-2 minutes apart) at the same time when the PK samples are taken: • Pre-dose (up to 60 minutes) **1st IMP intake**
2	1	E, H	24 hours Holter ECG will be hooked up **prior to 1st IMP** dosing on Day 1 and returned the day after. 12-lead ECG should be obtained (in triplicate approx.1-2 minutes apart) at the same time when the PK sample is taken: • pre-dose (up to 60 minutes), 0.5, 1, 2, 4, 6, and 8 hours post-dose **1st IMP intake**
2	15	E	12-lead ECG should be obtained (in triplicate approx.1-2 minutes apart) at the same time when the PK sample is taken (i.e., pre-dose, up to up to 60 minutes **1st IMP intake**).
3,4,5,6	1	E	A 12-lead ECG should be obtained (in triplicate approx.1-2 minutes apart) at the same time when the PK sample is taken (respect to the **1st IMP intake)**.
EOT	Within 14 days after last dose	E, H	24 hours Holter ECG and returned the day after. 12-lead ECG should be obtained (in triplicate approx.1-2 minutes apart).
After cycle 6	1	E	A 12-lead ECG should be obtained (in triplicate approx.1-2 minutes apart).

Table 17 Part B (Phase IIA, expansion) ECG schedule – BID regimen

Cycle	Day	12-lead (E) ECG	Timing and details
-	Screening	E	Triplicate ECGs will be recorded to evaluate for potential exclusion criteria.
Within 7 days prior to 1st dose	Baseline	H	24 hours Holter recording will be recorded as baseline assessment.
1	1, 8,15	E	12-lead ECG should be obtained (in triplicate approx.1-2 minutes apart) at the pre-dose time point **of the 1st IMP intake**.
2 till 12	1	E	12-lead ECG should be obtained (in triplicate approx.1-2 minutes apart) at the pre-dose time point **of the 1st IMP intake**.
EOT	Within 14 days after last dose	E	A 12-lead ECG should be obtained (in triplicate approx.1-2 minutes apart).
After cycle 12	1	E	A 12-lead ECG should be obtained (in triplicate approx.1-2 minutes apart).

8.2.3.3 Cardiac Imaging – ECHO or MUGA

An ECHO or MUGA should be performed at baseline (within 7 days of first treatment), at Day 8 Cycle 1, at Day 1 Cycle 3 and at EOT visit to assess LVEF. These assessments will be done locally and may be repeated at the Investigator's discretion if there are signs or symptoms of cardiotoxicity. The ECHO or MUGA scans will be reviewed, signed and dated by the Investigator or designee in a timely fashion and print-outs must be filed with the source documentation. The data records will be sent to the CRO for collection and storage. Details for the ECHO and MUGA scans will be provided in a separate Laboratory Manual.

8.2.3.4 Cardiac Laboratory – Cardiac Markers

Evaluation of cardiac markers will be included as part of the laboratory safety assessments and will be assessed at the time points provided in Appendix 1 and Appendix 2. Cardiac markers include troponin [Trop] I or Trop T and N-terminal propeptide BNP (NT-pro-BNP). These assessments may be repeated at the Investigator's discretion if there are signs or symptoms of cardiotoxicity.

8.2.4 Laboratory Safety Assessments

Laboratory safety tests shall be performed at time-points specified in the Schedule of Assessments (Appendix 1 and Appendix 2).

Additional blood or urine samples may be taken at the discretion of the Investigator if the results of any test fall outside the reference ranges, or clinical symptoms necessitate additional testing to monitor patient's safety. Where the clinical significance of abnormal

lab results is considered uncertain, screening lab tests may be repeated before enrolment to confirm eligibility.

In the event of unexplained abnormal clinically significant laboratory test values, the tests should be repeated immediately and followed up until they have returned to the normal range and/or an adequate explanation of the abnormality is found. Results of clinical laboratory testing will be recorded on the eCRF.

Samples for the following blood and urine laboratory tests will be collected as specified in the Schedule of Assessments (Appendix 1 and Appendix 2) and sent to the local laboratory for analysis.

- **Haematology:** Haemoglobin, haematocrit, erythrocytes (RBC), reticulocyte count, platelets, leukocytes (WBC), differentials (counts): neutrophils, eosinophils, lymphocytes, monocytes, basophils.
- **Coagulation:** prothrombin time (expressed as INR) and activated partial thromboplastin time (aPTT).
- **Blood chemistry:** AST, ALT, total and conjugated bilirubin, ALP, gamma-glutamyl-transferase (γ-GT), creatine phosphokinase (CPK), albumin, creatinine, urea nitrogen, total protein, sodium, chloride, calcium, bicarbonate, phosphate, potassium, triglycerides, total cholesterol, glucose, C-reactive protein (CRP), lipase, urate and lactate dehydrogenase.
- **Serology:** human immunodeficiency virus (HIV), hepatitis B (HBV) or C (HCV).
- **Pregnancy test:** All women of childbearing potential (including those who have had a tubal ligation) will have serum or urine pregnancy tests at the time-points specified in the Schedule of Assessments (Appendix 1 and Appendix 2). Pregnancy tests will also be done whenever one menstrual cycle is missed during the active treatment period (or when potential pregnancy is otherwise suspected) to confirm the patient has not become pregnant during the study.
- **Urinalysis**, including dipstick (pH, specific gravity, glucose, protein, ketones, red and white blood cells) and microscopic examination, if clinically significant positive results from the dipstick (sediment, RBCs, WBCs, casts, crystals, epithelial cells, bacteria).
- **Cardiac markers:** Trop I or Trop T and NT-pro-BNP.

8.3 EFFICACY ASSESSMENTS

Tumour assessments will be performed at baseline, during treatment period and at treatment completion at the time-points specified in the Schedule of Assessments (Appendix 1 and Appendix 2). All radiographic assessments for the different indications will be defined in the imaging manual and all radiographic images (x-ray, CT, PET-CT, MRI) will be collected and archived centrally.

A chest X-ray must be performed at baseline and should be repeated if clinically indicated. If a chest CT is performed at baseline to assess tumour lesions, then a chest X-ray may not be required. If any brain involvement is suspected, a brain scan should also be performed at baseline to identify any brain metastasis and document them into the respective tumour assessment eCRFs. For selected cancer indications, positron emission tomography–computed tomography (PET-CT) scans are to be performed and used for the tumour assessments at baseline and, if positive, on C2D15 (before tumour biopsy).

For the different solid tumour indications enrolled in the study, the following criteria for radiographic tumour response assessments will be used:

- **For solid tumours:** Radiographic tumour response assessments will be based on CT/MRI scans throughout the study and response determined by Investigator based on the RECIST v1.1 criteria (Eisenhauer et al., 2009). Response criteria by response subcategory are provided in Appendix 7. The same imaging method used for tumour assessment at screening should be used throughout the study.

- **In addition, in some indications,** CT scan will be replaced by PET-CT (or PET scan added to CT scan) at baseline (prior to tumour biopsy) **and if positive,** repeated on treatment at C2D15 (prior to tumour biopsy) to explore changes in metabolism of the tumour. See Section 8.6 and Appendix 9.

8.4 PHARMACOKINETIC ASSESSMENTS

Blood samples for determination of plasma concentrations of CB-103, and its potential metabolite(s) as applicable, will be collected as detailed in Appendix 1 and Appendix 2.

Details regarding the collection, processing, storage and shipping of the blood samples will be provided in a separate Laboratory Manual.

Part A pharmacokinetic sample collection (for patients on a once-daily dose regimen of CB-103) will be obtained on:

Cycle 1 (total of 22 samples):

- Day 1: pre-dose, 0.5, 1, 2, 4, 6, 8 hours post-dose (± 5 minutes) and 12 hours post-dose (± 15 minutes)
- Day 2: 24 hours post Day 1 dose (± 60 minutes), before drug intake on Day 2
- Day 3: pre-dose
- Day 8: pre-dose, 0.5, 1, 2, 4, 6 and 8 hours post-dose (± 5 minutes)
- Day 9: 24 hours post Day 8 dose (± 60 minutes), before drug intake on Day 9
- Day 15: pre-dose and 1 hour post-dose (± 5 minutes)
- Day 22: pre-dose and 1 hour post-dose (± 5 minutes)

Cycle 2 (total of 8 samples):

- Day 1: pre-dose, 0.5, 1, 2, 4, 6, and 8 hours post-dose (± 5 minutes)
- Day 15: pre-dose

Note: the pre-dose PK should be collected up to 1 hour of CB-103 intake.

Cycle 3 till cycle 6 (total of 2 samples per cycle)

- One sample at every visit (pre- or post-dose). The timing can be flexible as long as the time of prior drug intake and PK sampling is recorded exactly.

Part B pharmacokinetic sample collection will be obtained on:

Cycle 1 (total of 22 samples):

- Day 1: pre-dose, 0.5, 1, 2, 4, 6, 8 hours post-dose (± 5 minutes) and 12 hours post-dose (± 15 minutes)
- Day 2: 24 hours post Day 1 dose (± 60 minutes), before drug intake on Day 2
- Day 3: pre-dose
- Day 8: pre-dose, 0.5, 1, 2, 4, 6 and 8 hours post-dose (± 5 minutes)
- Day 9: 24 hours post Day 8 dose (± 60 minutes), before drug intake on Day 9
- Day 15: pre-dose and 1 hour post-dose (± 5 minutes)
- Day 22: pre-dose and 1 hour post-dose (± 5 minutes)

Cycle 2 (total of 8 samples):

- Day 1: pre-dose, 0.5, 1, 2, 4, 6, and 8 hours post-dose (± 5 minutes)
- Day 15: pre-dose

Cycle 3 till cycle 12 (total of 2 samples per cycle)

- One sample at every visit (pre- or post-dose). The timing can be flexible as long as the time of drug intake and PK sampling is recorded exactly.

For both Part A and Part B changes to the PK sampling scheme may be implemented based on emerging data. Any adjustments will be recorded in the study file and the total number of PK samples taken from an individual patient within a cycle will not be exceeded.

All efforts will be made to obtain the PK samples at the scheduled nominal-time relative to the dosing. However, samples obtained within the specified deviation of the nominal time (see above time window) will be considered protocol compliant, and the exact time of the sample collection noted on the eCRF. If a scheduled blood sample collection cannot be collected for any reason, the missed sample time may be re-scheduled with agreement of clinical Investigators, patient and Sponsor. PK samples will be assayed for CB-103 using a validated analytical method in compliance with the standard operating procedures of the central PK laboratory.

8.4.1 PK Sample Collection for BID Dosing Regimens of CB-103

In case an oral BID dosing regimen of CB-103 is implemented, the PK sampling scheme during cycle 1 will be adjusted to allow an evaluation of the concentration-versus-time curves after the morning and the evening dose on the first day of dosing (Day 1) and again after multiple days of administration (Day 8).

The PK sampling scheme from cycle 2 and onwards is identical to that described above for the once-daily dosing of CB-103. However, the time points are related to the 1st IMP intake of a day unless otherwise indicated.

Part A and B of the study: Cycle 1 (total of 23 samples):

- Day 1: pre-dose, 1st intake, 0.5, 1, 2, 4 hours post-1st intake (± 5 minutes)
- Day 1: pre-dose, 2nd intake, 0.5, 1, 2, 4 hours post-2nd intake (± 5 minutes)
- Day 2: pre-dose, 1st intake (up to 60 minutes prior to dose)
- Day 8: pre-dose, 1st intake, 0.5, 1, 2, 4 hours post-1st intake (± 5 minutes)
- Day 8: pre-dose, 2nd intake, 0.5, 1, 2, 4 hours post-2nd intake (± 5 minutes)
- Day 9: pre-dose, 1st intake (up to 60 minutes prior to dose)
- Day 15: pre-dose, 1st intake (up to 60 minutes prior to dose)

For any other dose regimen (e.g., intermittent oral dosing) the PK sampling scheme may require further adaptations based on new emerging data. Any adjustments will be recorded in the study file and the total number of PK samples taken from an individual patient within a cycle will not be exceeded.

8.4.2 PK Sub-study

It can be decided to explore certain dosing conditions and their effect on the PK of CB-103 (e.g., influence of food, influence of co-medications such as acid reducing agents, influence of formulation changes such as additional excipients, i.v. formulation, tablets or drinkable solutions) in a sub-set of patients during Cycle 2. The PK assessments on Day 1 of Cycle 2 will serve as reference and a second set of PK samples will be taken on Day 2 of Cycle 2 under the testing conditions. The total number of PK samples during Cycle 2 in this sub-set of patients will not exceed 20 samples.

All the procedural details including PK sampling time points of the PK sub-study(ies) will be described in a Note to File and the concerned authorities/ethics will be informed accordingly.

It is possible to initiate several PK sub-studies to test different dosing conditions (as above), but each patient will participate in only one sub-study.

Refer to the Appendix 11 and Appendix 12 for the PK sub-studies already initiated.

8.4.3 PK in CSF

In T-ALL/T-LBL patients, a CSF sample should be taken on or around cycle 1 day 28, if clinically feasible, to determine the intra-thecal concentration of CB-103.

8.5 PHARMACODYNAMIC/BIOMARKER ASSESSMENTS

8.5.1 Tumour tissue in Patient with Solid Tumours

The required fresh tumour tissue(s) will be assessed for various PD markers/biomarkers and a potential role for safety, PD and anti-cancer activity of CB-103 will be investigated. Samples will be processed and shipped as described in a separate Laboratory Manual. The timing of sampling may change, but the total number of samples will not increase. The respective time points for each tumour tissue sampling are provided in Appendix 1 and Appendix 2.

- **For patients enrolled in Part A (escalation):** fresh tumour biopsies are not mandatory; however, patients should be encouraged to participate. Sufficient archival tumour tissue samples not older than 6 months prior to screening will be required to characterise the NOTCH alterations in tumours retrospectively.
- **For patients enrolled in Part A (MTD/RP2D confirmatory cohort) and Part B (expansion):** fresh tumour biopsies will be collected from all patients enrolled at the timepoints defined in the Schedule of Assessments (Appendix 1 and Appendix 2). Sufficient archival tumour tissue samples are allowed, if not older than 6 months prior to pre-screening, to be used for the characterisation of NOTCH alterations for the pre-screening of patients, however, a pre-dose fresh tumour tissue sample should be taken to confirm the NOTCH activation in tumour cells as well as to detect newly developed NOTCH and NOTCH-related pathway activation.

8.5.2 Hair follicles in patients with solid tumours

Hair follicles collection will be obtained at the following time-points:

- Cycle 1 Day 1: pre-dose and 1 hour post-dose (± 10 minutes)
- Cycle 2 Day 1 and Day 15: pre-dose and 1 hour post-dose (± 10 minutes)
- Day 1 of each subsequent cycle*: 1 hour post-dose (± 10 minutes)

For the BID dosing regimen of CB-103 the hair follicles collection is as follows:

- Cycle 1 Day 1: pre-dose 1st intake, and 1 hour (± 10 minutes) post-dose 2nd intake
- Cycle 2 Day 1 and Day 15: pre-dose and 1 hour (± 10 minutes) post-dose 1st intake
- Day 1 of each subsequent cycle*: 1 hour (± 10 minutes) post-dose 1st intake

*up to cycle 6 Part A and up to cycle 12 Part B. After the dose-escalation portion of Part A of the study, hair follicles will be collected only for selected patient groups.

Changes to the sampling scheme may be required based on the emerging data. Any adjustment will be recorded in the study file and the total number of samples taken will not be exceeded.

The time of collection of the hair follicles should be captured in the patient's record and in the specific sample requisition form to send to the concerned central laboratory along with

the samples. More details regarding the collection, processing, storage and shipping of the hair follicle samples will be provided in a separate Laboratory Manual.

8.5.3 Whole blood plasma and saliva

Serial blood samples (whole blood, plasma) in all patients (and bone marrow samples in T-ALL/T-LBL patients, as indicated) will be obtained to measure NOTCH/NOTCH target gene expression as well as to investigate changes of gene expression by CB-103 treatment in immune cell subsets, T- and B- lymphocytes. Serial blood samples will be obtained to measure several soluble markers (plasma).

Whole blood and plasma will be obtained at the time points indicated in the Schedule of Assessments in Appendix 1 and Appendix 2. The collection time window is as follows:

- Cycle 1 Day 1: pre-dose and 1 hour post-dose (± 10 minutes)
- Cycle 2 Day 1 and Day 15*: pre-dose and 1 hour post-dose (± 10 minutes)
- Day 1 of each subsequent cycle: 1 hour post-dose (± 10 minutes)

For the BID dosing regimen of CB-103 the samples collection is as follows:

- Cycle 1 Day 1: pre-dose 1st intake, and 1 hour (± 10 minutes) post-dose 2nd intake
- Cycle 2 Day 1 and Day 15*: pre-dose and 1 hour (± 10 minutes) post-dose 1st intake
- Day 1 of each subsequent cycle: 1 hour (± 10 minutes) post-dose 1st intake

* for T-ALL/T-LBL patients the collection at C2D15 in NOT requested.

A sample of saliva together with one blood sample will be obtained from T-ALL/T-LBL patients to determine the Notch mutational status in leukaemic blasts prior to start of treatment. If the Notch status of the patient is unknown, the samples will be taken during pre-screening. If the Notch status is known, the samples will be taken at baseline.

Changes to the sampling scheme may be required based on the emerging data. Any adjustment will be recorded in the study file and the total number of samples taken will not be exceeded.

More details regarding the collection, processing, storage and shipping of the blood, plasma and saliva samples will be provided in a separate Laboratory Manual.

8.6 POSITRON EMISSION TOMOGRAPHY (PET) IN PATIENTS WITH BREAST CANCER OR T-ALL/T-LBL WITH EXTRAMEDULLARY DISEASE

FDG-PET can identify sign of biological effect early, before tumour size is reduced. Moreover, a reduction in the FDG-PET signal within days or weeks of initiating therapy (e.g., in lymphoma, non–small cell lung, and esophageal cancer) has been shown to correlate with prolonged survival and other clinical end points now used. These findings suggest that FDG-PET could facilitate drug development as an early marker of drug effect.

At baseline, and if positive at baseline, also at cycle 2 day 15, the FDG ([^{18}F]-Fluoro-Deoxy-Glucose) PET imaging will be performed with CT in place of the CT scan alone. PET-CT will be done for patients with breast cancer in the MTD/RP2D confirmatory cohort of Part A and for patients with T-ALL/T-LBL if clinically indicated.

FDG-PET must be performed before taking the fresh tumour biopsies. Refer to Appendix 9 for more details.

8.7 DRUG METABOLISM AND GENETICS

Genotype testing will be performed in all patients in Part A and Part B to allow the determination of the haplotype of selected metabolic enzymes in order to identify differential metabolisers. For these assessments, an extra blood sample will be taken at screening and at Day 1 of the first cycle. Based on the results from the investigation of fast and slow metabolisers in Part A on certain enzymes, patients may be excluded from the population for Part B (expansion) of this study or the dosing in each patient may be adapted based on the determined metabolic status of each patient.

8.8 OPTIONAL BIOMARKER STUDIES ON ADDITIONAL OR REMAINING SAMPLES

Remaining blood and/or tumour tissue samples may be used for DNA, RNA and/or protein-based analyses.

8.9 ASSAYS AND DIAGNOSTIC METHODS FOR CHARACTERISATION OF THE NOTCH PATHWAY

Established diagnostic methods will be used for the characterisation of NOTCH signalling at study-entry screening in the confirmatory cohort of Part A and Part B of the study (expansion) to detect alterations and activation of the NOTCH pathway in tumour tissue samples, in order to select patients eligible for the study. For the dose escalation cohorts in Part A of the study, patient selection based on NOTCH activation is not required and their NOTCH activation status in tumours will be retrospectively assessed, therefore the results will not be used to determine patient eligibility for the study.

Where NOTCH testing is not done locally, a central laboratory will have diagnostic methods established for the assessment of alterations of the NOTCH pathway.

Details on the criteria used for determining a patient to qualify as NOTCH positive (NOTCH pathway activation) will be provided in a separate Laboratory Manual for the diagnostic methods used in this study.

8.10 TIMING OF STUDY ASSESSMENTS

8.10.1 Screening and Pre-treatment Assessments

Written informed consent for participation in the study must be obtained before performing any study-related procedures. The ICFs for enrolled patients and for patients who are not subsequently enrolled will be maintained at the investigational site.

All screening and pre-treatment assessments must be completed and reviewed to confirm that patients meet all eligibility criteria. The Investigator will complete the Eligibility Check List form after completing the screening procedures as detailed in the Patient Registration Plan.

Screening, baseline and pre-treatment assessments will be performed between 1 to 28 days prior to Day 1 (according to the Schedule of Assessments in Appendix 1 and Appendix 2). Patients cannot commence the enrolment procedure until all the entry criteria have been fulfilled. Where the clinical significance of an abnormal screening test result (laboratory or any other tests) is considered uncertain, the test should be repeated to confirm the result.

8.10.2 Assessments during Treatment

Patients who enrolled in the lower dose cohorts in this study and (i) who had completed treatment as specified and discontinued the study,* or (ii) who have not been dosed for other reasons besides ineligibility, may be allowed to be re-screened and to be re-enrolled into higher dose level cohorts in the study, upon a case-by-case level discussion and documented agreement with the Sponsor.

*patients that had tolerated treatment well and experienced temporary benefit from treatment (e.g. long-term stable disease) in the lower dose cohorts and could be expected to benefit from treatment again at higher dose.

These patients are to be seen as “new” subjects. Therefore, informed consent must be obtained and they will have to undergo all study-related procedures starting from screening; a previous analysis of an archival tumour tissue biopsy does not need to be repeated. The inclusion/exclusion criteria apply.

The assessments to be performed during the treatment period are given in Appendix 1 and Appendix 2.

8.10.3 Assessments at Study Completion

Patients who complete the study will be followed-up for survival (Appendix 1 and Appendix 2).

8.10.4 Assessments at Unscheduled Visits

Assessments as listed in Appendix 1 and Appendix 2 (as deemed necessary by the Investigator and/or Sponsor/delegate CRO in particular for safety) and any other additional

examinations and assessments deemed necessary, can be performed at unscheduled visits at the discretion of the investor and Sponsor/delegate CRO.

8.11 PATIENT, STUDY, AND SITE DISCONTINUATION

8.11.1 Patient Discontinuation

The Investigator has the right to discontinue a patient from treatment with CB-103 or withdraw a patient from the study at any time. In addition, patients have the right to voluntarily discontinue study drug or withdraw from the study at any time for any reason. The date and reason for discontinuation must be documented in the eCRF. Reasons for discontinuation of study drug or withdrawal from the study may include, but are not limited to, the following:

- Patient withdrawal of consent at any time.
- Any medical condition that the Investigator or Sponsor determines may jeopardise the patient's safety if he or she continues in the study.
- Investigator or Sponsor determines it is in the best interest of the patient.
- Patient non-compliance.

8.11.1.1 Discontinuation from Study Drug and Withdrawal from the Study

Patients must discontinue the study drug if they experience any of the following:

- Pregnancy
- Unable to continue to comply with study requirements

Patients who discontinue study treatment before completing the study should be scheduled for an EOT and safety follow-up visits within 14 days and 28 days (respectively) after discontinuing study treatment, at which time all of the assessments listed for the EOT and safety follow-up visits will be performed. An end of treatment eCRF should be completed, giving the date and reason for stopping the study treatment. Patients who discontinue study drug in Part A prematurely during the DLT period will be replaced, unless the reason for discontinuation is a DLT.

Every effort should be made to obtain information on patients who withdraw from the study. The Investigator should inquire about the reason for withdrawal, requests the patient to return for a final visit, if applicable, and follow-up with the patient regarding any unresolved adverse events. The primary reason for withdrawal from the study should be documented in the eCRF.

Patients will not be followed for any reason after consent from participation in the study has been withdrawn.

When a patient voluntarily withdraws from the study, or is withdrawn by the Investigator, the reason for withdrawal should be reported in the eCRF. Samples collected until the

date of withdrawal will be analysed, unless the patient specifically requests for these to be discarded or local laws require their immediate destruction.

Patients who withdraw prematurely in Part A of the study during the DLT period from the study for any other reason besides a DLT will be replaced. For Part B, discontinued patients will be replaced if they do not have at least one post-baseline efficacy assessment and did not discontinue due to clinical progression.

Criteria for withdrawal from the study are given in Section 9.2.4.

8.11.2 Study and Site Discontinuation

The Sponsor has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of adverse events indicates a potential health hazard to patients.
- Patient enrolment is unsatisfactory.

The Sponsor will notify the Investigator and Health Authorities if the study is placed on hold, or if the Sponsor decides to discontinue the study or development program.

The Sponsor has the right to replace an investigational site at any time. Reasons for replacing a site may include, but are not limited to, the following:

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with the ICH guideline for GCP

9. ASSESSMENT OF SAFETY

9.1 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording adverse events, including serious adverse events and non-serious adverse events of special interest, measurement of protocol-specified safety laboratory assessments, measurement of protocol-specified vital signs, ECGs, and any other protocol-specified tests that are deemed critical to the safety evaluation of the study.

Certain types of events require immediate reporting to the Sponsor, as outlined in Section 9.4.

9.1.1 Adverse Events

According to the ICH guideline for GCP, an adverse event is any untoward medical occurrence in a clinical investigation patient administered a pharmaceutical product, regardless of causal attribution. An adverse event can therefore be any of the following:

- Any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition), except as described in Section 9.3.5.10.
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline.
- Any deterioration in a laboratory value or other clinical test (e.g., ECG) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug.
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., invasive screening procedures such as biopsies).

9.1.2 Serious Adverse Events

A serious adverse event is any adverse event that meets any of the following criteria:

- Fatal (i.e., the adverse event actually causes or leads to death).
- Life-threatening (i.e., the adverse event, in the view of the Investigator, places the patient at immediate risk of death).
- Requires or prolongs inpatient hospitalisation (see Section 9.3.5.10).

- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions).
- Congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug or to a mother whose partner was exposed to study drug.
- Significant medical event in the Investigator's judgment (e.g., may jeopardise the patient or may require medical/surgical intervention to prevent one of the outcomes listed above).

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (rated as mild, moderate, or severe, or according to a pre-defined grading criteria (e.g., NCI CTCAE v4.03 criteria; see Section 9.3.3); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each adverse event recorded on the eCRF.

Pregnancy of a female patient or of the female partner of a male patient is not reported as a serious adverse event and are reported on a specific Clinical Trial Pregnancy Reporting Form immediately, within 24 hours to the Sponsor (see description in Section 9.4.3).

Serious adverse events are required to be reported by the Investigator to the Sponsor immediately (i.e., no more than 24 hours after becoming aware of the event; see Section 9.4.2 for reporting instructions).

9.1.3 Non-Serious Adverse Events of Special Interest

Not applicable in Part A. Based on the results from Part A, non-serious adverse events of special interest [AESI]) might be defined for Part B of the study. These AESIs are required to be reported by the Investigator to the Sponsor immediately (i.e., no more than 24 hours after becoming aware of the event; see Section 9.4 for reporting instructions).

9.2 SAFETY PLAN

9.2.1 Safety Precautions

Safety will be assessed by close monitoring and timely assessment of adverse events, serious adverse events, DLTs, laboratory parameters, robust cardiovascular assessments (blood pressure, heart rate, ECG, periodical Holter ECG monitoring, ECHO or MUGA, cardiac markers), the patient's medical condition (physical examination), and general well-being and activities of daily life (ECOG performance status). The CTCAE v4.03 will be used.

Safety will be evaluated by:

- Adverse events (according to CTCAE v4.03), AESIs in Part B if applicable, serious adverse events and adverse events leading to discontinuation or death
- The results of safety laboratory test, physical examination, vital signs, 12-lead ECGs, Holter Monitoring, LVEF and ECOG performance status
- Drug exposure, including dose intensities and dose modifications

9.2.2 Dose-Limiting Toxicity (DLT)

Refer to Section 7.4.4.

9.2.3 Cardiac Monitoring

Cardiovascular assessments will be performed as outlined in the Schedule of Assessments (Appendix 1 and Appendix 2), and as detailed in Section 8.2.3.

9.2.4 Criteria for Withdrawal from the Study

Patients will be withdrawn from the study if the following criteria are met:

- Unequivocal disease progression
- Death
- Intervening illness that prevents further administration of treatment
- Unacceptable adverse events
- Intercurrent cardiac disease, especially drop in LVEF < 40% or drop > 15% from baseline (if LVEF with > 15% drop is still > 55% a second measurement after 1 week would be allowed before discontinuing the patient)
- Intercurrent interstitial lung disease or pneumonitis
- Patient non-compliance
- Pregnancy
- The patient decides to withdraw from study or is lost to follow-up
- General or specific changes in the patient's condition that render the patient not eligible for further treatment in the judgment of the Investigator
- If a patient experiences a DLT
- If a patient requires a continuous dose delay of more than 14 days (Part A and Part B) from the intended day of the next scheduled dose of CB-103
- If a patient is non-compliant and misses or forgets more than 3 sequential dosings on more than 1 occasion

9.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The Investigator is responsible for ensuring that all adverse events (see Section 9.1.1 for definition) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Sections 9.4 to 9.5.

For each adverse event recorded on the Adverse Event eCRF, the Investigator will make an assessment of seriousness (see Section 9.1.2 for seriousness criteria), severity (see Section 9.3.3), and causality (see Section 9.3.4).

Follow-up by the Investigator may be required until the event or its sequelae resolve or stabilise at a level acceptable to the Investigator, and Sponsor concurs with that assessment. As part of ongoing safety reviews conducted by the Sponsor, any non-serious adverse event that is determined by the Sponsor to be serious will be reported by the Sponsor as a serious adverse event. To assist in the determination of case seriousness further information may be requested from the Investigator to provide clarity and understanding of the event in the context of the clinical trial.

9.3.1 Adverse Event Reporting Period

Investigators will seek information on adverse events at each patient contact. All adverse events, whether reported by the patient or noted by study personnel, will be recorded in the patient's medical records. Adverse events will then be reported on the Adverse Event eCRF as follows:

From informed consent until the initiation of study drug, only serious adverse events related to study procedures. Any other adverse events occurring in this period should be only recorded on the Medical History.

After initiation of study drug, all adverse events regardless of relationship to study drug, will be reported until 4 weeks after the last dose of study drug.

Instructions for reporting adverse events that occur after the adverse event reporting period are provided in Section 9.6.

9.3.2 Eliciting Adverse Event Information

Investigators are advised to use a consistent method of non-directive questioning to elicit adverse event information at all patient evaluation time-points. Some examples of non-directive questions are: "How have you felt since your last clinic visit?" or "Have you experienced any changes to your health since your last visit?"

9.3.3 Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE (v4.03) will be used to assess adverse event severity. Table 18 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 18 Adverse event severity grading scale

Grade	Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated.
2	Moderate; minimal, local, or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living[a]
3	Severe or medically significant, but not immediately life-threatening; hospitalisation or prolongation of hospitalisation indicated; disabling; or limiting self-care activities of daily living[b,c,d]
4	Life-threatening consequences or urgent intervention indicated[e]
5	Death related to AE[e]

Abbreviations: NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

Based on the NCI CTCAE (v4.03), which can be found at: https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

[a] Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[b] Examples of self-care activities of daily living include bathing, dressing and undressing, feeding one's self, using the toilet, and taking medications, as performed by patients who are not bedridden.

[c] If an event is assessed as a "significant medical event," it must be reported as a serious adverse event (Section 9.4.2 for reporting instructions), per the definition of a serious adverse event in Section 9.1.2.

[d] Grade ≥ 2 skin or subcutaneous, pharyngeal/laryngeal or mucosal reaction, clinically relevant retinal abnormalities detected by OCT should be reported as Adverse Events of Special Interest, as indicated in Section 9.1.3.

[e] Grade 4 and Grade 5 events must be reported as serious adverse events (Section 9.4.2 for reporting instructions), per the definition of serious adverse events in Section 9.1.2.

9.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the information about the investigational drug and its non-clinical effects described in the Investigator Brochure, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether or not an adverse event is considered to be related to the study drug, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration:

- Temporal relationship of event onset to the initiation of study drug.
- Course of the event, considering especially the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug.
- Known association of the event with the study drug or with similar treatments.
- Known association of the event with the disease under study.

- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event.
- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event.

9.3.5 Procedures for Recording Adverse Events

Investigators should use correct medical terminology/concepts when recording adverse events on the Adverse Event eCRF. Avoid colloquialisms and abbreviations.

Only one adverse event term should be recorded in the event field on the Adverse Event eCRF.

9.3.5.1 Diagnosis versus Signs and Symptoms

For adverse events, a diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterised as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported adverse events based on signs and symptoms should be nullified and replaced by one adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

9.3.5.2 Adverse Events Occurring Secondary to Other Events

In general, adverse events occurring secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. However, medically significant adverse events occurring secondary to an initiating event that are separated in time should be recorded as independent events on the Adverse Event eCRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.
- If a severe GI haemorrhage leads to renal failure, both events should be reported separately on the eCRF.
- If dizziness leads to a fall and subsequent fracture, all three events should be reported separately on the eCRF.

All adverse events should be recorded separately on the Adverse Event eCRF if it is unclear as to whether the events are associated.

9.3.5.3 Reporting of Progression of Disease

Progression of the underlying malignancy should not be captured as an (S)AE (including fatal AEs). Clinical symptoms may be reported as AEs, if the symptom cannot be determined as exclusively due to the progression of the underlying disease or does not fit the expected pattern of progression for the disease under study. If a new malignancy appears, it will be considered an AE.

9.3.5.4 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between patient evaluation time-points. If the initial severity of a persistent adverse event worsens, the entry in the Adverse Event eCRF should be marked as resolved and a new separated entry with the worsening severity should be added. If the event becomes serious, the Adverse Event eCRF should be updated to reflect this.

A recurrent adverse event is one that resolves between patient evaluation time-points and subsequently recurs. Each recurrence of an adverse event should be recorded separately on the Adverse Event eCRF.

9.3.5.5 Abnormal Laboratory Values

Not every laboratory abnormality qualifies as an adverse event. A laboratory test result should be reported as an adverse event if it meets any of the following criteria:

- Accompanied by clinical symptoms.
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation).
- Results in a medical intervention (e.g., potassium supplementation for hypokalaemia) or a change in concomitant therapy.
- Clinically significant in the Investigator's judgment.

Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an adverse event.

9.3.5.6 Abnormal Vital Sign Values

Not every vital sign abnormality qualifies as an adverse event. A vital sign result should be reported as an adverse event if it meets any of the following criteria:

- Accompanied by clinical symptoms.
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation).
- Results in a medical intervention or a change in concomitant therapy.
- Clinically significant in the Investigator's judgment.

Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an adverse event.

9.3.5.7 Abnormal Liver Function Tests

The finding of an elevated ALT or AST ($> 3 \times$ ULN) in combination with either an elevated total bilirubin ($> 2 \times$ ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinaemia is considered to be an indicator of severe liver injury (Hy's Law). Therefore, Investigators must report as a serious adverse event the occurrence of either of the following:

- Treatment-emergent ALT or AST $> 3 \times$ ULN in combination with total bilirubin $> 2 \times$ ULN (Hy's Law). In the event of suspected Hy's Law CB-103 administration has to be put on hold immediately and permanent discontinuation of treatment should be considered.
- Treatment-emergent ALT or AST $> 3 \times$ ULN in combination with clinical jaundice.

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section 9.3.5.1) and reported to the Sponsor immediately (i.e., no more than 24 hours after becoming aware of the event) as a serious adverse event (see Section 9.4.2).

9.3.5.8 Deaths

Deaths that occur during the protocol-specified Adverse Event reporting period that are attributed by the investigator solely to the progression of the underlying cancer, will be recorded on the EoT/EoS pages in the eCRF and not as an Adverse Event. All other deaths that occur during the protocol-specified adverse event reporting period (see Section 9.3.1), regardless of relationship to study drug, must be recorded on the Adverse Event eCRF and immediately, within 24 hours reported to the Sponsor (see Section 9.4.2).

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded on the Adverse Event eCRF. Generally, only one such event should be reported. The term "sudden death" should only be used for the occurrence of an abrupt and unexpected death (i.e., due to presumed cardiac causes in a patient with or without pre-existing heart disease). If the cause of death is unknown and cannot be ascertained at the time of reporting, "unexplained death" should be recorded on the Adverse Event eCRF. If the cause of death later becomes available, "unexplained death" should be replaced by the established cause of death.

9.3.5.9 Pre-existing Medical Conditions

A pre-existing medical condition is a condition which is listed in Medical History and/or has an onset prior to the date the informed consent is obtained.

A pre-existing medical condition should be recorded as an adverse event only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the Adverse Event eCRF, it is important to convey the concept

that the pre-existing condition has changed by including applicable descriptors (e.g., “more frequent headaches”).

9.3.5.10 Hospitalisation or Prolonged Hospitalisation

Any adverse event that results in hospitalisation or prolonged hospitalisation should be documented and reported as a serious adverse event (per the definition of serious adverse events in Section 9.1.2), except as outlined below.

The following hospitalisation scenarios are not considered to be serious adverse events:

- Hospitalization for treatment of T-ALL/T-LBL
- Hospitalisation for respite care.
- Planned hospitalisation required by the protocol (e.g., tissue biopsy).
- Hospitalisation for a pre-existing condition, i.e. hospitalisation that was planned prior to the study.

The following hospitalisation scenarios are not considered to be serious adverse events, but should be reported as adverse events instead:

- Hospitalisation for an adverse event that would ordinarily have been treated in an out-patient setting had an outpatient clinic been available
- Admission to emergency room that does not result in hospitalisation.

Diagnostic and therapeutic non-invasive and invasive procedures, such as surgery, should not be reported as adverse events. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an adverse event. For example, an acute appendicitis that begins during the adverse event reporting period should be reported as the adverse event, and the resulting appendectomy should be recorded as the treatment of the adverse event.

9.3.5.11 Overdose

Study drug overdose is the accidental or intentional use of the drug in an amount higher than the dose being studied. An overdose or incorrect administration of study drug is not an adverse event unless it results in untoward medical effects. Administration of the precise dosage must always be ensured.

Any study drug overdose of study drug should be noted on the Study Drug Administration eCRF.

All adverse events associated with an overdose of study drug should be recorded on the Adverse Event eCRF. If the associated adverse event fulfils serious criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after becoming aware of the event; see Section 9.4).

In the case of study drug overdose, it is at the discretion of the Investigator to consider hospitalization of the patient for observation of at least 24 hours with frequent cardiac monitoring (frequent ECG, cardiac markers), repeated physical examinations, laboratory

tests as indicated and as usually performed locally, as well as any other specialised examinations deemed necessary to ensure the safety of the patient. Depending on the amount of study drug taken in excess of the planned dose and according to the symptoms observed in the patient, measures may also include admission to an intensive care unit and measures to empty the stomach if the timing of the administration enables study drug removal from the stomach before it becomes fully absorbed.

9.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

Certain events require immediate reporting to allow the Sponsor to take appropriate measures to address potential new risks in a clinical trial. The Investigator must report such events to Covance Pharmacovigilance immediately; under no circumstances should reporting take place more than 24 hours after the Investigator becomes aware of the event. The following is a list of events that the Investigator must report to Covance Pharmacovigilance within 24 hours after becoming aware of the event, regardless of relationship to study drug:

- Serious adverse events
- Non-serious adverse events of special interest
- Pregnancies

The Investigator must report new significant follow-up information for these events to Covance Pharmacovigilance immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information
- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

Investigators must also comply with local requirements for reporting serious adverse events to the local Health Authority and IEC/IRB.

9.4.1 Emergency Medical Contacts

To ensure the safety of study patients, access to the Medical Monitors is available 24 hours a day, 7 days a week. The Medical Monitor contact details for all investigational sites are listed in the separate document "Administrative and Contact Information & List of Investigators".

9.4.2 Reporting Requirements for Serious Adverse Events and Non-Serious Adverse Events of Special Interest

For reports of serious adverse events and non-serious adverse events of special interest (see Sections 9.1.2 and 9.1.3), Investigators should record all case details that can be gathered on the Serious Adverse Event eCRF page and submit to Covance Pharmacovigilance within 24 hours of awareness. Details on the reporting of these adverse events are described in the separate eCRF Completion Guidelines.

In case of system failure or any reason why electronic reporting is not possible, the paper Serious Adverse Event Reporting Form must be completed and forwarded to Covance Pharmacovigilance, no more than 24 hours after becoming aware of the event. Any safety information reported by paper must be retrospectively added to the eCRF as soon as access has been restored.

Contact details for Covance Pharmacovigilance are as follows:

Email: GlobalSAEInbox@covance.com

Fax (Part A & B planned countries):	Spain:	+34 (0) 800-529-34043
	Netherlands:	+31 (0) 800-529-34043
	Switzerland:	+41 (0) 800-529-34043
	Germany:	+49 (0) 800-529-34043
	UK:	+44 (0) 800-529-34043
	France:	+33 (0) 800-529-34043
	US:	+1 888 726 8416

When using the Freephone Universal International Freephone Number (UIFN) numbers listed above, they must be dialled using the international prefix from the country the fax is being sent from. The exception is for the UK where the 44 pre-fix may not be required. Most countries require the first zero to be dropped, but this depends on local fax number conventions.

9.4.3 Reporting Requirements for Pregnancies

9.4.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed to immediately inform the Investigator if they become pregnant during the study or within 90 days after the last dose of study drug. A Clinical Trial Pregnancy Reporting Form should be completed by the Investigator and submitted to Covance Pharmacovigilance within 24 hours after becoming aware of the pregnancy. Pregnancy should not be recorded on the Adverse Event eCRF. The Investigator should discontinue study drug and counsel the patient, discussing the risks of the pregnancy and the possible effects on the foetus. Monitoring of the patient should continue until conclusion of the pregnancy.

9.4.3.2 Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the ICF to immediately inform the Investigator if their partner becomes pregnant during the study or within 90 days after the last dose of study drug. A Clinical Trial Pregnancy Reporting Form should be completed by the Investigator and submitted to Covance Pharmacovigilance within 24 hours after becoming aware of the pregnancy. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study drug.

9.4.3.3 Abortions

Any spontaneous abortion should be classified as a serious adverse event (as the Sponsor considers spontaneous abortions to be medically significant events), recorded on the Adverse Event eCRF, and reported to Covance Pharmacovigilance immediately (i.e., no more than 24 hours after becoming aware of the event; see Section 9.4.2).

Any induced abortion due to maternal toxicity and/or embryo-foetal toxicity should also be classified as serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after becoming aware of the event; see Section 9.4.2).

Elective abortion not associated with toxicity (e.g., induced abortion for personal reasons) does not require expedited reporting but should be reported as outcome of pregnancy on the Clinical Trial Pregnancy Reporting Form.

9.4.3.4 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient or female partner of a male patient exposed to study drug should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to Covance Pharmacovigilance immediately (i.e., no more than 24 hours after becoming aware of the event; Section 9.4.2).

9.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

9.5.1 Investigator Follow-Up

The Investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the Investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study drug or trial-related procedures until a final outcome can be reported.

During the study period, resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the patient's medical record to facilitate source data verification. If, after follow-up, return to baseline status or stabilisation cannot be established, an explanation should be recorded on the Adverse Event eCRF.

All pregnancies reported during the study should be followed until pregnancy outcome and reported according to the instructions provided in Section 9.4.3.

9.5.2 Sponsor Follow-Up

For serious adverse events, non-serious adverse events of special interest, and pregnancies, the Sponsor or its designee may follow up by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

9.6 POST-STUDY ADVERSE EVENTS

The Investigator is not required to actively monitor patients for adverse events after the end of the adverse event reporting period (defined as 4 weeks after the last dose of study drug). If the Investigator becomes aware of any other serious adverse event occurring after the end of the adverse event reporting period, if the event is believed to be related to prior study drug treatment, the event should be reported directly to the Sponsor or its designee.

9.7 EXPEDITED REPORTING TO HEALTH AUTHORITIES, INVESTIGATORS, INSTITUTIONAL REVIEW BOARDS, AND ETHICS COMMITTEES

The Sponsor will promptly evaluate all serious adverse events and non-serious adverse events of special interest against cumulative product experience to identify and expeditiously communicate possible new safety findings to Investigators, IECs/IRBs, and applicable health authorities based on applicable legislation. If the new information may adversely affect the safety of patients or the conduct of the study, a "*Dear Doctor Letter*" is sent to the sites with further instructions that may differ from the protocol or even instruct the sites to stop IMP treatment. The patients are timely informed by the investigator and the communication documented on medical records along with the confirmation whether the patient is willing to remain in the study. If any information in the ICF needs to be changed, it must be re-approved by the IEC/IRB and the patient must be re-consented.

To determine reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of these events using the following reference document:

- CB-103 Investigator's Brochure
  Section 6 of the Investigator's Brochure contains the reference safety information (RSI) of CB-103 to be used for assessing expectedness of a respective adverse event and serious adverse event. The RSI of CB-103 in the Investigator's Brochure will be updated based on new findings occurring in the clinical study, however for the assessment of expectedness for a specific event, only the approved current version of the Investigator's Brochure should be used.

The Sponsor will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the Investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.
An aggregate report of any clinically relevant imbalances that do not favour the test product will be submitted to Health Authorities.

10. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in a Statistical Analysis Plan (SAP) covering Part A and Part B of this study. The SAP will provide all data handling rules, including the management of missing values and the handling of data for withdrawn patients. The SAP will also outline protocol deviation criteria. Any deviations from the planned analyses specified or populations defined within the SAP will be justified in writing and presented within the final clinical study report (CSR) for Part A and for Part B.

The clinical database locks, for Part A and Part B respectively, will occur after all data for the respective part of the study are reconciled (i.e., “cleaned”) for all patients who participate in the dose escalation Part A for the Part A CSR and in the expansion Part B at the MTD/RP2D for the Part B CSR. Two CSRs will be generated for this study, one for Part A (dose escalation) and one for Part B (dose expansion). The SAPs for each part of the study will be finalised and signed before the database lock.

In all tables, listings and figures of Part A, the dose-escalating cohorts will be reported from the lowest to the highest dose. In the Part B of the study expansion arms will be reported by indication. Where appropriate, for efficacy assessment, in addition those patients analysed by “NOTCH+” status who received what becomes identified as the MTD/RP2D during Part A and B, will be combined and summarised under the same dose level.

10.1 ANALYSIS SETS

The **safety set** will consist of all patients who received at least one dose of CB-103 and had at least one post-baseline safety assessment (where the statement that a patient had no adverse event on the Adverse Events eCRF constitutes a safety assessment). The safety set will be the primary population for all efficacy and safety related endpoints except determination of the dose-DLT relationship.

The **dose-determining set (DDS),** which is the analysis set used for determination of the MTD, will consist of all patients in the safety set, who have (a) experienced DLT at any time during Cycle 1, and/or (b) met the minimum treatment and safety evaluation requirements without experiencing DLT within Cycle 1, as described below.

For all dose levels, from starting dose to the respective dose escalation levels, 3-6 patients will be enrolled and treated with CB-103 according to a staggered inclusion scheme to ensure adequate time for safety observation between inclusions, and before dose escalation. Depending on the BLRM, additional patients may be enrolled in some dose cohorts. The minimum treatment and safety evaluation requirements will have been met if, in Cycle 1, the patient has been treated with the planned dose of CB-103 for ≥ 21 days (≥ 75% of the planned dose; minimum exposure criterion), was observed for ≥ 28 days following the Cycle 1 Day 1 dose, and has completed the required safety evaluations for Cycle 1. Patients who do not meet these minimum treatment and safety evaluation

requirements will be regarded as ineligible for inclusion in the DDS. Unless they experienced a DLT, patients will be replaced until the minimum number of 3 patients required for evaluation is reached.

The DDS will be used in the BLRM to estimate the dose-DLT relationship.

The **PK set** consists of all patients who have at least received one dose of study drug and have at least one post-dose PK measurement.

Patients who were screened and have signed the informed consent but did not receive any treatment will be listed including reason for screen failure and any serious adverse event that is related to study procedure. These patients will not be part of any summary table except for summarising disposition.

10.1.1 Missing Data/Discontinuation

Due to the dose escalation design of Part A and the exploratory design of Part B of the study no missing imputation of missing values will be done for any analysis. Reasons for discontinuation of the study and the study treatment will be listed and summarised.

Currently no drop-outs are foreseen. However, if patients in the escalation phase do not fulfil the minimum treatment and safety evaluation requirements and discontinue for a reason other than DLT, they will be replaced. For Part B, discontinued patients will be replaced if they do not have at least one post-baseline efficacy assessment and did not discontinue due to clinical progression.

10.2 DEMOGRAPHICS, MEDICAL HISTORY, PRIOR MEDICATION AND OTHER BASELINE CHARACTERISTICS

Demographic characteristics, prior anti-cancer therapies and surgeries, medical history, prior medication and other baseline data will be listed and summarised using descriptive statistics for numerical data and contingency tables for categorical data. Medical history and prior medication will be listed. Prior anti-cancer therapies will be coded by World Health Organization (WHO) Anatomical, Therapeutic and Chemical (ATC) terms and summarised. Prior cancer surgeries will be summarised.

10.3 STUDY TREATMENT

The actual dose received and the duration of CB-103 as well as the dose intensity (actual dose received/actual duration) will be listed and summarised by cycle and overall using descriptive statistics.

10.4 CONCOMITANT MEDICATION

Concomitant medication and significant non-drug therapies after the start of study treatment will be listed and summarised by WHO ATC term in contingency tables.

10.5 PRIMARY ANALYSIS

10.5.1 Part A (Escalation)

10.5.1.1 Bayesian Logistic Regression Model for Dose Escalation Determination

An adaptive BLRM guided by the EWOC principle will be used in the dose escalation. The use of Bayesian response adaptive models for Phase I studies has been advocated by the EMA guideline on small populations (2006) and by (Rogatko et al., 2007) and is one of the key elements of the FDA's Critical Path Initiative.

10.5.1.2 Dose-Finding of Single Agent CB-103

A 2-parameter BLRM (Neuenschwander et al., 2008) will be used for dose escalation. Standardised doses will be used such that one of the doses (d*) equals 1, e.g., doses are rescaled as d/d*. As a consequence, α is equal to the odds of the probability of toxicity at d*. All information currently available about the dose-DLT relationship of CB-103 is summarised in a prior distribution. For this study, this includes pre-clinical data about the starting dose and predicted MTD of CB-103 within different animal species. This prior distribution is then updated after each cohort of patients with all of the DLT data available in the DDS from the current trial. Once updated, the distribution summarises the probability that the true rate of DLT for each dose lies in the following categories:

- [0,16%) under-dosing
- [16%,33%) targeted toxicity
- [33%,100%] excessive toxicity

The EWOC principle (Babb et al., 1998, Neuenschwander et al., 2008) mandates that any dose of CB-103 that has more than a 25% chance of being in the excessive toxicity category is not considered for the next dose cohort. After a clinical synthesis of the available toxicity information (including adverse events that are not DLTs), PK, PD, and efficacy information as well as the recommendations from the Bayesian model, the CRC will determine the dose regimen for the next cohort at a dose-escalation teleconference. In case that another regimen is evaluated during the study, a separate 2-parameter logistic regression will be used for the assessment of the respective DLT rates. However, all data that are available from the other regimen (or regimens) before "First Patient First Visit" (FPFV) for the new regimen has happened will be incorporated into an informative, meta-analytic predictive (Neuenschwander et al 2015) prior distribution. This prior distribution will be mixed with a weakly informative prior distribution to hedge against a potential prior-data conflict.

The frequency of DLTs will be tabulated by dose for patients in the dose escalation phase and information about the DLTs will be listed by dose.

10.5.1.3 Bayesian Logistic Regression Model for MTD Determination

The objective of the design is to determine the MTD defined as the highest dose with less than 25% risk of the true DLT rate being above 33%. The Part A dose-finding will be guided by a Bayesian 2-parameter logistic regression model with overdose control. These designs have been shown to be superior regarding the precision of MTD determination compared to 3+3 designs and have been particularly endorsed by the FDA.

The model is formulated as follows:

$\text{logit}(p(d)) = \log(\alpha) + \beta * \log(d/d^*)$,

where logit(p) = log(p/(1-p)). p(d) represents the probability of having a DLT in the first cycle at dose d, d* = 150 mg is the reference dose, allowing for the interpretation of α as the odds of a DLT at dose d*, and θ = (log(α), log(β)) with α, β > 0 is the parameter vector of the model.

Since a Bayesian approach is applied, a prior distribution π(θ) for the unknown parameter vector θ needs to be specified. This prior distribution will be specified as a mixture of two multivariate normal distribution, i.e.

$\pi(\theta) = \varphi_1 \pi_1(\theta) + \varphi_2 I_2(\theta)$

with

φ_i, i = 1, 2 the prior mixture weights ($\varphi_1 + \varphi_2 = 1$)

and

$\pi_i(\theta) = MVN(\mu_i, \Sigma_i)$

the multivariate normal distribution of the i-th component with mean vector μ_i and covariance matrix Σ_i, with

$$\Sigma_i = \begin{pmatrix} \sigma_{i,11}^2 & \sigma_{i,11}\sigma_{i,22}\rho_i \\ \sigma_{i,11}\sigma_{i,22}\rho_i & \sigma_{i,22}^2 \end{pmatrix}$$

Mixture prior distributions have the advantage that they allow for specification of different logistic dose-toxicity curves, therefore making the prior more robust.

Prior derivation

For the current study, data from the pre-clinical animal studies were available. Therefore, the following prior will be used: A combination of the observed toxicity data from a study in rats further supported by data from a study in dogs.

Prior from rat data:

Based on the IMPD, the starting dose of CB-103 will be 15 mg, which is expected to achieve an exposure (AUC_{0-24}) in humans of approximately 600 µg*h/mL. This exposure is comparable with 1/10th of the exposure at the HNSTD (30 mg/kg/day) in male rats. It is therefore highly unlikely that a DLT would occur at this dose, leading to the prior

assumption that the median DLT rate at 15 mg is 0.1%. On the other hand, assuming dose-proportionality in humans, a dose of 150 mg would approximately have an exposure of 6000 µg*h/mL, i.e., the same as the exposure at the HNSTD in rats. Using a cautious approach, the median DLT rate at d*= 150 mg was therefore assumed 25%.

Prior from dog data:
Based on the IMPD, the exposure at 1/10th of the HNSTD (8.6 mg/kg/day) in (male) dogs is approximately 9000 µg*h/mL, which we assume would correspond to a human dose of 15*9000/600 = 225 mg. A cautious approach was chosen again, using a median 25% DLT rate at d = 225 mg.

Table 19 Summary of prior distribution

Prior Component	Mixture Weight	Mean vector	STD vector	Correlation
1: Rat	0.500	-1.122, 0.299	1.98476, 0.9906	-0.0004715777
2: Dog	0.500	-1.682, -0.101	1.9847620 0.9906	-0.0004715777

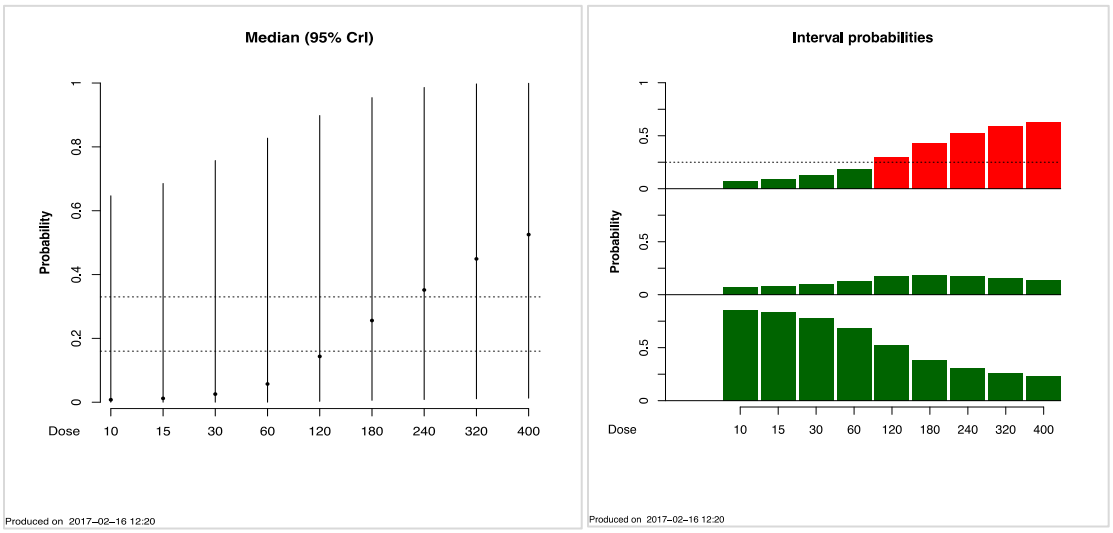
A summary of the prior probabilities of DLT at different doses, as well as the corresponding probability of under-, targeted and overdosing, are shown in Table 20. Graphically, the prior medians with accompanying 95% credible intervals are shown in Figure 6. As can be seen from both Table 20 and Figure 6, the prior medians of the DLT probabilities are in line with the prior medians derived from the two animal studies, and the uncertainty around the medians is large, showing the low amount of in-men information this prior provides.

Table 20 Prior probabilities of DLT at selected doses

Dose	Probability of true DLT rate in					Quantiles		
	[0–0.16)	[0.16–0.33)	[0.33–1]	Mean	STD *	2.5%	50%	97.5%
10 mg	0.857	0.069	0.075	0.077	0.162	0	0.008	0.647
15 mg	0.832	0.079	0.089	0.089	0.173	0	0.012	0.685
30 mg	0.775	0.101	0.123	0.118	0.197	0	0.025	0.757
60 mg	0.688	0.129	0.182	0.165	0.228	0	0.057	0.828
120 mg	0.524	0.178	0.298	0.253	0.266	0.003	0.144	0.898
180 mg	0.384	0.186	0.429	0.347	0.3	0.006	0.256	0.954
240 mg	0.31	0.171	0.519	0.418	0.324	0.008	0.352	0.986
320 mg	0.26	0.153	0.588	0.479	0.339	0.011	0.449	0.998
400 mg	0.229	0.141	0.63	0.52	0.345	0.013	0.525	0.999

Doses printed in bold type meet the overdose criterion, P(overdose) < 0.25.
* STD = standard deviation.

Figure 6 Prior medians and 95% credible intervals.



The MTD may be considered reached if one of the following criteria is fulfilled:

1. The posterior probability of the true DLT rate in the target interval (16%-33%) of the MTD above 50%

OR

2. At least 6 patients have been treated at MTD, including the MTD/RP2D confirmatory cohort

Statistical model assessment

The single agent model was assessed using two different metrics:

1. Hypothetical data scenarios: for various potential data constellations as they could occur in the actual trial, the maximal next doses as allowed by the model and by the 100% escalation limit are investigated. Data scenarios thus provide a way to assess the “on-study” behaviour of the model.

2. Simulated operating characteristics: these illustrate for different assumed true dose-toxicity relationships, how often a correct dose would be declared as MTD by the model. They are a way to assess the “long-run” behaviour of the model.

In summary, the model showed very good behaviour as assessed by these metrics. More details can be found in Appendix 10.

10.5.2 Part B (Expansion)

Once the MTD/RP2D is determined, enrolment into Part B (expansion) can be started by enrolling patients into several expansion arms for selected cancer indications. All patients in Part B will need to have tumours characterised by alterations and over-activation of the NOTCH signalling pathway (mutations, translocations, over-expressions).

For the primary analysis of the expansion arms a Bayesian hierarchical exchangeable binomial design will be used. The assumption of the model is that the true response rate in each of the preliminary indications for the Part B expansion arms is fully exchangeable.

For these indications the response criteria for success is a point estimate (from the model) above 25%.

The T-ALL/T-LBL indications are assumed to be only partially exchangeable with other indications. The success criteria for this indication is a point estimate (from the model) above 40%.

A robust hierarchical model (Neuenschwander et al., 2015) will be used for the analysis of the response rate p_k in the different indications $k = 1, \dots, K$. The number of responders in each indication follows a binomial likelihood function. For exchangeable indications ($k = 1, \dots, K-1$) it is assumed that

$$logit(p_k) \sim N(\mu, \tau^2)$$

On the other hand, for the partially (or non-) exchangeable indication K we use the mixture

$logit(p_K) \sim N(\mu, \tau^2)$ with probability π ,

$logit(p_K) \sim N(m, s^2)$ with probability $1 - \pi$

setting $m = logit(0.3)$ and $s = 2.2$.

Further, the following weakly informative priors (Friede et al., 2016; Friede et al., 2017) are used:

$$\mu \sim N(logit(0.2), 2.5^2)$$
$$\tau \sim HN(1)$$

For these exchangeable indications, the advantage of this model is the fact that borrowing information across indications improves the precision of the estimators of the response rate. On the other hand, for the possibly different indication, the mixture approach hedges for a too-optimistic assumption about similarity. Therefore, the described approach captures the design adequately.

Other characterisations of the posterior distribution will be evaluated as appropriate. The final analysis will take place after the last expansion arm was closed for futility or the last patient of the last expansion arm had the final end-of-study visit.

10.6 SECONDARY ANALYSES

The following sections describe the secondary analyses that will be performed for Part A (escalation) & Part B (expansion) of this study.

10.6.1 Safety Analyses

10.6.1.1 Adverse Events

The Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary will be applied for the coding of AEs. NCI-CTCAE toxicity Grades will be utilised for classifying severity.

Adverse events, related adverse events, serious adverse events and related serious adverse events, adverse events with NCI CTCAE Grades ≥ 3, related adverse events with NCI CTCAE Grades ≥ 3, adverse events leading to premature discontinuation, interruptions or discontinuation of study drug or dose modification will be analysed descriptively utilising corresponding MedDRA System Organ Classes (SOCs) and Preferred Terms (PTs).

Deaths within 28 days after the last dose and the corresponding reasons will be summarised. Also, all deaths overall will be summarised.

10.6.1.2 Safety Laboratory

Laboratory values will be graded by NCI CTCAE version 4.03, if no grading exists values will be classified into low/normal/high based on laboratory normal ranges. Each parameter will be presented by descriptive statistics at each visit including change from baseline (screening). Shift tables for CTCAE grades and normal ranges will be presented. All laboratory values will be listed. A separate listing for abnormal lab values (Grade 3 and higher, and low/high values) will be presented.

10.6.1.3 Vital Signs

Vital signs will be summarised by descriptive statistics at each visit including change from baseline will be presented and a listing will be provided.

10.6.1.4 Electrocardiogram

Centrally read ECG data will be listed overall and a separate listing for any clinically significant finding in ECG values will be provided. Change from baseline in QT intervals by cohort will be summarised for each visit as well as change from baseline in all other ECG parameters. Also, the worst change from baseline will be summarised. The frequency and percentage of patients with notable ECGs and newly occurring qualitative ECG abnormalities will be tabulated by cohort.

10.6.2 Efficacy Analyses

Overall response rate:

For solid tumours, overall response rate as defined by achieving confirmed complete response (CR) and/or partial response (PR) will be presented by percentage rates and 95% confidence intervals. For changes in solid tumour size waterfall plots will be

presented. For all response assessments, swimmers plots will be presented. All response assessments will be listed.

In T-ALL/T-LBL, overall response rate defined as achieving confirmed Complete Remission (CR) and/or Complete Remission with Incomplete Hematologic Recovery (CRi) will be presented by percentage rates and 95% confidence intervals (CI).

Clinical benefit rate for solid tumours at Month 3, 6, and 9, and for T-ALL/T-LBL at 1, 2, and 3 months, and every 2 months from Month 3 to Month 9:

Clinical benefit rate as defined by achieving complete response and/or partial response and/or stable disease (SD) will be presented by percentage rates and 95% confidence intervals. Waterfall plots will be presented.

- For solid tumour indications: Clinical benefit rate (CR + PR + SD), assessed by RECIST 1.1.

Duration of response: The duration of response defined as time from first assessment of PR or CR in solid tumours or CR/CRi in T-ALL/T-LBL to follow-on first assessment of PD or relapse will be summarised by descriptive statistics including median duration of response and respective 95% CIs. Duration of response will also be listed.

Progression free survival (PFS) and overall survival (OS):

Time from first treatment received until disease progression/overall survival will be summarised by Kaplan-Meier estimates, median PFS/OS and respective 95% CIs. Patients with no event will be censored at the last available tumour assessment for PFS and at the last timepoint known alive for OS.

10.6.3 Pharmacokinetic Analyses

CB-103 concentrations will be determined by a validated high-performance liquid chromatography (HPLC) tandem mass spectrometry (LC/MS/MS) method and the following PK parameters of CB-103 including: C_{max}, t_{max}, C_{min}, C_{last}, t_{last}, AUC_{0-8}, AUC_{0-24}, $AUC_{0-\infty}$, V_d/F, V_{ss}/F, CL/F, $t_{1/2}$ and AR. All pharmacokinetic parameters will be calculated from the curves constructed from the individual patients. Non-compartmental analysis will be performed using Phoenix WinNonlin version 6.3 (Pharsight Corporation, Mountain View, CA, USA).

No formal statistical analysis beyond descriptive statistics is planned. For each PK parameter, individual and mean data and summary statistics (including number of patients, arithmetic mean, geometric mean, standard deviation [StD], confidence value [CV], median, Min and Max) will be presented (note that for time to maximum plasma concentration [t_{max}] and time to last measurable plasma concentration [t_{last}] no geometric means will be calculated).

10.6.4 Pharmacokinetic / Pharmacodynamic Analyses

With the PK timepoints collected, a population PK model will be built and then used to estimate individual AUCs or CL/F of CB-103. CB-103 AUC, as well as the observed C_{max}, will then be tested for association with signs of efficacy and safety. If an observable trend exists, a PK/PD model will be developed to evaluate the exposure-response relationship between CB-103 plasma exposure and outcome measures. Demographic and clinical data (ethnicity, current age, body weight, sex, disease status, etc.) will be utilised to assess interpatient variability in the PK and PK/PD relationships.

10.7 EXPLORATORY ANALYSES

10.7.1 Additional PK, metabolite, PD markers, Genomic, Pharmacogenetics, and Protein Analyses, CB-103 metabolic expressions

Exploratory PK assessments, plasma (or other matrix, e.g., urine) levels of metabolite(s), PD markers (genes, proteins) in tumour tissue biopsies and in whole blood, plasma samples and hair follicles, genotypes, protein expression and circulating tumour DNA in blood samples will be analysed as required by the Sponsor or by a delegated Laboratory or investigational site. A separate analysis plan and report for such assessments will be written.

10.7.2 Biomarker Analyses

Summary statistics of PD, mechanistic and tumour profiling biomarkers will be reported by dose group and may be examined for possible correlations with CT/MRI/PET-CT efficacy endpoints. Additional analyses include comparing PD modulation with exposure.

10.7.3 CSF Exposure of CB-103 in Haematological Malignancies

Summary statistics of the CB-103 concentration in CSF will be reported in selected patients with haematological malignancies. The concentrations in CSF will be compared with serum concentrations.

10.8 INTERIM ANALYSES

10.8.1 Part A (Escalation)

Each dose escalation step is considered to be an interim analysis. The BLRM will be updated with the respective number of patients treated and the number of DLTs observed in the last cohort. The updated model will then give a statistical recommendation for the next escalation step. However, a risk-benefit assessment that includes a comprehensive analysis of safety and available clinical information will be done to decide on the next escalation steps. The aggregate safety data from the additional patients in the MTD/RP2D confirmatory cohort will be continuously reviewed at least on a quarterly basis for all CTCAEs ≥ grade 3, all SAEs, all clinically significant laboratory abnormalities and

available safety data, from all patients receiving RP2D, to confirm that the proposed dose for the expansion part is safe and well tolerated.

10.8.2 Part B (Expansion)

Interim analyses will be triggered each time 10 patients in an arm have completed their first response assessment, this includes patients from the MTD/RP2D confirmatory cohort of Part A that qualify for any of the extension arms. An interim analysis will include all patients enrolled at, or prior to the cut-off (set by the completion of the 10th patient), and will be conducted once all patients have completed sufficient assessments to be categorised under the response endpoint, or have withdrawn from study. All arms that remain open to recruitment, and for which the minimum data efficacy requirements have been met, will be assessed for futility. For the interim and final analyses, a hierarchical model will be used. This model leads to more precise estimates of the indication-specific treatment effects as compared to those from stratified analyses. Details of the model can be found above and further descriptions are given in Appendix 10. The results of the interim analyses will be non-binding. Safety criteria will also be evaluated to decide of the continuation of the study arms. Since this is a non-comparative multiple arm study no adjustment for multiple testing is made.

10.9 SAMPLE SIZE

10.9.1 Part A - Dose Escalation and Dose Confirmation

For all dose levels, from starting dose to the respective dose escalation levels, 3-6 patients will be enrolled and treated with CB-103 according to a staggered inclusion scheme to ensure adequate time for safety observation between inclusions, and before dose escalation. During the study, a minimum of 3 patients evaluable for the DDS will be treated per dose cohort until determination of the MTD or RP2D. Depending on the BLRM, additional patients may be enrolled in some dose cohorts. Approximately 11 dose cohorts are considered for this study with at least 3 patients per dose cohort. It is estimated that approximately 55 patients will be enrolled taking into account the drop-outs and additional patients enrolled for some of the dose groups. Based on the decision of the CRC approximately 45 patients in total may be enrolled on the MTD/RP2D confirmatory cohort to confirm safety before opening Part B.

10.9.2 Part B - Dose Expansion, Stratified by Indication

Part B of the study will consist of one or several expansion arm(s) with selected tumour indications. For the analysis of the expansion arms a Bayesian Hierarchical binomial-design will be applied with enrolment of at least 10 patients into each arm. With 10-20 patients enrolled into each expansion arm it is estimated that about 100-140 patients (pending of the number of arms) will need to be recruited. Patients from the MTD/RP2D confirmatory cohort of Part A that qualify for any of the expansion arms will be included into the analyses of Part B and will contribute to the total sample size per arm.

20 patients per Indication arm will give sufficient evidence to determine early signs of clinical benefit. Assuming a true response rate of 30% for exchangeable and partially-exchangeable indications (based on response criteria) the lower limit of the credible band for the point estimate would be greater equal to 19%.

The following indications for patients with NOTCH activated pathway are considered and grouped into the respective expansion arms:

1. Adenoid cystic carcinoma (ACC)
2. Triple Negative Breast Cancer (TNBC)
3. Breast Cancer (ER+/-, HER2+/-)
4. Osteosarcoma, Malignant glomus tumour
5. GI cancers (resistant to oxaliplatin or irinotecan-based therapy colorectal cancer, hepatocellular carcinoma)
6. r/r T-ALL/T-LBL
7. Any other cancer (haematologic or solid) with confirmed Notch pathway activation (basket arm)

Table 21 Sample size consideration for potential indications

	Indication				
	1.ACC	**2.TNBC**	**3.Breast Cancer**	**4. Osteosarcoma, Malignant glomus tumour**	**5.GI**
	n/N Median; (CI)	n/N Median; (CI)	n/N Median; (CI)	n/N Median; (CI)	n/N Median; (CI)
strong homogenicity	6/20 30% (18%-43%)	6/20 30% (18%-43%)	6/20 30% (18%-47%)	6/20 30% (18% - 43%)	6/20 30% (18%- 43%)

The indications considered for the expansion arms in Part B might be adapted and/or additional arms added by a protocol amendment based on the outcome of Part A and further findings from non-clinical studies with CB-103 and the planned interim analysis, this might increase the planned sample size.

11. DATA COLLECTION AND MANAGEMENT

11.1 DATA QUALITY ASSURANCE

Delegated CRO Covance will be responsible for data management of this study, including quality checking of the data. Investigational sites will be responsible for data entry into the Electronic Data Capture (EDC) system.

A comprehensive validation check program will verify the data. Discrepancies will be flagged automatically in the system at the point of entry or will be added manually for resolution by the Investigator.

CRO Covance will produce a Data Management Plan that describes the quality checking to be performed on the data. Laboratory data will be sent directly to CRO Covance, using CRO`s standard procedures to handle and process the electronic transfer of these data.

System backups for data stored by CRO Covance and records retention for the study data will be consistent with CRO Covance`s standard procedures.

11.2 ELECTRONIC CASE REPORT FORMS

Data for this study will be captured via an online EDC system. The data collected in the source documents is entered onto the study eCRF. A complete electronic audit trail will maintain a record of initial entries and changes made; reasons for change; time and date of entry; and user name of person authorising entry or change. For each patient enrolled, an eCRF must be completed and electronically signed by the investigational site Investigator or authorised delegate from the study staff (as per 21 CFR Part 11). If a patient withdraws from the study, the reason must be noted on the eCRF. If a patient is withdrawn from the study because of a treatment‑limiting adverse event, thorough efforts should be made to clearly document the outcome.

The Investigator should ensure the accuracy, completeness and timeliness of the data reported to the Sponsor/CRO in the eCRFs and in all required reports.

All eCRF entries, corrections, and alterations must be made by the Investigator or other, authorised, investigational site personnel and only by individuals who have received training on the EDC system. Site staff may be allowed access to the system only after training is completed. Training must be documented and a log of all EDC users and their rights within the system be maintained.

11.3 SOURCE DATA DOCUMENTATION

Study monitors will perform ongoing source data verification to confirm that critical protocol data (i.e., source data) entered into the eCRFs by authorised site personnel are accurate, complete, and verifiable from source documents.

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical

and office charts, laboratory notes, memoranda, patient-reported outcomes, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico‑technical departments involved in a clinical trial.

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 11.4.

To facilitate source data verification, the Investigators and institutions must provide the Sponsor or its designee direct access to applicable source documents and reports for trial−related monitoring, Sponsor audits, and IEC/IRB review. The investigational site must also allow inspection by applicable Health Authorities.

All source document forms should be completed to ensure the entries are ALCOAC, and must be legible. Errors should be crossed out but not obliterated, or is documented by means of a comprehensive audit trail the correction inserted (if necessary, the reason must be noted), and the change initialled and dated by the Investigator, sub-Investigator, or study nurse.

All source documents will be retained by the investigational site. Photocopies of completed source documents will be provided only if essential (i.e., for regulatory purposes) at the request of the Sponsor. In accordance with ICH GCP, the location of data identified as source data will be specified on the Source Document Identification List.

11.4 RETENTION OF RECORDS AND DOCUMENTS

To enable evaluations and/or audits from regulatory authorities or Sponsor, the Investigator agrees to keep records and documents pertaining to the conduct of this study, including the identity of all participating patients (sufficient information to link records, e.g., CRFs and hospital records), all original signed ICFs, copies of all CRFs, laboratory test results, serious adverse event forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (e.g., letters, meeting minutes, telephone calls reports). According to the EU Clinical Trial Regulation 536/2014, unless other Union law requires archiving for a longer period, the Sponsor and the investigator shall archive the content of the clinical TMF for at least 25 years after the end of the clinical trial. However, the medical files of subjects shall be archived in accordance with national law.

If the Investigator cannot guarantee this archiving requirement at the investigational site for any or all of the documents, special arrangements, respecting the data confidentiality, must be made between the Investigator and Sponsor to store these documents outside the site, so that they can be retrieved in case of a regulatory inspection.

After that retention period, the documents may be destroyed, subject to local regulations. No records/documents may be disposed of without the written approval of the Sponsor. Written notification should be provided to the Sponsor prior to transferring any records to another party or moving them to another location.

If the site is using an electronic/computerised system to store patient medical records, it can be used for the purpose of the clinical study if it is validated (as per 21 CFR Part 11 or equivalent standard) and if the monitor has been provided personal and restricted access to study patients only, to verify consistency between electronic source data and the eCRF during monitoring visits.

If the site is using an electronic/computerised system to store patient medical records but it could not be confirmed that the system is validated, the site is requested to print the complete set of source data needed for verification by the monitor. The printouts must be numbered, stapled together with a coversheet, signed and dated by the Investigator/delegate to confirm that these certified copies are exact copies having the same information as the original patient's data. The printouts will be considered as the official clinical study records.

In order to verify that the process the site uses to prepare certified copies is reliable, the monitor must verify and confirm that copies generated from electronic/computerised system are ALCOAC. If it were not possible for the monitor to observe this process, it would not be possible to rely on the site's certified copies and therefore the site cannot be selected for the clinical study.

The site master file must be stored in a secure and access-restricted area during and after the study. It must be kept by the site for as long as needed to comply with any applicable rules and regulations (ref. EU Clinical Trial Regulation 536/2014 when coming into force). If the site needs to transfer the site master file to another location and/or if site facility can no longer store the site master file the Investigator must inform the Sponsor immediately.

The site master file will contain all the essential documents that are required to always be up-to-date and filed at site as per ICH GCP Section 8. If the Investigator will change, or if the site will relocate, the monitor must be notified as soon as possible.

12. ETHICAL CONSIDERATIONS

12.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for GCP and the principles of the Declaration of Helsinki, and the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a US Investigational New Drug (IND) application will comply with US FDA regulations and applicable local, state, and federal laws. Studies conducted in the European Union (EU)/European Economic Area (EEA) will comply with the EU Clinical Trial Directive (2001/20/EC) and when coming into force the EU Clinical Trial Regulation (536/2014). In Germany, the requirement to secure approval from and provide notification to the BfS respectively, pursuant to §§ 31 ff. StrlSchG, will have been met.

12.2 INFORMED CONSENT

12.2.1 Patient Informed Consent Forms

The ICF and pre-screening ICF (collectively, the “Consent Forms”) will be provided to each investigational site. The pre-screening ICF applies only to the MTD/RP2D confirmatory cohort (Part A) and to the Phase IIA (expansion) part of the study.

The final IEC/IRB-approved Consent Forms must be provided to the Sponsor for Health Authority submission purposes according to local requirements.

For US only, according to HIPAA regulations, the individual institution may require that the Informed Consent and/or HIPAA Acknowledgement/Authorization Form be reviewed by their Privacy Board. In the instance of a Privacy Board review, approval must be received on the Informed Consent Form and Subject Acknowledgment/Authorization Form prior to initiating any study related procedures.

It is the responsibility of the Investigator/delegate to obtain informed consent according to ICH GCP guidelines and local regulations from each individual participating in this study and/or legal representative.

The Investigator/delegate will obtain a voluntary written consent from each patient after an appropriate explanation of the aims, methods, anticipated benefits, risks and any other aspect of the study relevant to the patient’s decision to participate. Consent Forms and all verbal study related information must be in a language fully comprehensible to the prospective patient.

Patients will be informed that they are free not to participate in the study and that they may withdraw consent to participate at any time. They will be told which alternative treatments are available if they refuse to take part and that such refusal will not prejudice future treatment. Site staff authorised to participate to the consent process and/or to obtain

consent from the patient and/or legal representative will be listed on Sponsor Delegation of Authority form. A study physician must always be involved in the consent process.

A written “Patient Information Sheet” will be given to each patient to complete the verbal information. This written form should be reviewed orally with the patient. Patient must be given ample opportunity to inquire about details of the study.

The Consent Forms must be signed and dated by the Investigator and the patient (or the patient’s legally authorised representative) before any exposure to a study-related procedure, including screening tests for eligibility. The Consent Forms must also be signed, personally dated and timed (if appropriate) by the authorised site staff listed on the Delegation of Authority form. A copy of the signed and dated Consent Forms is given to the patient and/or legal representative; the original is filed in the site documentation.

The medical records for each patient shall document the informed consent process including study reference, patient number, date/time (if applicable) when the patient was first introduced to the clinical study, date and time (if applicable) of consent, who consented the patient and any additional person present during the consent process (e.g., patient’s family member), copy of the signed ICF given to the patient / legal representative.

The Consent Forms should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the patient to participate. The final revised IEC/IRB-approved Consent Forms must be provided to the Sponsor for Health Authority submission purposes.

Patients must be re-consented to the most current version of the Consent Forms (or to a significant new information/findings addendum in accordance with applicable laws and IEC/IRB policy) during their participation in the study. For any updated or revised Consent Forms, the medical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study.

A copy of each signed and dated Consent Form must be given to the patient. The originals must remain in each patient’s study file or in the site file and must be available for verification by study monitors at any time.

12.2.2 Exploratory Biomarker Sub-Study Consent Form

Exploratory biomarker sub-studies will be integrated in the main consent form. If a patient opts not to participate in such sub-studies , this in no way affects the patient’s ability to participate in the main research Study.

12.3 ETHICS AND GOOD CLINICAL PRACTICE

Cellestia, delegate CRO Covance and the Investigators will ensure that the study is conducted in full compliance with ICH GCP Guidelines, the principles of the “Declaration of Helsinki” and with the laws and regulations of the country in which the research is conducted.

12.4 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the ICFs, any information to be given to the patient, and relevant supporting information must be submitted to the IEC/IRB by the Investigator or by CRO delegated by Cellestia (as required) of each participating investigational site/country and reviewed and approved by the IEC/IRB before the study is initiated. In addition, any patient recruitment materials must be approved by the IEC/IRB.

Approval from the committee must be documented in a dated letter, clearly identifying the study, the documents reviewed, and the date of approval.

The Investigator is responsible for providing written summaries of the status of the study to the respective investigational site/country IEC/IRB annually or more frequently in accordance with the requirements, policies, and procedures established by the IEC/IRB. Investigators are also responsible for promptly informing the IEC/IRB of any protocol amendments (see Section 13.5).

In addition to the requirements for reporting all adverse events to Sponsor or delegate CRO Covance, Investigators must comply with requirements for reporting serious adverse events to the local health authority and IEC/IRB. Investigators may receive written safety reports or other safety−related communications from the Sponsor or delegate CRO Covance. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with Health Authority requirements and the policies and procedures established by their IEC/IRB, and archived in the site's study file.

12.5 CONFIDENTIALITY

Sponsor and delegate CRO Covance maintain confidentiality standards by coding each patient enrolled in the study through the assignment of a unique patient identification number. Therefore, patient names and other personal identifiers are not included in the datasets that are transmitted to Sponsor or delegate CRO Covance.

Patient medical information obtained from this study is confidential and may only be disclosed to third parties as permitted by the ICF (or separate authorisation for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare, for treatment purposes.

Data generated by this study must be available for inspection upon request by representatives of the EMA, US FDA and other national and local Health Authorities, Sponsor monitors, auditors, representatives, and collaborators, and the IEC/IRB for each investigational site, as appropriate.

By signing this protocol, the Investigator agrees to keep all information provided by the Sponsor and delegate CRO Covance in strict confidence, and to request similar confidentiality from his or her staff and the IEC/IRB. Study documents provided by

Cellestia or delegate CRO Covance (including Investigator's Brochures [IBs], protocols, eCRFs, and other protocol-related documents) will be stored appropriately to ensure their confidentiality. The information provided by the Sponsor or delegate CRO Covance to the Investigator may not be disclosed to others without direct written authorisation from Sponsor or the delegate CRO Covance, except to the extent necessary to obtain informed consent from patients who wish to participate in the trial.

12.6 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor and the delegate CRO Covance with sufficient, accurate financial information in accordance with local regulations to allow Sponsor and the delegate CRO Covance to submit complete and accurate financial certification or disclosure statements to the appropriate Health Authorities. Investigators are responsible for providing information on financial interests during the course of the study and for one year after completion of the study.

13. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

13.1 STUDY DOCUMENTATION

The Investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including but not limited to the protocol, protocol amendments, ICFs, and documentation of IEC/IRB approval. In addition, at the end of the study, the Investigator will receive the patient data, which includes an audit trail containing a complete record of all changes to the data.

13.2 SITE AUDIT AND INSPECTIONS

Investigational site visits will be conducted by the Sponsor (or an authorised representative) or by the delegate CRO Covance for audit of study data, patients' medical records, and eCRFs. The Investigator will permit national and local Health Authorities, Cellestia and delegate CRO Covance monitors, representatives, and collaborators, and IECs/IRBs to inspect facilities and records relevant to this study.

13.3 MONITORING

Sponsor or delegate CRO Covance's monitor must contact and visit the Investigator regularly, and must be allowed, on request, to have access to all study-related documents and facilities used in the study, as well as all source documents needed, to verify the entries on the eCRFs; provided that patient confidentiality is maintained in agreement with local regulations.

On all documents submitted to the Sponsor or delegate CRO Covance, patients must not be identified by their names and date of birth, but by patient number only. The Investigator must keep a patient identification log showing the patient number, the patient's name, date of birth, and address or any other locally accepted identifiers. Documents identifying the patients (e.g., patients' signed ICFs) must not be sent to Sponsor or delegate CRO Covance, and must be kept by the Investigator in strict confidence.

The Investigator and sub-Investigators agree to cooperate with the monitor(s) to ensure that any issues detected in the course of these monitoring visits are resolved. If the patient is hospitalised or dies in a hospital other than the investigational site, the Investigator is responsible for contacting that hospital in order to document the serious adverse event.

An initiation visit will be performed before the first patient is screened. Following the initiation visit, a copy of the completed initiation visit report and follow-up letter will be provided to the Investigator and filed in the Investigator site file.

Monitoring visits and contacts will occur at regular intervals thereafter, and a close-out visit will be performed after study database closure.

A close-out visit will be performed for any initiated site when there are no more active patients and all follow-up issues have been resolved. In case a site does not enrol any patients, the close-out visit may be performed prior to study database closure at the discretion of Sponsor.

13.4 PUBLICATION OF DATA BY INVESTIGATORS AND PROTECTION OF TRADE SECRETS

The results of this study may be published or presented at scientific meetings. However, to ensure against inadvertent disclosure of Confidential Information or Unprotected Inventions, the Investigator will provide the Sponsor with an opportunity to review any proposed publication or any other type of disclosure before it is submitted or otherwise disclosed.

Study results will be documented in a CSR that will be signed by Sponsor representatives and the Investigator or its designee. The Investigator will have the opportunity to review the analysis of the data and to discuss the interpretation of the study results with the Sponsor prior to publication. The Sponsor or its delegate will post results from its clinical studies on external/national registries, as required by law.

The Investigator will provide manuscripts, abstracts, or the full text of any other intended disclosure (poster presentation, invited speaker or guest lecturer presentation, etc.) to the Sponsor at least 30 days before they are submitted for publication or otherwise disclosed.

The Investigator will, on request, remove any previously undisclosed Confidential Information (other than the study results themselves) before disclosure.

If the study is part of a multi-centre study, the Investigator agrees that the first publication is to be a joint publication covering all investigational sites. However, if a joint manuscript has not been submitted for publication within 12 months of completion or termination of the study at all participating sites, the Investigator is free to publish separately, subject to the other requirements outlined in this section.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements. The list of authors of any publication of study results may include representatives of Sponsor, and will be determined by mutual agreement.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of data from this study will become and remain the exclusive and unburdened property of the Sponsor, unless agreed otherwise.

Publication of study results is also provided for in the Clinical Study Agreement between Sponsor/the delegate CRO Covance and the institution. In this section the defined terms shall have the meanings given to them in the Clinical Study Agreement.

13.5 PROTOCOL AMENDMENTS

Any change to a protocol must be considered to be an amendment if the documents have already been submitted to IECs/IRBs or Health Authorities. An amendment could therefore occur before or after the approval of these documents by IECs/IRBs or Health Authorities. Each amendment must be documented in writing and approved by Sponsor.

Changes to the Core Patient Information and Informed Consent requested by IECs/IRBs are not considered to be formal amendments, as long as they do not significantly change the core document or affect the protocol.

13.5.1 Substantial Amendments

A substantial amendment is required for significant changes not stipulated by the protocol (e.g., new data affecting the safety of patients, and changes to the objectives or endpoints of the study, eligibility criteria, study assessments) with or without the need to modify the Core Patient Information and Informed Consent.

Any substantial protocol amendments will be submitted to the IEC/IRB and to regulatory authorities in accordance with local regulatory requirements. Approval must be obtained from the IEC/IRB and regulatory authorities (as required according to local regulations) before implementation of any changes, except for those changes deemed necessary to eliminate an immediate hazard to patients or any non-substantial changes, as defined by regulatory requirements.

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Appendix 1 Schedule of Assessments for Part A

Table 1 Schedule of Assessments (Part A)

Study Period	Pre-screening*	Screening	Baseline	Six cycle treatment period (28-day cycles, until PD or toxicity)													EOT [29]	Safety follow-up[30]	After Cycle 6 (28-day cycles, until PD or toxicity)	Un-scheduled visit
				Cycle 1 (DLT Period)							Cycle 2				Cycles 3 to 6				Cycle n	
Visit No.[1]	-	SCR[2]	BL	1	2	3	4	5	6	7	8	8a	8b	9	10	…	EOT	EOS-A	Cycle n	UNSCHED
Study Day[1]	-	-	-	1	2	3	8	9	15	22	29	30	36	43	57	...				
Day of cycle	-	-28 to -4	-3 to -1	1	2	3	8	9	15	22	1	2	8	15	1	15			1	
Overnight hospital stays				X[3]			(X)													
Assessment																				
Informed Consent[4]	X*	X																		
Demography		X																		
Medical history[5]		X																		
Inclusion/Exclusion		X	X																	
Serum pregnancy test[6]		X																		
Urine pregnancy test[6]			X						X		X				X		X	X	X	X
Vital Signs and body measurement																				
Body height (cm)		X																		
Body weight (kg)			X								X				X		X	X		X
ECOG perf. Status[7]		X	X		X	X	X		X	X	X			X	X	X	X	X	X	X
Physical examination[8]		X	X	X	X	X	X		X	X	X			X	X	X	X		X	X
Body temperature			X	X	X	X	X		X	X	X				X		X	X	X	X
Respiratory rate			X		X	X	X		X	X	X				X		X			

Study Period	Pre-screening*	Screening	Baseline	Six cycle treatment period (28-day cycles, until PD or toxicity)													EOT [29]	Safety follow-up [30]	After Cycle 6 (28-day cycles, until PD or toxicity)	Un-scheduled visit
				Cycle 1 (DLT Period)							Cycle 2				Cycles 3 to 6				Cycle n	
Visit No.[1]	-	SCR[2]	BL	1	2	3	4	5	6	7	8	8a	8b	9	10	…	EOT	EOS-A	Cycle n	UNSCHED
Study Day[1]	-	-	-	1	2	3	8	9	15	22	29	30	36	43	57	...				
Day of cycle	-	-28 to -4	-3 to -1	1	2	3	8	9	15	22	1	2	8	15	1	15			1	
Cardiac Assessments																				
Blood pressure		X		X	X	X	X		X	X	X			X	X	X	X	X	X	X
Heart rate		X		X	X	X	X		X	X	X			X	X	X	X	X	X	X
12-lead ECG[9]		X		X			X		X	X	X			X	X		X		X	X
Holter monitoring[9]			X[9]	X			X				X						X			
ECHO or MUGA for LVEF assessment[9]			X[9]				X								X[9a]		X			X
Cardiac serum markers[10]			X[10]						X		X			X	X	X	X		X	X
Other Assessments																				
Ophthalmological exams[11]		X															X	X[12]		
Clinical chemistry[13]		X		X		X	X		X	X	X			X	X	X	X		X	X
Hematology[13]		X		X		X	X		X	X	X			X	X	X	X		X	X
Coagulation[13]		X		X		X	X		X	X	X			X	X	X	X		X	X
Serology		X																		
Urinalysis		X		X		X	X		X	X	X			X	X	X	X		X	X
PK profile blood sampling[14]				X	X	X	X	X	X	X	X			X	X	X				X
PK sub-study												X								
Blood sampling for genotype testing		X		X																
Stool sample[15]											◄	———	———	►						

Study Period	Pre-screening*	Screening	Baseline	Six cycle treatment period (28-day cycles, until PD or toxicity)													EOT [29]	Safety follow-up [30]	After Cycle 6 (28-day cycles, until PD or toxicity)	Un-scheduled visit
				Cycle 1 (DLT Period)							Cycle 2				Cycles 3 to 6				Cycle n	
Visit No.[1]	-	SCR[2]	BL	1	2	3	4	5	6	7	8	8a	8b	9	10	…	EOT	EOS-A	Cycle n	UNSCHED
Study Day[1]	-	-	-	1	2	3	8	9	15	22	29	30	36	43	57	...				
Day of cycle	-	-28 to -4	-3 to -1	1	2	3	8	9	15	22	1	2	8	15	1	15			1	
Chest X-ray [16]			X																	
Efficacy Assessment (PFS)																	X			
Survival follow-up [17]																	X	X	X	
Concomitant medication		X	X	X	X	X	X	X	X	X	X			X	X	X	X	X	X	X
Safety assessment incl. AE/SAEs [18]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Other Assessments (Solid Tumours only)																				
Archival tumour biopsies[19]	X*	X																		
Fresh tumour biopsies[20]			X											X			X			X
Liquid biopsy			X						X		X			X	X		X			X
Tumour assessment (CT/MRI/PET-CT) [21]			X											X		X[22]	X		X[22]	X
Hair follicles [23]				X							X			X	X					
Whole blood, plasma[23a]				X							X			X	X					
Other Assessments (T-ALL/T-LBL only)																				
Bone marrow biopsy and/or aspirate[24]		X									X		X		X				X	X
Lumbar puncture[25]		X									X				X				X	X
CSF sample[26]											X									
Tumour assessment (PET-CT)[27]			X								X				X		X		X	X

Study Period	Pre-screening*	Screening	Baseline	Six cycle treatment period (28-day cycles, until PD or toxicity)													EOT [29]	Safety follow-up [30]	After Cycle 6 (28-day cycles, until PD or toxicity)	Un-scheduled visit
				Cycle 1 (DLT Period)							Cycle 2				Cycles 3 to 6				Cycle n	
Visit No.[1]	-	SCR[2]	BL	1	2	3	4	5	6	7	8	8a	8b	9	10	…	EOT	EOS-A	Cycle n	UNSCHED
Study Day[1]	-	-	-	1	2	3	8	9	15	22	29	30	36	43	57	...				
Day of cycle	-	-28 to -4	-3 to -1	1	2	3	8	9	15	22	1	2	8	15	1	15			1	
Liquid biopsy			X						X		X				X		X			X
Whole blood, plasma[28]				X							X				X					
Whole blood and Saliva	X*		X*																	

Abbreviations: BL, baseline; CT, computed tomography; CSF, cerebrospinal fluid; DLT, Dose limiting toxicity; ECG, electrocardiogram; ECHO, echocardiogram; ECOG, Eastern Cooperative Oncology Group; EOS-A, End of Study Part A; EOT, End of Treatment; F-up; Follow-up; ICF, Informed Consent Form; LVEV, left ventricular ejection fraction; MRI, magnetic resonance imaging; MUGA, multigated acquisition; PD, pharmacodynamics; PE, physical examination; PET-CT, positron emission tomography–computed tomography; PK, pharmacokinetic; SAE, serious adverse event; SCR, screening.

* Pre-screening: it applies ONLY to the MTD/RP2D confirmatory cohort for patients whose Notch pathway activation status is not known; the patient must sign the pre-screening consent form. For solid tumour patients: if there is no sufficient archival tumour sample available or if older than 6 months prior to the pre-screening, a fresh pre-dose tumour biopsy is to be obtained. For T-ALL/T-LBL patients: when Notch status in unknown the whole blood and saliva will be collected at pre-screening, otherwise at BL to confirm the Notch status.

1 Visit windows: DLT treatment phase (first cycle): ± 0 day; cycles 2-6: ± 3 days. After cycle 6, visits are planned every 4 weeks (± 7 days) if no medical issue or complication occurred in the previous cycles.

2 Screening: may be performed in one or more visits.

3 Overnight stays at C1D1: it may not be required if reduced ECG&PK sampling is implemented.

4 Informed Consent: must be obtained prior to undergoing any study-related procedure.

5 Medical history (including relevant disease history)

6 Pregnancy test: for women of childbearing potential only. The serum pregnancy test must be performed within a maximum of 7 days of first CB-103 administration. The urine pregnancy test will also be done whenever one menstrual cycle is missed during the active treatment period (or when potential pregnancy is otherwise suspected) to confirm the patient has not become pregnant during the study.

7 ECOG: performance scale is available in Table 13 of the protocol. ECOG performance status will be assessed within 14 days prior to the first administration of CB-103, during the screening period.

8 Physical examination: will be performed at the screening, baseline and at the indicated patient visit, even if administration of study medication is being withheld. More frequent examinations may be performed at the Investigator's discretion, if medically indicated. If the baseline examinations are performed within 72 hours prior to the first administration of CB-103, they need not be repeated on C1D1, except for patients with T-ALL/T-LBL who need to repeat the PE at C1D1.

[9] 12-lead ECG: at each time point, three consecutive high-quality (without artefacts/lead misplacement) 12-lead ECGs will be performed approx.1-2 minutes apart. Refer to Table 14 and Table 16 of the protocol for further details. ECG and PK blood samples need to be obtained at the same time-points and the ECG should be performed just prior to the drawing of the blood. A 15-minute window for ECG collection is allowed around each nominal ECG time point except for the 24 hour ECG time point, where a 1 hour window is allowed.

[9] Holter monitoring: 3-lead Holter ECG monitoring with 24 hours ECG profiles. Refer to Table 14 and Table 16 of the protocol for the scheduling and further details. At BL allowed from Day -7. Holter recording should start 1 to 2 hours before the CB-103 intake.

[9] ECHO/MUGA: allowed from Day -7. It may be repeated at the Investigator's discretion if there are signs or symptoms of cardiotoxicity.

[9a] Between cycles 3 and 6 the ECHO/MUGA is only requested on C3D1.

[10] Cardiac markers: allowed from Day -7. They will be performed locally and may be repeated at the Investigator's discretion if there are signs or symptoms of cardiotoxicity.

[11] Ophthalmological exams: they will be performed by an ophthalmologist/eye doctor at screening, End of Treatment and when clinically indicated. Refer to Section 8.2.2.2

[12] Ophthalmological exams: will be done at the safety follow-up if the patient had ocular symptoms during the treatment phase

[13] Clinical chemistry/Haematology/coagulation will be performed locally; at screening (within 14 days of C1D1), and at the indicated visits. Refer to Section 8.2.4 of the protocol for the testing required. May be performed within a window of ± 24 hours during the DLT period and throughout all treatment cycles.

[14] PK time sampling: blood sampling will be collected as per the schedule and time window indicated in Section 8.4 of the protocol. Changes to the PK sampling scheme may be required based on emerging data. In case of twice daily intake of CB-103 the sampling schedule is slightly adjusted for cycle 1 (refer to Section 8.4.1)

[15] Stool specimen collection: only one sample is to be possibly collected during cycle 2 and 3.

[16] Chest X-ray: a baseline chest x-ray should be performed and be repeated if clinically indicated. If a chest CT is performed at baseline to assess tumour lesions, then a chest X-ray may not be required.

[17] Survival follow-up: it is planned for one year, every three months, after the End-of-Study visit or after the last treatment cycle (if outside of the 6 cycles period).

[18] Between the signature of the ICF and the initiation of CB-103, only the SAEs caused by study-related procedures will be reported; any other AEs will be only recorded on the Medical History in the eCRF. After initiation of CB-103, all AEs/SAEs will be reported until four weeks after the last dose of CB-103.

[19] Archival tumour biopsy tissue (Solid Tumour): for the patients enrolled in Part A (dose-escalation) it should be not older than 6 months prior to screening and if not available a pre-dose fresh tumour biopsy must be taken. If the lesion is not accessible for a fresh tumour biopsy, a liquid biopsy may be used after confirmation with the Sponsor.

[20] Fresh tumour biopsy (Solid Tumour): mandatory in the MTD/RP2D confirmatory cohort of Part A of the study; to be collected pre-dose at BL, then on-treatment at C2D15 ± 3 days and at disease progression or when clinically indicated. The pre-dose fresh biopsy is not required if already obtained during the pre-screening. In individual cases, where the lesion is not accessible for a fresh tumour biopsy, a liquid biopsy may be used after confirmation with the Sponsor

[21] Tumour assessments (Solid Tumours): will be performed at baseline, then 6 weeks after the first administration of CB-103 (i.e., day 15 of cycle 2) then see note 22. For breast cancer patients enrolled in the MTD/RP2D confirmatory cohort (refer to Appendix 9) the CT scan will be replaced with PET-CT (or add PET) at baseline (and if positive, also at C2D15, before tumour biopsy). A time window of ± 3 days is allowed for the tumour assessments. A wider time window is allowed only at baseline however assessments should be performed as close as possible to the 1st drug administration and if feasible, not later than 2 weeks prior to the 1st drug administration.

[22] Tumour assessments (Solid Tumours): after cycle 2 will be performed, every 8 weeks and after cycle 6 every 12 weeks until EOT or disease progression/overall survival. The response will be determined as per the RECIST 1.1 and, if applicable, with confirmation as per RECIST.

[23] Hair follicles (Solid Tumour): samples will be collected for solid tumour indications only as per the schedule and time window indicated in Section 8.5.2. In the MTD/RP2D confirmatory cohort they will be collected only on selected patient groups.

[23a] Whole blood, plasma (Solid Tumour): samples will be collected as per the schedule and time window indicated in Section 8.5.3.

[24] Bone marrow biopsy and/or aspirate (T-ALL/T-LBL): a bone marrow biopsy and/or aspirate will be obtained to assess bone marrow cellularity and to determine the percentage of leukemic blasts, including assessment of minimal residual disease (MRD) to confirm remission status. At the baseline assessment, bone marrow biopsy and/or aspirate is within 2 weeks and no less than 1 day before the first dose of CB-103. Then patients are assessed for disease response by bone marrow biopsy and/or aspirate on day 29. If the blasts in bone marrow are <5% but marrow is hypocellular (cellularity ≤15%) on day 29 (±3 days), then a repeat bone marrow biopsy and/or aspirate is obtained 1 week

later to assess response; if residual leukaemia is present, repeated bone marrow biopsy and/or aspirate will be obtained per 28 days until CR or CRi. A response (CR or CRi) must be confirmed no less than 28 days from the first evidence of response by bone marrow core biopsy as indicated. In case of CR or CRi confirmed by bone marrow biopsy and/or aspirate on 2 bone marrow biopsy and/or aspirate assessments no less than 28 days apart (the interval between assessments), bone marrow biopsy and/or aspirate assessment may be increased to every 8 weeks until to PD or EOS (whichever is earlier).

[25] Lumbar puncture (T-ALL/T-LBL) for prophylactic intrathecal therapy: if prophylactic intrathecal therapy is foreseen by the treating physician, a lumbar puncture may be performed up to 3 days before the first dose of CB-103, and, depending on the response of the patient, may be repeated at the discretion of the treating physician at the end of the first cycle of treatment with CB-103, and at the end of any subsequent cycle of treatment with CB-103, if more than one is warranted.

[26] CSF sample (T-ALL/T-LBL): in patients in whom a lumbar puncture is done (e.g., for intrathecal prophylaxis) a CSF sample should be taken on or around cycle 1 day 28, if clinically feasible, to determine the exposure of CB-103 in the CSF.

[27] Tumour assessments (T-ALL/T-LBL): only for patients with extramedullary disease or as clinically indicated a PET-CT will be performed at baseline and if positive, also at C2D1, C3D1 and thereafter as clinically indicated. A time window of ± 3 days is allowed for the tumour assessments. A wider time window is allowed only at baseline; however, assessments should be performed as close as possible to the 1st drug administration and if feasible, not later than 2 weeks prior to the 1st drug administration.

[28] Whole blood, plasma (T-ALL/T-LBL): samples will be collected as per the schedule and time window indicated in Section 8.5.3.

[29] EOT: within 14 days after the last administration of CB-103. All participating patients must complete this visit even if they have had to prematurely discontinue treatment with CB-103.

[30] Safety Follow-up: within 28 days after the last dose of CB-103. All patients must have this visit, even if they have prematurely discontinued CB-103 treatment.

Appendix 2 Schedule of Assessments for Part B (Expansion)

Table 2 Schedule of Assessments (Part B)

Study Period	Pre-screening*	Screening	Baseline	Twelve cycle treatment period (28-day cycles, until PD or toxicity)													EOT[26]	Safety follow-up[27]	After cycle 12 (28-day cycles, until PD or toxicity)[28]	Un-scheduled visit
				Cycle 1							Cycle 2				Cycles 3 to 12				Cycle n	
Visit No.[1]	-	SCR[2]	BL	1	2	3	4	5	6	7	8	8a	8b	9	10	…	EOT	EOS	Cycle n	UNSCHED
Study Day[1]	-	-	-	1	2	3	8	9	15	22	29	30	36	43	57	...				
Day of cycle	-	-28 to -4	-3 to -1	1	2	3	8	9	15	22	1	2	8	15	1	15			1	
Overnight hospital stays						(X)														
Assessment																				
Informed Consent[3]	X*	X																		
Demography		X																		
Medical history[4]		X																		
Inclusion/Exclusion		X	X																	
Serum pregnancy test[5]		X																		
Urine pregnancy test[5]			X						X		X				X		X	X	X	X
Vital Signs and body measurement																				
Body height (cm)		X																		
Body weight (kg)			X								X				X		X	X		X
ECOG perf. Status[6]		X	X				X		X	X	X			X	X	X	X	X	X	X
Physical examination[7]		X	X	X			X		X	X	X			X	X	X	X		X	X
Body temperature			X	X			X		X	X	X				X		X	X	X	X

Study Period	Pre-screening*	Screening	Baseline	Twelve cycle treatment period (28-day cycles, until PD or toxicity)													EOT[26]	Safety follow-up[27]	After cycle 12 (28-day cycles, until PD or toxicity)[28]	Un-scheduled visit
				Cycle 1							Cycle 2				Cycles 3 to 12				Cycle n	
Visit No.[1]	-	SCR[2]	BL	1	2	3	4	5	6	7	8	8a	8b	9	10	…	EOT	EOS	Cycle n	UNSCHED
Study Day[1]	-	-	-	1	2	3	8	9	15	22	29	30	36	43	57	...				
Day of cycle	-	-28 to -4	-3 to -1	1	2	3	8	9	15	22	1	2	8	15	1	15			1	
Respiratory rate			X				X		X	X	X				X		X			
Cardiac Assessments																				
Blood pressure		X		X			X		X	X	X			X	X	X	X	X	X	X
Heart rate		X		X			X		X	X	X			X	X	X	X	X	X	X
12-lead ECG[8]		X		X			X		X	X	X				X		X		X	X
Holter monitoring[8]			X[8]																	
ECHO or MUGA for LVEF assessment[8]			X[8]				X								X[8a]		X			X
Cardiac serum markers[9]			X[9]						X		X			X	X	X	X		X	X
Other Assessments																				
Ophthalmological exams[10]		X															X	X[11]		
Clinical chemistry[12]		X		X			X		X	X	X			X	X	X	X		X	X
Hematology[12]		X		X			X		X	X	X			X	X	X	X		X	X
Coagulation[12]		X		X			X		X	X	X			X	X	X	X		X	X
Serology		X																		
Urinalysis		X		X			X		X	X	X			X	X	X	X		X	X
PK profile blood sampling[13]				X	X	X	X	X	X	X	X			X	X	X				X
PK sub-study												X								
Blood sampling for genotype testing		X		X																

Study Period	Pre-screening*	Screening	Baseline	Twelve cycle treatment period (28-day cycles, until PD or toxicity)													EOT[26]	Safety follow-up[27]	After cycle 12 (28-day cycles, until PD or toxicity)[28]	Un-scheduled visit
				Cycle 1							Cycle 2				Cycles 3 to 12				Cycle n	
Visit No.[1]	-	SCR[2]	BL	1	2	3	4	5	6	7	8	8a	8b	9	10	…	EOT	EOS	Cycle n	UNSCHED
Study Day[1]	-	-	-	1	2	3	8	9	15	22	29	30	36	43	57	...				
Day of cycle	-	-28 to -4	-3 to -1	1	2	3	8	9	15	22	1	2	8	15	1	15			1	
Chest X-ray[14]			X																	
Efficacy Assessment (PFS)																	X			
Survival follow-up[15]																	X	X	X	
Concomitant medication		X	X	X	X	X	X	X	X	X	X			X	X	X	X	X	X	X
Safety assessment incl. AE/SAEs[16]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Other Assessments (Solid Tumours only)																				
Archival tumour biopsies	X*	X																		
Fresh tumour biopsies[17]			X											X			X			X
Liquid biopsy			X						X		X			X	X		X			X
Tumour assessment (CT/MRI/PET-CT)[18]			X											X		X[19]	X		X[19]	X
Hair follicles[20]				X							X			X	X					
Whole blood, plasma[20a]				X							X			X	X					
Other Assessments (T-ALL/T-LBL only)																				
Bone marrow biopsy and/or aspirate[21]		X									X		X		X				X	X
Lumbar puncture [22]		X									X				X				X	X
CSF sample[23]											X									
Tumour assessment (PET-CT)[24]			X								X				X		X	X	X	X

Study Period	Pre-screening*	Screening	Baseline	Twelve cycle treatment period (28-day cycles, until PD or toxicity)													EOT[26]	Safety follow-up[27]	After cycle 12 (28-day cycles, until PD or toxicity)[28]	Un-scheduled visit
				Cycle 1							Cycle 2				Cycles 3 to 12				Cycle n	
Visit No.[1]	-	SCR[2]	BL	1	2	3	4	5	6	7	8	8a	8b	9	10	…	EOT	EOS	Cycle n	UNSCHED
Study Day[1]	-	-	-	1	2	3	8	9	15	22	29	30	36	43	57	...				
Day of cycle	-	-28 to -4	-3 to -1	1	2	3	8	9	15	22	1	2	8	15	1	15			1	
Liquid biopsy			X						X		X				X		X			X
Whole blood, plasma[25]				X							X				X					
Whole blood, Saliva	X*		X*																	

Abbreviations: CT, computed tomography; CSF, cerebrospinal fluid; DLT, Dose limiting toxicity; ECG, electrocardiogram; ECHO, echocardiogram; ECOG, Eastern Cooperative Oncology Group; EOS, End of Study; EOT, End of Treatment; F-up; Follow-up; LVEV, left ventricular ejection fraction; MRI, magnetic resonance imaging; MUGA, multigated acquisition; PD, pharmacodynamics; PE, physical examination; PET-CT, positron emission tomography–computed tomography; PK, pharmacokinetic; SAE, serious adverse event; SCR, screening; BL, baseline; ICF, Informed Consent Form.

* Pre-screening: the patient whose Notch pathway activation status is not known must sign the pre-screening consent form. For solid tumour patients: if there is no sufficient archival tumour sample available or if older than 6 months prior to the pre-screening, a fresh pre-dose tumour biopsy is to be obtained. For T-ALL/T-LBL patients: when Notch status in unknown the whole blood and saliva will be collected at pre-screening, otherwise at BL to confirm the Notch status.

1 Visit windows: treatment phase cycles 1-6: ± 3 days. After cycle 6 visits are planned every 4 weeks (± 7 days) if no medical issue or complication occurred in the previous cycles.
2 Screening: may be performed in one or more visits.
3 Informed Consent: must be obtained prior to undergoing any study-related procedure.
4 Medical history (including relevant disease history)
5 Pregnancy test: for women of childbearing potential only. The serum pregnancy test must be performed within a maximum of 7 days of first CB-103 administration. The urine pregnancy test will also be done whenever one menstrual cycle is missed during the active treatment period (or when potential pregnancy is otherwise suspected) to confirm the patient has not become pregnant during the study.
6 ECOG: performance scale is available in Table 13 of the protocol. ECOG performance status will be assessed within 14 days prior to the first administration of CB-103, during the screening period.
7 Physical examination: will be performed at the screening, baseline and at the indicated patient visit, even if administration of study medication is not being held. More frequent examinations may be performed at the Investigator's discretion, if medically indicated. If the baseline examinations are performed within 72 hours prior to the first administration of CB-103, they need not be repeated on C1D1, except for patients with T-ALL/T-LBL who need to repeat the PE at C1D1.
8 12-lead ECG: at each time point, three consecutive high-quality (without artefacts/lead misplacement) 12-lead ECGs will be performed approx.1-2 minutes apart. Refer to Table 15 and Table 17 of the protocol for further details. ECG and PK blood samples need to be obtained at the same time-points and the ECG should be performed just prior to the drawing of the blood. A 15-minute window for ECG collection is allowed around each nominal ECG time point except for the 24 hour ECG time point, where a 1 hour window is allowed.

[8] Holter monitoring: 3-lead Holter ECG monitoring with 24 hours ECG profiles. Refer to Table 15 and Table 17 of the protocol for the scheduling and further details. At BL allowed from Day -7.

[8] ECHO/MUGA: At BL allowed from Day -7. These assessments may be repeated at the Investigator's discretion if there are signs or symptoms of cardiotoxicity.

[8a] Between cycles 3 and 12 the ECHO/MUGA is only requested on C3D1.

[9] Cardiac markers: At BL allowed from Day -7. They will be performed locally and may be repeated at the Investigator's discretion if there are signs or symptoms of cardiotoxicity.

[10] Ophthalmological exams: they will be performed by on ophthalmologist/eye doctor at screening, End of Treatment and when clinically indicated. Refer to Section 8.2.2.2.

[11] Ophthalmological exams: will be done at the safety follow-up if the patient had ocular symptoms during the treatment phase.

[12] Clinical chemistry/Haematology/coagulation: will be performed locally; at the screening (within 14 days of C1D1), and at the indicated visits. Refer to Section 8.2.4 of the protocol for the testing required. May be performed within a window of ± 24 hours throughout all treatment cycles.

[13] PK time sampling: blood sampling will be collected as per the schedule and time window indicated in Section 8.4 of the protocol. Changes to the PK sampling scheme may be required based on emerging data. In case of twice daily intake of CB-103 the sampling schedule is slightly adjusted for cycle 1 (refer to Section 8.4.1)

[14] Chest X-ray: a baseline chest x-ray should be performed and be repeated if clinically indicated. If a chest CT is performed at baseline to assess tumour lesions, then a chest X-ray may not be required.

[15] Survival follow-up: it is planned for one year, every three months, after the End-of-Study visit or after the last treatment cycle (if outside of the 12 cycles period), then every 6 months for the second year.

[16] Between the signature of the ICF and the initiation of CB-103, only the SAEs caused by study-related procedures will be reported; any other AEs will be recorded on the Medical History in the eCRF. After initiation of CB-103, all AEs/SAEs will be reported until 4 weeks after the last dose of CB-103.

[17] Fresh tumour biopsy (Solid Tumour): to be collected pre-dose during the screening/BL period, then on-treatment at C2D15 ± 3 days and at disease progression or when clinically indicated. The pre-dose fresh biopsy is not required if obtained during the pre-screening. If the lesion is not accessible for a fresh tumour biopsy, a liquid biopsy may be used after confirmation with the Sponsor.

[18] Tumour assessments (Solid Tumours): will be performed at baseline, then 6 weeks after the first administration of CB-103 (i.e., day 15 of cycle 2), then see note 19. For breast cancer patients enrolled in the MTD/RP2D confirmatory cohort (refer to Appendix 9) the CT scan will be replaced with PET-CT (or add PET) at baseline (and if positive, also at C2D15, before tumour biopsy). A time window of ± 3 days is allowed for the tumour assessments. A wider time window is allowed only at baseline however assessments should be performed as close as possible to the 1st drug administration and if feasible, not later than 2 weeks prior to the 1st drug administration.

[19] Tumour assessments (Solid Tumours): after cycle 2 will be performed, every 8 weeks and after cycle 6 every 12 weeks until EOT or disease progression/overall survival. The response will be determined as per the RECIST 1.1 and, if applicable, with confirmation as per RECIST.

[20] Hair follicles (Solid Tumour): samples will be collected for solid tumour indications only and only in selected patient groups as per the schedule and time window indicated in Section 8.5.2.

[20a] Whole blood, plasma (Solid Tumour): samples will be collected as per the schedule and time window indicated in Section 8.5.3.

[21] Bone marrow biopsy and/or aspirate (T-ALL/T-LBL): a bone marrow biopsy and/or aspirate will be obtained to assess bone marrow cellularity and to determine the percentage of leukemic blasts, including assessment of minimal residual disease (MRD) to confirm remission status. At the baseline assessment by bone marrow biopsy and/or aspirate is within 2 weeks and no less than 1 day before the first dose of CB-103.
Then Patients are assessed for disease response by Bone marrow biopsy and/or aspirate on day 29,if the blasts in bone marrow <5% but marrow is hypocellular (cellularity ≤ 15%) on day 29 (±3 days), then a repeat bone marrow biopsy and/or aspirate is obtained 1 week later to assess response; if residual leukaemia is present, repeated bone marrow biopsy and/or aspirate will be obtained per 28 days until to CR or Cri. A response (CR or Cri) must be confirmed no less than 28 days from the first evidence of response by bone marrow core biopsy as indicated. In case of CR or Cri confirmed by bone marrow biopsy and/or aspirate on 2 bone marrow biopsy and/or aspirate assessments no less than 28 days apart the interval between assessments, bone marrow biopsy and/or aspirate assessment may be increased to every 8 weeks until to PD or EOS (whichever is earlier).

[22] Lumbar puncture (T-ALL/T-LBL) for prophylactic intrathecal therapy: if prophylactic intrathecal therapy is foreseen by the treating physician, a lumbar puncture may be performed up to 3 days before the first dose of CB-103, and, depending on the response of the patient, may be repeated at the discretion of the treating physician at the end of the first cycle of treatment with CB-103, and at the end of any subsequent cycle of treatment with CB-103, if more than one is warranted.

[23] CSF sample (T-ALL/T-LBL): In patients in whom a lumbar puncture is done (e.g., for intrathecal prophylaxis) a CSF sample should be taken on or around cycle 1 day 28, if clinically feasible, to determine the exposure of CB-103 in the CSF.

[24] Tumour assessments (T-ALL/T-LBL): only for patients with extramedullary disease or as clinically indicated a PET-CT will be performed at baseline and if positive, also at C2D1, C3D1 and thereafter as clinically indicated. A time window of ± 3 days is allowed for the tumour assessments. A wider time window is allowed only at baseline however assessments should be performed as close as possible to the 1st drug administration and if feasible, not later than 2 weeks prior to the 1st drug administration.

[25] Whole blood, plasma (T-ALL/T-LBL): samples will be collected as per the schedule and time window indicated in Section 8.5.3.

[26] EOT: within 14 days after the last administration of CB-103. All participating patients must complete this visit even if they have had to prematurely discontinue treatment with CB-103.

[27] Safety Follow-up: within 28 days after the last dose of CB-103 after which the End-of-Study is reached. All patients must have this visit, even if they have prematurely discontinued CB-103 treatment.

[28] Continuation after cycle 12: patients on treatment at that time may be eligible to continue treatment with CB-103. The Sponsor reserves the unilateral right, at its sole discretion, to determine whether to supply CB-103, and by what mechanism, after the end of study is reached or termination of the trial and before it is commercially available.

Appendix 3 Overview of Selected Cancer Indications for the Study

Table 1 Solid Tumour Indications

INDICATION (SOLID TUMOURS)	NOTCH-EXPRESSION (MODE OF ACTIVATION)
Breast Cancer (TNBC)	• 9% chromosomal translocations (NOTCH1/2)[1] • 13% GOF mutations (NOTCH1-3)[2,3] • 46% JAG1/NOTCH1,3 up-regulation (resistant/refractory TNBC) [4]
Breast Cancer (ER+, HER2-)	• 38% NOTCH4 upregulated[5] • 14% NUMB deficient/reduced[6]
Breast Cancer (HER2+, ER-)	• 70% of Trastuzumab resistance leading to NOTCH up-regulation[7]
Colorectal Cancer (CRC)	• 70% NOTCH up-regulation[8]
Hepatocellular Carcinoma (HCC)	• 5% JAG1 / NOTCH2 overexpression[9]
Osteosarcoma	• 11% NOTCH3 amplification[10]
Adenoid Cystic Carcinoma	• 18% NOTCH1 GOF mutations[11,12] • 40% NOTCH pathway alterations[12,13]
Malignant Glomus Tumour[14]	• 52% with NOTCH2 gene rearrangements • 9% with NOTCH3 gene rearrangements
T-cell lymphoblastic leukaemia/ lymphoma (T-ALL/T-LBL)	• 55% NOTCH1 GOF mutations[15] • ~30% FBXW7 LOF mutations[16]

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Appendix 4 QT Prolonging Drugs with Risk of Torsades de Pointes.

Table 1 List of prohibited QT prolonging drugs with a known risk to induce Torsades de Pointes

Drug	QT risk (*)	Comment
Aclarubicin	Known risk for TdP	Not available in US
Amiodarone	Known risk for TdP	Females >Males, TdP risk regarded as low
Anagrelide	Known risk for TdP	
Arsenic trioxide	Known risk for TdP	
Astemizole	Known risk for TdP	Removed from US market
Azithromycin	Known risk for TdP	Females>Males
Bepridil	Known risk for TdP	Removed from US market; Females>Males
Chloroquine	Known risk for TdP	
Chlorpromazine	Known risk for TdP	
Cilostazol	Known risk for TdP	
Ciprofloxacin	Known risk for TdP	
Cisapride	Known risk for TdP	Removed from US market; Females>Males
Citalopram	Known risk for TdP	
Clarithromycin	Known risk for TdP	
Cocaine	Known risk for TdP	
Disopyramide	Known risk for TdP	Females>Males
Dofetilide	Known risk for TdP	
Domperidone	Known risk for TdP	Not available in the US
Donepezil	Known risk for TdP	
Dronedarone	Known risk for TdP	
Droperidol	Known risk for TdP	
Erythromycin	Known risk for TdP	
Escitalopram	Known risk for TdP	
Flecainide	Known risk for TdP	
Fluconazole	Known risk for TdP	
Gatifloxacin	Known risk for TdP	Removed from US market
Grepafloxacin	Known risk for TdP	Removed from US market
Halofantrine	Known risk for TdP	Not available in US; Females>Males
Haloperidol	Known risk for TdP	When given i.v. or at higher than recommended doses, risk of sudden death, QT prolongation and torsades increased
Hydroquinidine	Known risk for TdP	Not available in US
Hydroxychloroquine	Known risk for TdP	
Ibogaine	Known risk for TdP	Not available in US
Ibutilide	Known risk for TdP	Females>Males
Levofloxacin	Known risk for TdP	
Levomepromazine	Known risk for TdP	Not available in the US
Levomethadyl acetate	Known risk for TdP	Removed from US market
Levosulpiride	Known risk for TdP	Not available in US
Mesoridazine	Known risk for TdP	Removed from US market

Drug	QT risk (*)	Comment
Methadone	Known risk for TdP	Females>Males
Moxifloxacin	Known risk for TdP	
Nifekalant	Known risk for TdP	Not available in US
Ondansetron	Known risk for TdP	
Oxaliplatin	Known risk for TdP	
Papaverine HCl	Known risk for TdP	Intracoronary
Pentamidine	Known risk for TdP	Females>Males
Pimozide	Known risk for TdP	Females>Males
Probucol	Known risk for TdP	Removed from US market
Procainamide	Known risk for TdP	
Propofol	Known risk for TdP	
Quinidine	Known risk for TdP	Females>Males
Roxithromycin	Known risk for TdP	Not available in US
Sevoflurane	Known risk for TdP	
Sotalol	Known risk for TdP	Females>Males
Sparfloxacin	Known risk for TdP	Removed from US market
Sulpiride	Known risk for TdP	Not available in US
Sultopride	Known risk for TdP	Not available in US
Terfenadine	Known risk for TdP	Removed from US market
Terlipressin	Known risk for TdP	Not available in US
Terodiline	Known risk for TdP	Not available in US
Thioridazine	Known risk for TdP	
Vandetanib	Known risk for TdP	

Source:
(*) Classification according to the Qtdrugs org advisory board of the Arizona CET. Updated versions of medications which may prolong the QTc interval may be found at the following website: https://crediblemeds.org/index.php/?cID=328

Table 2 List of QT prolonging drugs with a conditional risk to induce Torsades de Pointes

Drug	QT risk (*)
Abiraterone	Conditional risk for TdP
Amantadine	Conditional risk for TdP
Amisulpride (not available in the US)	Conditional risk for TdP
Amitriptyline	Conditional risk for TdP
Amphotericin B	Conditional risk for TdP
Amsacrine (not available in the US)	Conditional risk for TdP
Atazanavir	Conditional risk for TdP
Bendroflumethiazide or bendrofluazide	Conditional risk for TdP
Chloral hydrate	Conditional risk for TdP
Cimetidine	Conditional risk for TdP
Diphenhydramine	Conditional risk for TdP
Doxepin	Conditional risk for TdP
Eperisone (not available in the US)	Conditional risk for TdP
Esomeprazole	Conditional risk for TdP
Famotidine	Conditional risk for TdP
Fluoxetine	Conditional risk for TdP
Fluvoxamine	Conditional risk for TdP
Furosemide (frusemide)	Conditional risk for TdP
Galantamine	Conditional risk for TdP
Garenoxacin (not available in the US)	Conditional risk for TdP
Hydrochlorothiazide	Conditional risk for TdP
Hydroxyzine	Conditional risk for TdP
Indapamide	Conditional risk for TdP
Itraconazole	Conditional risk for TdP
Ivabradine	Conditional risk for TdP
Ketoconazole	Conditional risk for TdP
Lansoprazole	Conditional risk for TdP
Loperamide	Conditional risk for TdP
Metoclopramide	Conditional risk for TdP
Metolazone	Conditional risk for TdP
Metronidazole	Conditional risk for TdP
Nelfinavir	Conditional risk for TdP
Olanzapine	Conditional risk for TdP
Omeprazole	Conditional risk for TdP
Pantoprazole	Conditional risk for TdP
Paroxetine	Conditional risk for TdP
Piperacillin/Tazobactam	Conditional risk for TdP
Posaconazole	Conditional risk for TdP
Propafenone	Conditional risk for TdP
Quetiapine	Conditional risk for TdP
Quinine sulfate	Conditional risk for TdP
Ranolazine	Conditional risk for TdP
Risperidone	Conditional risk for TdP
Sertraline	Conditional risk for TdP
Solifenacin	Conditional risk for TdP
Telaprevir	Conditional risk for TdP
Torsemide (Torasemide)	Conditional risk for TdP
Trazodone	Conditional risk for TdP

Drug	QT risk (*)
Voriconazole	Conditional risk for TdP
Ziprasidone	Conditional risk for TdP

Source:
(*) Classification according to the Qtdrugs org advisory board of the Arizona CET. Updated versions of medications which may prolong the QTc interval may be found at the following website: https://crediblemeds.org/index.php/?cID=328

Table 3 List of QT prolonging drugs with a possible risk to induce Torsades de Pointes

Drug	QT risk (*)
Abarelix (not available in the US)	Possible risk for TdP
Alfuzosin	Possible risk for TdP
Alimemazine (not available in the US)	Possible risk for TdP
Apalutamide	Possible risk for TdP
Apomorphine	Possible risk for TdP
Aripiprazole	Possible risk for TdP
Artemether/Lumefantrine	Possible risk for TdP
Artenimol+piperaquine (not available in the US)	Possible risk for TdP
Asenapine	Possible risk for TdP
Atomoxetine	Possible risk for TdP
Bedaquiline	Possible risk for TdP
Bendamustine	Possible risk for TdP
Benperidol (not available in the US)	Possible risk for TdP
Betrixaban	Possible risk for TdP
Bortezomib	Possible risk for TdP
Bosutinib	Possible risk for TdP
Buprenorphine	Possible risk for TdP
Cabozantinib	Possible risk for TdP
Capecitabine	Possible risk for TdP
Ceritinib	Possible risk for TdP
Clofazimine (not available in the US)	Possible risk for TdP
Clomipramine	Possible risk for TdP
Clotiapine (not available in US)	Possible risk for TdP
Clozapine	Possible risk for TdP
Cobimetinib	Possible risk for TdP
Crizotinib	Possible risk for TdP
Cyamemazine (not available in the US)	Possible risk for TdP
Dabrafenib	Possible risk for TdP
Dasatinib	Possible risk for TdP
Degarelix	Possible risk for TdP
Delamanid (not available in the US)	Possible risk for TdP
Desipramine	Possible risk for TdP
Deutetrabenazine	Possible risk for TdP
Dexmedetomidine	Possible risk for TdP
Dextromethorphan/Quinidine	Possible risk for TdP
Dolasetron	Possible risk for TdP
Efavirenz	Possible risk for TdP
Eliglustat	Possible risk for TdP
Encorafenib	Possible risk for TdP

Drug	QT risk (*)
Entrectinib	Possible risk for TdP
Epirubicin	Possible risk for TdP
Eribulin mesylate	Possible risk for TdP
Ezogabine (Retigabine)	Possible risk for TdP
Felbamate	Possible risk for TdP
Fingolimod	Possible risk for TdP
Fluorouracil (5-FU)	Possible risk for TdP
Flupentixol (not available in the US)	Possible risk for TdP
Gemifloxacin	Possible risk for TdP
Gilteritinib	Possible risk for TdP
Glasdegib	Possible risk for TdP
Granisetron	Possible risk for TdP
Hydrocodone - ER	Possible risk for TdP
Iloperidone	Possible risk for TdP
Imipramine (melipramine)	Possible risk for TdP
Inotuzumab ozogamicin	Possible risk for TdP
Isradipine	Possible risk for TdP
Ivosidenib	Possible risk for TdP
Ketanserin (not available in the US)	Possible risk for TdP
Lacidipine (not available in the US)	Possible risk for TdP
Lapatinib	Possible risk for TdP
Lefamulin	Possible risk for TdP
Lenvatinib	Possible risk for TdP
Leuprolide	Possible risk for TdP
Levomethadone (not available in the US)	Possible risk for TdP
Lithium	Possible risk for TdP
Lofexidine	Possible risk for TdP
Lopinavir/Ritonavir	Possible risk for TdP
Maprotiline	Possible risk for TdP
Melperone (not available in the US)	Possible risk for TdP
Memantine	Possible risk for TdP
Mianserin (not available in the US)	Possible risk for TdP
Midostaurin	Possible risk for TdP
Mifepristone	Possible risk for TdP
Mirabegron	Possible risk for TdP
Mirtazapine	Possible risk for TdP
Moexipril/HCTZ	Possible risk for TdP
Necitumumab	Possible risk for TdP
Nicardipine	Possible risk for TdP
Nilotinib	Possible risk for TdP
Norfloxacin	Possible risk for TdP
Nortriptyline	Possible risk for TdP
Nusinersen	Possible risk for TdP
Ofloxacin	Possible risk for TdP
Osimertinib	Possible risk for TdP
Oxytocin	Possible risk for TdP
Paliperidone	Possible risk for TdP
Palonosetron	Possible risk for TdP
Panobinostat	Possible risk for TdP
Pasireotide	Possible risk for TdP
Pazopanib	Possible risk for TdP

Drug	QT risk (*)
Perflutren lipid microspheres	Possible risk for TdP
Perphenazine	Possible risk for TdP
Pilsicainide (not available in the US)	Possible risk for TdP
Pimavanserin	Possible risk for TdP
Pipamperone (not available in the US)	Possible risk for TdP
Pitolisant	Possible risk for TdP
Pretomanid	Possible risk for TdP
Primaquine phosphate	Possible risk for TdP
Promethazine	Possible risk for TdP
Prothipendyl (not available in the US)	Possible risk for TdP
Ribociclib	Possible risk for TdP
Rilpivirine	Possible risk for TdP
Romidepsin	Possible risk for TdP
Saquinavir	Possible risk for TdP
Sertindole (not available in the US)	Possible risk for TdP
Siponimod	Possible risk for TdP
Sorafenib	Possible risk for TdP
Sunitinib	Possible risk for TdP
Tacrolismus	Possible risk for TdP
Tamoxifen	Possible risk for TdP
Telavancin	Possible risk for TdP
Telithromycin	Possible risk for TdP
Tetrabenazine	Possible risk for TdP
Tiapride (not available in the US)	Possible risk for TdP
Tipiracil and Trifluridine	Possible risk for TdP
Tizanidine	Possible risk for TdP
Tolterodine	Possible risk for TdP
Toremifene	Possible risk for TdP
Tramadol	Possible risk for TdP
Trimipramine	Possible risk for TdP
Tropisetron (not available in the US)	Possible risk for TdP
Valbenazine	Possible risk for TdP
Vardenafil	Possible risk for TdP
Vemurafenib	Possible risk for TdP
Venlafaxine	Possible risk for TdP
Vorinostat	Possible risk for TdP
Zotepine (not available in the US)	Possible risk for TdP
Zuclopenthixol, Zuclopentixol (not available in the US)	Possible risk for TdP
Source: (*) Classification according to the Qtdrugs org advisory board of the Arizona CET. Updated versions of medications which may prolong the QTc interval may be found at the following website: https://crediblemeds.org/index.php/?cID=328	

Appendix 5 Classification of Cytochrome Substrates

Table 1 Examples (1) of sensitive *in vivo* CYP substrates and CYP substrates with narrow therapeutic range

CYP Enzymes	Sensitive substrates[2]	Substrates with narrow therapeutic range[3]
CYP1A2	Alosetron, caffeine, duloxetine, melatonin, ramelteon, tacrine, tizanidine	Theophylline, tizanidine
CYP2B6 [4]	Bupropion, efavirenz	
CYP2C8	Repaglinide[5]	Paclitaxel
CYP2C9	Celecoxib	Warfarin, phenytoin
CYP2C19	Lansoprazole, omeprazole, S-mephenytoin	S-mephenytoin
CYP3A[6]	Alfentanil, aprepitant, budesonide, buspirone, conivaptan, darifenacin, darunavir, dasatinib, dronedarone, eletriptan, eplerenone, everolimus, felodipine, indinavir, fluticasone, lopinavir, lovastatin, lurasidone, maraviroc, midazolam, nisoldipine, quetiapine, saquinavir, sildenafil, simvastatin, sirolimus, tolvaptan, tipranavir, triazolam, vardenafil	Alfentanil, astemizole,[7] cisapride,[7] cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus, terfenadine[7]
CYP2D6	Atomoxetine, desipramine, dextromethorphan, metoprolol, nebivolol, perphenazine, tolterodine, venlafaxine	Thioridazine

(1) Source: www.fda.gov; list from 7/28/2011. Note that this is not an exhaustive list. For an updated list, see the following link: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm
(2) Sensitive CYP substrates refers to drugs whose plasma AUC values have been shown to increase 5-fold or higher when co-administered with a known CYP inhibitor.
(3) CYP substrates with narrow therapeutic range refers to drugs whose exposure-response relationship indicates that small increases in their exposure levels by the concomitant use of CYP inhibitors may lead to serious safety concerns (e.g., Torsades de Pointes).
(4) The AUC of these substrates were not increased by 5-fold or more with a CYP2B6 inhibitor, but they represent the most sensitive substrates studied with available inhibitors evaluated to date.
(5) Repaglinide is also a substrate for OATP1B1, and it is only suitable as a CYP2C8 substrate if the inhibition of OATP1B1 by the investigational drug has been ruled out.
(6) Because a number of CYP3A substrates (e.g., darunavir, maraviroc) are also substrates of P-gp, the observed increase in exposure could be due to inhibition of both CYP3A and P-gp.
(7) Withdrawn from the United States market because of safety reasons.

Appendix 6 List of CYP3A Inhibitors and Inducers

Table 1 List of drugs inhibiting or inducing CYP3A enzymes

Strong CYP3A inhibitors	Moderate CYP3A inhibitors	Strong CYP3A inducers	Moderate CYP3A inducers
clarithromycin	amprenavir	carbamazepine*	felbamate *
conivaptan	aprepitant	phenobarbital *	topiramate *(> 200 mg/day)
indinavir	atazanavir	Phenytoin*	oxcarbazepin *
itraconazole	cimetidine	fosphenytoin *	eslicarbazepin *
ketoconazole	ciproflaxin	primidone *	rufinamide *
lopinavir	darunavir	avasimibe	bosentan
mibefradil	diltiazem	Rifabutin	efavirenz
nefazodone	elvitegravir	Rifampin	etravirine
nelfinavir	erythromycin	St.John's Wort	modafenil
posaconazole	fluconazole		nafcillin
ritonavir	grapefruit juice		ritonavir
saquinavir	schisandra sphenanthera		talviraline
telithromycin	tipranavir		tipranavir
troleandomycin	tofisopam		
voriconazole	verapamil		

*These drugs are Enzyme-Inducing Anti-Epileptic drugs.
This database of CYP inhibitors and inducers was compiled from the University of Washington's Drug Interaction Database based on *in vitro* studies and from the FDA's "Guidance for Industry, Drug Interaction Studies" from the Indiana University of School of Medicine's "Clinically Relevant" Table

Appendix 7 Tumour Response Assessment Based on RECIST v1.1 Criteria for Solid Tumours

The following sections are applicable to this protocol and contain some relevant explanations. For details please refer to the original publication.

Evaluation of tumour response according RECIST v1.1 for solid tumour indications with protocol specific modifications

Tumour response will be evaluated according to RECIST v1.1 (Eisenhauer et al., 2009).

The RECIST version 1.1 may be accessed at the following link:
http://www.eortc.be/recist/documents/RECISTGuidelines.pdf

Additional information regarding using RECIST is available at the following link:
http://www.recist.com/

Measurability of tumour lesions at baseline

At baseline, tumour lesions/lymph nodes will be categorised as measurable or non-measurable as follows:

Measurable

Tumour lesions must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm by CT scan (CT scan slice thickness no greater than 5 mm; refer to the Imaging Manual)
- 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable)
- 20 mm by chest X-ray

  Malignant lymph nodes: to be considered pathologically enlarged and measurable, a lymph node must **be ≥ 15 mm in short axis** when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed

Non-measurable

All other lesions, including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis) as well as truly non-measurable lesions.

Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, and abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

Special considerations regarding the measurability of the lesions

Types of lesions

- Bone lesions, cystic lesions and lesions previously treated with local therapy:
  - Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
  - Lytic bone lesions or mixed lytic-blastic lesions with identifiable soft tissue components that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.
  - Blastic bone-lesions are non-measurable.
  - If a patient enrolled in this study has known bone metastases, these should be followed by CT or MRI in case they are measurable.
  - If they are not measurable, a baseline bone scan should be performed and repeated only if the patient has suspected progression of bone metastases or if a CR of other lesions has been documented.
- Cystic lesions
  - Cystic lesions thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patients, these are preferred for selection as target lesions.
- Previously irradiated lesions and lesions with prior local treatment

Tumour lesions situated in a previously irradiated area or lesions that have been subject to other loco-regional therapy are usually not considered measurable ***unless there has been a demonstrated progression of the lesion***.

Specification of methods of measurement

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start.

Method of assessment

The same method of assessment and the same technique should be used to characterise each identified and reported lesion at baseline and during follow-up. Imaging–based evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

- Clinical lesions*:* Clinical lesions will be only considered measurable when they are superficial and ≥ 10 mm diameter as assessed using calipers (e.g. skin nodules). Skin lesions will be documentation by colour photography including a ruler to estimate the size of the lesions. As noted above, when lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be

undertaken since it is more objective and may also be reviewed at the end of the study.

- CT, MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less.

  When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slide thickness. MRI is also acceptable in certain situations (e.g. for body scans). More details concerning the use of both CT and MRI for assessment of objective tumour response evaluation including use of i.v. contrast are provided in Appendix II of the RECIST publication (Eisenhauer et al., 2009).

- Ultrasound: Ultrasound should not be used as a method of measurement. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised.

- Endoscopy, laparoscopy: The use of these techniques for objective tumour evaluation is not advised. However, they can be useful to confirm a complete pathological response when biopsies are obtained.

- Cytology, histology: In case a new effusion will appear or worsen during study treatment and the measurable tumour has met criteria for response or SD a cytological confirmation of the neoplastic origin of the effusion can be considered in order to differentiate between response/SD and progressive disease.

- Biopsy of skin lesions: Biopsy and histological examination may be used to confirm or define responses of skin lesions (e.g. after regression of melanoma skin lesions to differentiate between residual pigmented areas and residual malignant lesions). A biopsy of residual pigmented areas or other residual masses suspected to no longer contain tumour can be obtained from a lesion at any time-point to confirm a partial or complete response.

Assessment of overall tumour burden and measurable disease

Overall tumour burden should be estimated at baseline and used as comparator for subsequent measurements.

Baseline documentation of target and non-target lesions

For patients enrolled in this protocol lesions will be considered measurable (refer to criteria for measurability). When more than one measurable lesion is present at baseline, all lesions up to a **total of 5 lesions** and a maximum of **2 lesions per organ** will be recorded under target lesions.

Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected.

Lymph nodes must meet the criterion of a short axis of ≥ 15 mm in order to be evaluated as target lesions. Only the short axis of these nodes will contribute to the baseline sum.

Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scans this is almost always the axial plane, for MRI the plane of acquisition may be axial, sagittal or coronal). The smaller of these measures is the short axis.

Baseline sum of diameters

A sum of diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added to the sum as noted above.

The baseline sum of diameters will be used as reference to further characterise any objective tumour regression in the measurable dimension of the disease.

All lesions or sites of disease not recorded as target lesions should be recorded as non-target lesions at baseline. There is no limit to the number of non-target lesions that can be recorded at baseline.

- Measurable non-target lesions: measurements are required and will be recorded in the eCRF (longest diameter for non-nodal lesions and short axis diameter for nodal lesions). Lesions should be nevertheless followed up qualitatively as “present”, “absent”, or “unequivocal progression”.
- All other non-target lesions: measurements are not required, these lesions should be followed as “present”, “absent”, or “unequivocal progression”. In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (e.g. “multiple enlarged pelvic lymph nodes” or “multiple liver metastases”).

Response criteria

Evaluation of target lesions

- Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have a reduction in short axis to < 10 mm.
- Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions; the baseline sum diameters serve as reference.
- Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm (Note: the appearance of one or more new lesions is also considered progression).
- Stable Disease (SD): Neither sufficient shrinkage to qualify for PR, nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measurement in the same anatomical plane as the baseline examination) even if the nodes regress to below 10 mm on study.

In the CRF, the target nodal lesions will be recorded in a separate section, where, in order to qualify for CR, each node must achieve a short axis of < 10 mm. For PR, SD and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

Target lesions that become "too small to measure"

If in the opinion of the radiologist the lesion has likely disappeared, the measurement should be recorded as 0 mm in the CRF. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned. However, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm.

Lesions that split or coalesce at treatment

When non-nodal lesions "fragment", the longest diameter of the fragmented portions should be added together to calculate the target lesion sum.

As lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the "coalesced lesion".

Evaluation of non-target lesions

While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.

- Complete Response (CR): Disappearance of all non-target lesions and normalisation of tumour marker (CEA, CYFRA 21) levels. All lymph nodes must be non-pathological in size (< 10 mm short axis).
- Non-CR/Non-PD: Persistence of one or more non-target lesion(s) or/and maintenance of tumour markers (CEA, CYFRA 21) above the normal limits.
- Progressive Disease (PD): Unequivocal progression of existing non-target lesions. The appearance of one or more new lesions is also considered progression. To achieve 'unequivocal progression', there must be an overall level of substantial worsening in non-target disease that is of a magnitude that, even in the presence of SD or PR in target disease, the treating physician seriously considers changing therapy.

New lesions

The finding of a new lesion should be unequivocal: i.e., not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumour. This is particularly important when the patient's baseline lesions show partial or complete response.

A lesion identified on a follow up study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitively a new lesion, then progression should be declared using the date of the initial scan.

For more details, refer to the Imaging Manual and the RECIST publication (Eisenhauer et al., 2009).

Evaluation of best overall response

The best overall response is the best response recorded from the start of study treatment until the EOT taking into account any requirement for confirmation. A response occurring after the end of study treatment but prior to the start of a new cancer treatment will also be considered for the assessment of best overall response. This assessment should be performed as per clinical standard practice. When a response assessment according to RECIST 1.1 is available, the result should be recorded in the eCRF. If no results of response assessment according to RECIST are available, then the result of other tumour evaluation should be recorded in the eCRF including the method used.

Table 1 Overall Response assessment for patients with target and non-target lesions at a given timepoint

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease

Missing assessments and not evaluable designation

When no imaging/measurement is done at a particular time point, the patient is not evaluable (NE) for this time point. If only a subset of lesion measurements is made at an assessment, usually a convincing argument can be made that the contribution of individual missing lesion(s) would not change response at the assigned time point. This would be most likely to happen in the case of PD. For example, if a patient had a baseline sum of 50 mm with 3 measured lesions and at follow–up, only two lesions

were assessed, but those had a sum of 80 mm, the patient would have achieved PD status, regardless of the contribution of the missing lesion.

Confirmation of responses

Any complete or partial response should be confirmed by the next routinely scheduled scan or at least 4 weeks after the 1st occurrence of the respective response.

Table 2 Best overall response

Overall response first time point	Overall response second time point	BEST overall response
CR	CR	CR
CR	PR	SD, PD or PR [A]
CR	SD	SD provided minimum criteria for SD duration [B] are met, otherwise PD
CR	PD	SD provided minimum criteria for SD duration [B] are met, otherwise PD
CR	NE	SD provided minimum criteria for SD duration [B] are met, otherwise NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration [B] are met, otherwise PD
PR	NE	SD provided minimum criteria for SD duration [B] are met, otherwise NE
NE	NE	NE

CR = complete response; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease

[A] If a CR is truly met at the first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline makes the disease PD at that time point (since disease must have reappeared after CR). Best Response would depend on whether minimum duration for SD was met. However, sometimes “CR” may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had a PR, not CR at the first time point. Under these circumstances, the original CR should be changes to PR and the best response is PR.

[B] The minimum requirement for SD duration according to this protocol is that the follow-up scan has been performed at least 8 weeks (patients with HNSCC or ACC) or 12 weeks (patients with cMEL or cSCC) after the baseline assessment (i.e., the day of first vaccination).

Symptomatic deterioration

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as ‘symptomatic deterioration’. Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping study therapy. The objective response status of such patients is to be determined by evaluation of target and non-target disease.

References:

1. Eisenhauer, E.A., Therasse, P., Bogaerts, J., Schwartz, L.H., Sargent, D., Ford, R., Dancey, J., Arbuck, S., Gwyther, S., Mooney, M., *et al.* (2009). New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer *45*, 228-247.

Appendix 8 Response Assessment in Acute Lymphoblastic Leukaemia/ Lymphoblastic Lymphoma

Response criteria for Blood and Bone Marrow:

- CR
  - No circulating lymphoblasts or extramedullary disease
  - No lymphadenopathy, splenomegaly, skin/gum infiltration/testicular mass/CNS involvement
  - Trilineage haematopoiesis (TLH) and <5% blasts
  - Absolute neutrophil count (ANC) >1000/microL
  - Platelets >100,000/microL
  - No recurrence for 4 weeks
- CR with incomplete blood count recovery (CRi)
  - Meets all criteria for CR except platelet count or ANC
- Overall response rate (ORR = CR + CRi)
- NOTE: MRD assessment is not included in morphologic assessment and should be obtained
- Refractory disease
  - Failure to achieve CR at the end of induction
- Progressive disease (PD)
  - Increase of at least 25% in the absolute number of circulating or bone marrow blasts or development of extramedullary disease
- Relapsed disease
  - Reappearance of blasts in the blood or bone marrow (>5%) or in any extramedullary site after a CR

Response Criteria for CNS Disease:

- CNS remission: Achievement of CNS-1 status in a patient with CNS-2 or CNS-3 status at diagnosis.
- CNS relapse: New development of CNS-3 status or clinical signs of CNS leukemia such as facial nerve palsy, brain/eye involvement, or hypothalamic syndrome without another explanation.

Response Criteria for Lymphomatous Extramedullary Disease:

- CT of neck/chest/abdomen/pelvis with IV contrast and PET/CT should be performed to assess response for extramedullary disease.
- CR: Complete resolution of lymphomatous enlargement by CT. For patients with a previous positive PET scan, a post-treatment residual mass of any size is considered a CR as long as it is PET negative.
- PR: >50% decrease in the sum of the product of the greatest perpendicular diameters (SPD) of the mediastinal enlargement. For patients with a previous PET scan, post-treatment PET must be positive in at least one previously-involved site.
- PD: >25% increase in the SPD of the mediastinal enlargement. For patients with a previous positive PET scan, post-treatment PET must be positive in at least one previously-involved site.
- No Response (NR): Failure to qualify for PR or PD.

- Relapse: Recurrence of mediastinal enlargement after achieving CR. For patients with a previous positive PET scan, post-treatment PET must be positive in at least one previously-involved site.

Reference: National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology: Acute Lymphoblastic Leukemia, Version 1.2020, January 15, 2020. Accessible at: www.NCCN.org

Appendix 9 [^{18}F] FDG-PET

FDG ([^{18}F]-Fluoro-Deoxy-Glucose) PET imaging will be performed in this study for patients with certain cancers at baseline and - if positive at baseline - at cycle 2 day 15.

To assure reproducibility of the examination, please refer to the PET-CT site procedure manual from BMS/ERT to see details on imaging acquisition and patient preparation.

All PET scans should start between 60-70 minutes after ^{18}F-FDG injection and patients should be always imaged on the same PET/CT scanner. It is particularly important that the time interval between injection and start of the scan is the same at follow-up compared to baseline.

Blood glucose level will be checked on the day of the FDG PET scan and results assessed prior to the administration of FDG.

Regular diet can be resumed after the scan.

Of note FDG-PET must be performed before biopsy to avoid potential false positive findings whenever possible. However, during the screening period, baseline FDG-PET assessment should be performed at the closest date as possible from start of study treatment, at least one week after tumour biopsy and once the eligibility based on mutation status is known. All patients should be encouraged to increase fluid intake for a few hours after the scan to promote excretion of the FDG.

A diuretic (furosemide, typically 20-40 mg IV) may be administered at the discretion of the investigator before or during the FDG-PET scan in order to accelerate elimination of the [^{18}F]-FDG from the renal collecting system.

Diazepam may be used to promote muscle relaxation and reduce muscular uptake if tumour deposits are in the neck or shoulder girdle area. Diazepam administration and diuretic administration must be recorded in the Concomitant Medications eCRF page.

Appendix 10 Statistical Appendix including Model Performance and Data Scenarios

Part A (escalation):

The model was assessed by two different metrics: hypothetical on-study data scenarios and long-run operating characteristics.

Hypothetical data scenarios

Hypothetical data scenarios are shown in Table 1. These scenarios reflect potential on-study data constellations and related escalation as allowed by the model and the 100% escalation limit. For each scenario, the probability of overdose for the current dose, as well as the next potential dose and related probabilities of under-dosing, target dose and over-dosing are shown.

For example, scenario 1 represents the case that no DLT is observed in three patients at the starting dose of 15 mg. In this case, the next dose permitted by the model and by the 100% escalation rule is 30 mg. Similarly, scenario 2 represents the case that one DLT is observed in the first cohort of three patients at 15 mg, the model would than not allow to escalate to 30 mg and would require more patients enrolled on the dose level of 15 mg. Scenario 6 represents the case that two DLTs are observed in the second cohort in three patients at 30 mg. The model then allows a de-escalation to 15 mg. Despite the fact that no DLTs were seen in the previous cohort (6 patients in total), the model reacts immediately to the data observed at 30 mg and requires a de-escalation to 15 mg. This case illustrates the adaptive behaviour of the model even in extreme situations.

Table 1 Hypothetical data scenarios

Scenario	Dose	#DLT	#Pat	Current Dose -P(OD)	Next Dose	Next Dose - P(UD)	Next Dose - P(TD)	Next Dose - P(OD)
1	**15**	**0**	**3**	0.011	**30**	0.89	0.079	0.031
2	**15**	**1**	**3**	0.239	**15**	0.467	0.294	0.239
3	**15**	**2**	**3**	0.685				
4	**15**	**0**	**3**					
	30	**0**	**3**	0.007	**60**	0.871	0.094	0.035
5	**15**	**0**	**3**					
	30	**1**	**3**	0.121	**30**	0.602	0.277	0.121
6	**15**	**0**	**3**					
	30	**2**	**3**	0.4	**15**	0.439	0.356	0.206
7	**15**	**0**	**3**					
	30	**1**	**6**	0.034	**60**	0.53	0.308	0.162
8	**15**	**0**	**3**					
	30	**0**	**3**					
	60	**1**	**3**	0.102	**60**	0.61	0.289	0.102

Operating characteristics

Operating characteristics are a way to assess the long-run behaviour of a model. Under an assumed true dose-toxicity curve, metrics such as the probability of recommending a dose with true DLT rate in the target interval can be approximated via simulation. Table 2 describes 3 assumed true dose-toxicity scenarios which were used to assess the operating characteristics of the model. These scenarios reflect a wide range of possible cases as follows:

- Scenario 1 (P): aligned with prior means
- Scenario 2 (H): high-toxicity scenario
- Scenario 3 (LH): low-toxicity followed by high-toxicity

Table 2 Assumed true dose-toxicity scenarios

Scenario		Dose								
		10 mg	**15 mg**	**30 mg**	**60 mg**	**120 mg**	**180 mg**	**240 mg**	**320 mg**	**400 mg**
1 (P)	**P (DLT)**	0.08	0.09	0.12	**0.17**	**0.25**	0.35	0.42	0.48	0.52
2 (H)		0.12	**0.17**	**0.25**	0.42	0.55	0.63	0.7	0.8	0.9
3 (LH)		0.05	0.08	0.12	**0.16**	**0.2**	0.4	0.5	0.65	0.9

Bold numbers indicate true DLT rates in the target interval [0.16-0.33).

For each of these scenarios, 500 trials were simulated. It was then assessed how often a dose was declared as MTD with true DLT rate in the under-, targeted or over-dose range. Furthermore, the average, minimum and maximum number of patients per trial and the average number of DLTs per trial are reported. Results are shown in Table 3.

Table 3 Simulated operating characteristics

Scenario	% of trials declaring an MTD with true DLT rate in				# Patients	# DLT
	Underdose	**Target dose**	**Overdose**	**Stopped**	**Mean (Min-Max)**	**Mean (Min- Max)**
1 (P)	23.6	61.6	9.4	5.4	19.13 (3-51)	3.09 (1-11)
2 (H)	1.8	61.2	16.2	20.8	15.30 (3-39)	3.68 (1-11)
3 (LH)	22.6	67.4	9.1	3.6	19.89 (3-52)	3.25 (1-12)

In Scenario 1, which reflects the case that the true dose-toxicity is aligned with prior means, 61.6% of the simulated trials declared a dose as MTD with true DLT rate in the targeted dose range. Since this reflects a low toxicity prior assumptions the highest currently planned dose of 150 mg was identified quite often as MTD, namely in 61.4% of the simulated cases.

In Scenario 2 (high-toxicity scenario), the starting dose has already > 17% probability of observing at least 2 DLTs in the first cohort. This contributes to the high percentage (20.8%) of all simulated trials for which the trial is stopped since none of the doses is considered tolerable anymore. This is an expected situation for a high-toxicity scenario.

In Scenario 3, more than 67.4% of the simulated trials declared a dose as MTD with true DLT rate in the targeted dose range.

The mean patient numbers range from 15.30 patients (high-toxicity scenario) to 19.89 patients (low-high) and the maximum number of patients was 52. Therefore, the patient numbers are as expected and increase when moving away from the high-toxicity scenario.

In summary, the considered data scenarios show a reasonable behaviour of the model and the operating characteristics demonstrate a good precision of MTD determination.

Part B (Expansion):
The following indications for patients with NOTCH activated pathway are considered and grouped into the expansion arms for Part B of this study:

1. Adenoid cystic carcinoma (ACC)
2. Triple Negative Breast Cancer (TNBC)
3. Breast Cancer (ER+/-, HER2+/-)
4. Osteosarcoma, malignant glomus tumour
5. GI cancers (resistant to oxaliplatin or irinotecan-based therapy colorectal cancer, hepatocellular carcinoma)
6. r/r T-ALL/T-LBL
7. Any other cancer (haematologic or solid) with confirmed Notch pathway activation (basket arm)

Table 4 Hypothetical data scenarios for selected potential indications

	Dose				
	1.ACC	**2.TNBC**	**3.Breast Cancer**	**4. Osterosarcoma, Malignant glomus tumour**	**5.GI**
	n/N Median; (CI)	**n/N Median; (CI)**	**n/N Median; (CI)**	**n/N Median; (CI)**	**n/N Median; (CI)**
Interim 1:					
1. Low response	0/5 10% (0%-32%)	1/10 12% (2%-32%)	1/7 13% (2%-38%)	0/5 10 % (0%-32%)	3/5 29% (8%-74%)
2. High response	3/5 48% (26%-75%)	2/5 45% (21%-69%)	4/10 44% (23%-65%)	4/7 48% (27%-73%)	2/5 45% (21%-69%)
3. Strong hetero-geneity	4/5 65% (28%-94%)	3/5 51% (18%- 85%)	6/10 54% (27%- 81%)	0/7 10% (0%- 43%)	0/5 12% (0%- 48%)

Final analysis:					
1. Low response	5/20 19% (9%- 36%)	0/10 13% (1%- 27%)	5/20 19% (9%-37%)	1/10 15% (4%-30%)	3/20 16% (6%-29%)
2. High response	7/20 29% (17%- 46%)	2/10 26% (11% -42%)	5/20 26% (14%-41%)	4/10 29% (16%- 51%)	4/20 25% (12%-39%)
3. Strong hetero-geneity	4/20 20% (8%- 38%)	1/10 15% (2%-37%)	6/20 28% (13%- 47%)	0/10 10% (1%- 31%)	11/20 47% (26%-69%)

Table 5 Assumed true response scenarios and simulated operating characteristics

	Indication				
	1.ACC N=10	**2.TNBC N=20**	**3.Breast Cancer N=10**	**4. Osteosarcoma, Malignant glomus tumour N=10**	**5.GI N=10**
	Success criteria >25% **True Response Rate**	**Success criteria >25%** **True Response Rate**	**Success criteria >25%** **True Response Rate**	**Success criteria >25%** **True Response Rate**	**Success criteria >25%** **True Response Rate**
Low response	20%	20%	20%	20%	20%
success	17%	16%	16%	18%	18%
failure	83%	84%	84%	82%	82%
High response	30%	30%	30%	30%	30%
success	73%	72%	72%	71%	71%
failure	27%	28%	28%	29%	29%
Strong hetero-geneity	10%	10%	10%	30%	30%
success	2%	1%	2%	29%	26%
failure	98%	99%	98%	71%	74%

Appendix 11 PK SUB-STUDY 1

Background and rationale

The majority of the novel orally administered, molecularly targeted anti-cancer drugs are weak bases that exhibit pH-dependent solubility and suppression of gastric acidity with acid-reducing agents (ARAs) could impair their absorption[1]. In this context it is noted that a majority of cancer patients frequently take ARAs to alleviate symptoms of gastroesophageal reflux disease, thereby raising the potential for a common but underappreciated drug-drug interaction (DDI) that could decrease the exposure of anti-cancer medication and result in subsequent failure of therapy. A large survey using data from almost 3 million cancer patients has shown that the total prevalence proportion of ARA use was between 20% and 33% in this population[2]. Proton pump inhibitors were the most commonly prescribed agents, comprising 65% to 79% of all cancer patients receiving a prescription for an ARA. Clinically significant decreases in the exposure of dasatinib, gefitinib, erlotinib and nilotinib are thought to be the results of elevated gastric pH caused by concomitant use of ARAs.

CB-103 is a weak base and exhibits pH-dependent solubility. It is therefore possible that CB-103 absorption is dependent on the gastric pH and that ARAs change the absorption characteristics of the molecule. The study protocol per se currently forbids the concomitant use of ARAs.

Ranitidine is chosen as representative H2RA, as it is one of the strongest compounds in its class and the planned pH DDI evaluation is not expected to be confounded by additional cytochrome or transporter interactions of this compound, which were observed for example for cimetidine and famotidine[3]. The dose of ranitidine follows the prescription information for the compound. Ranitidine is commonly given as either 150 mg twice daily (evening and morning administration) or as 300 mg once daily (evening administration). For ranitidine the most reported AEs are:

- Uncommon AEs ($\geqslant$ 1/1000, $\leqslant$ 1/100): Abdominal pain, constipation, nausea (these symptoms mostly improved during continued treatment)

- Rare AEs ($\geqslant$ 1/10,000, $\leqslant$ 1/1000): Hypersensitivity reactions (urticaria, angioneurotic oedema, fever, bronchospasm, hypotension and chest pain), transient and reversible changes in liver function tests, skin rash, elevation of plasma creatinine (usually slight; normalised during continued treatment).

The administration of two doses of 150 mg ranitidine in the context of this sub-study is expected to be well tolerated; upon careful assessment it was determined that the benefit-risk ratio remains favourable and that this PK sub-study does not compromise the patient safety or represent a burden that could interfere with their willingness to complete their participation in the CB103-C-101 study, but to the contrary, will support to better define the safety profile of CB-103.

Objective PK sub-study 1

PK-sub-studies are part of the main study CB103-C-101 as described in Section 8.4.2 and schedule of assessments of the approved study protocol.

The objective of this first per-protocol PK sub-study is to investigate the effect of gastric pH on absorption of CB-103 when co-administered with standard dose of ranitidine (150 mg), a histamine H2-receptor antagonist (H2RA) that is a potent acid-reducing agent frequently prescribed to cancer patients.

Study conduct

Outline of Study Procedures

The patients will have to be instructed to:

- Take one single dose/tablet of ranitidine 150 mg in the evening of cycle 2 day 1 **before bed time** and to **remain fasted overnight** (water intake is allowed).
- Attend fasted to the clinic in the morning of cycle 2 day 2 (C2D2, study visit for the PK sub-study only) without taking ranitidine and/or CB-103, but bringing the dose of CB-103 to the clinic. If the patient is not able to adhere to the long fasting conditions, they can be allowed a small breakfast/snack up to 2 hours before arrival in the clinic on C2D2. If this happens, it should be documented in the patient's record.
  The patient will have to confirm the intake of ranitidine on C2D1 (as indicated in the above bullet) and the study team will document it in the patient's record/chart together with the exact time of ranitidine intake on C2D2.
- Take one single dose/tablet of ranitidine 150mg while at the clinic on C2D2 in the presence of the available study team and remain fasted up to 3 hours post CB-103 intake (water intake is allowed).
- Take CB-103 with a glass of 200 mL water, exactly 2 hours after the intake of the ranitidine, and in the presence of the available study team.

Overall, the co-administration of ranitidine is limited to two intakes (post-CB-103 dose on cycle 2 day 1 and pre-CB-103 dose on day 2) in order to test the on-off effect.

On C2D2 the PK sampling (7 in total) will have to be taken at the following time points (for the patients in the twice daily regimen of CB-103 the timepoints are relative to the first intake):

- Pre-dose (after ranitidine intake and within 30 mins before CB-103 administration)
- 0.5 hours post CB-103 dose (± 5 mins)
- 1 hour post CB-103 dose (± 5 mins)
- 2 hours post CB-103 dose (± 5 mins)
- 4 hours post CB-103 dose (± 5 mins)
- 6 hours post CB-103 dose (± 5 mins)
- 8 hours post CB-103 dose (± 5 mins)

The PK sampling scheme is the same as on C2D1 and allows the comparison of CB-103 PK in the absence (C2D1) and presence (C2D2) of ranitidine.

All other PK samples and assessments specified in the study protocol (pre and post C2D2) will remain the same and are to be performed.

Ranitidine provision

The clinical site(s) can choose the brand of ranitidine locally available, amongst the readily available marketed brands, and take it from the hospital pharmacy or as per the site's procurement procedures. The same brand of ranitidine should be used across the patients enrolled at the clinical site to reduce potential variability.
The clinical site staff will then dispense ranitidine to the patients and instruct them how to use the ARA.

eCRF recording

The concerned e-CRF form for the PK sub-study (i.e., Visit 8a – Cycle 2 Day 2) is to be properly completed by indicating the type of sub-study the patient is taking part in (in this case Sub-Study PK1), as well as, the exact time of ranitidine and CB-103 intake, and the date/time of the PK samples collection. In case, on C2D2 the patient vomits within 2 hours after drug administration either ranitidine or CB-103 this needs to be captured as well in the comment field of e-CRF.

References

1. Budha NR et al. Drug absorption interactions between oral targeted anticancer agents and PPIs: is pH-dependent solubility the Achilles heel of targeted therapy? Clin Pharmacol Ther 2012; 92 (2):203-13.
2. Smelick GS et al. Prevalence of acid-reducing agents (ARA) in cancer populations and ARA drug-drug interaction potential for molecular targeted agents in clinical development. Mol Pharm 2013; 10 (11): 4055-62.
3. Zhang L, Wu F, Lee SC, Zhao H, Zhang L. ph-dependent drug-drug interactions for weak base drugs: potential implications for new drug development. Clin Pharmacol Ther 2014; 96 (2): 266-77.

Appendix 12 PK SUB-STUDY 2

Background and rationale

Administration of a drug product with food may change the bioavailability (BA) by various means, including:

- Delay gastric emptying
- Stimulate bile flow
- Change gastrointestinal (GI) pH
- Increase splanchnic blood flow
- Change luminal metabolism of a drug substance
- Physically or chemically interact with a dosage form or a drug substance

Food effects on BA are generally greatest when the drug product is administered shortly after a meal is ingested. The nutrient and caloric contents of the meal, the meal volume, and the meal temperature can cause physiological changes in the GI tract in a way that affects drug product transit time, luminal dissolution, drug permeability, and systemic availability.

For immediate-release drug products of compounds with low solubility or low permeability, food effects are most likely to result from a complex combination of factors that influence the in vivo dissolution of the drug product and/or the absorption of the drug substance. In these cases, the relative direction and magnitude of food effects on BA are difficult, if not impossible, to predict without investigating it.

Objective PK sub-study 2

PK-sub-studies are part of the main study CB103-C-101 as described in Section 8.4.2 and schedule of assessments of the approved study protocol.

The objective of the second per-protocol PK sub-study is to evaluate the effect of a standard breakfast (moderate fat: composed of approximately 21g fat and 533 Kcal in total, with ca. 189 Kcal from fat, ca. 268 Kcal from carbohydrates and ca. 76 Kcal from protein).

Study conduct
Outline of Study Procedures

The patients will have to be instructed to:

- come to the clinic in the morning of cycle 2 day 2 (C2D2, extra study visit for the PK sub-study only) without taking CB-103, and bring the dose of CB-103 to the clinic.

- consume a standard breakfast supplied by the site based on the above indicated Kcal (e.g., four slices of bread, one slice of ham, one slice of cheese, butter, jelly and two cups of decaffeinated coffee or tea with milk and/or sugar, if desired) in its entirety within 30 minutes. The study team will document the type of meal given to the patient in the patient's record/chart together with the time of food intake.

- take CB-103 with a glass of 200mL water 30 minutes after the start of breakfast and in the presence of the available study team

- remain fasted, after the breakfast, for at least 4 hours post-dose (water intake is allowed)

On C2D2 the PK sampling (7 in total) will have to be taken at the following time points (for the patients in the twice daily regimen of CB-103 the timepoints are relative to the first intake):

- Pre-dose (within 30 mins before CB-103 administration)
- 0.5 hours post CB-103 dose (± 5 mins)
- 1 hour post CB-103 dose (± 5 mins)
- 2 hours post CB-103 dose (± 5 mins)
- 4 hours post CB-103 dose (± 5 mins)
- 6 hours post CB-103 dose (± 5 mins)
- 8 hours post CB-103 dose (± 5 mins)

The PK sampling scheme is the same as on C2D1 and allows the comparison of CB-103 PK in the absence (C2D1) and presence (C2D2) of food.

All other PK samples and assessments specified in the study protocol (pre and post C2D2) will remain the same and are to be performed.

eCRF recording

The concerned e-CRF form for the PK sub-study (i.e., Visit 8a – Cycle 2 Day 2) is to be properly completed by indicating the type of sub-study the patient is taking part in (in this case Sub-Study PK2), as well as, the exact time of food and CB-103 intake, and the date/time of the PK samples collection. In case the patient vomits within 2 hours after drug administration on C2D2, this needs to be captured it as well in the comment field of e-CRF.