Statistical Analysis Plan

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

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Glossary of Abbreviations

AE	Adverse Event
ALT	Alanine aminotransferase
aPTT	activated Partial Thromboplastin Time
AR	Accumulation ratio
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	Area under the curve
BID	twice daily
BL	Baseline
BLRM	Bayesian logistic regression model
BLQ	Below Limit of Quantification
BMI	Body mass index
BNP	Brain natriuretic peptide
BOR	Best overall response
Bpm	Beats per minute
BPM	Blood Pressure
BUN	Blood Urea Nitrogen
CBR	Clinical benefit rate
CCC	Cholangiocellular carcinoma
CI	Confidence Interval
CL/F	Clearance of drug after administration
C_{max}	Maximum observed plasma concentration
C_{min}	Minimum observed plasma concentration
CR	Complete response
CNS	Central nervous system
CRC	Cohort Review Committee
CRP	C-reactive Protein
CSF	Cerebrospinal Fluid
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
DDS	Dose-determining Set

DLT	Dose-limiting toxicity
DOR	Duration of Response
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case-report form
ER	Estrogen receptor
EOS	End-of-Study
EWOC	Escalation with overdose control
FU	Follow-up
GBM	Glioblastoma multiforme malignancies
GI	Gastrointestinal
HER2	Human epidermal growth factor receptor 2
HIV	Human immunodeficiency virus
HNSTD	Highest non-severely toxic dose
IA	Interim analysis
IHC	Immunohistochemistry
INR	International Normalized Ratio
LVEF	Left ventricular ejection fraction
kg	Kilogram
KM	Kaplan-Meier
MTD	Maximum tolerated dose
LLOQ	Lower Limit of Quantification
LVEF	Left ventricular ejection fraction
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
Min	Minimum
mL	millilitre
MTD	Maximum tolerated dose
MUGA	Multigated acquisition
NAT	N-acetyltransferases
NCI	National Cancer Institute
NE	Not evaluable
NSCLC	Non-small-cell Lung Cancer
ORR	Overall response rate
OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival
PK	Pharmacokinetics
PP	Per protocol
PR	Partial response
PT	Preferred Term
QRS	QRS complex
QD	Once daily
QT	QT interval
QTc	QT corrected for heart rate
QTcF	QT corrected for heart rate using the Fridericia's correction factor
RBC	Red Blood Cell
RP2D	Recommended phase 2 dose

RECIST	Response evaluation criteria in solid tumours
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Stable Disease
SOC	System Organ Class
SS	Safety Set
SD	Standard Deviation
$t_{1/2}$	Terminal half-life
TEAE	Treatment-emergent adverse event
t_{max}	Time to maximum plasma concentration
TNBC	Triple negative breast cancer
TTR	Time to Response
ULN	Upper limit of normal
Vd/F	Volume of distribution during terminal phase
Vss/F	Volume of distribution at steady-state
WBC	White Blood Cell
WHO	World Health Organization

1. Source Documents

The SAP is based on the following documentation and is for the Part A of the study.

Document	Date	Version
Protocol	03 August 2020	4.1
eCRF	17 May 2021	4.0-4.2

2. Protocol Details

2.1 Overall Study Design

2.1.1 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 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 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

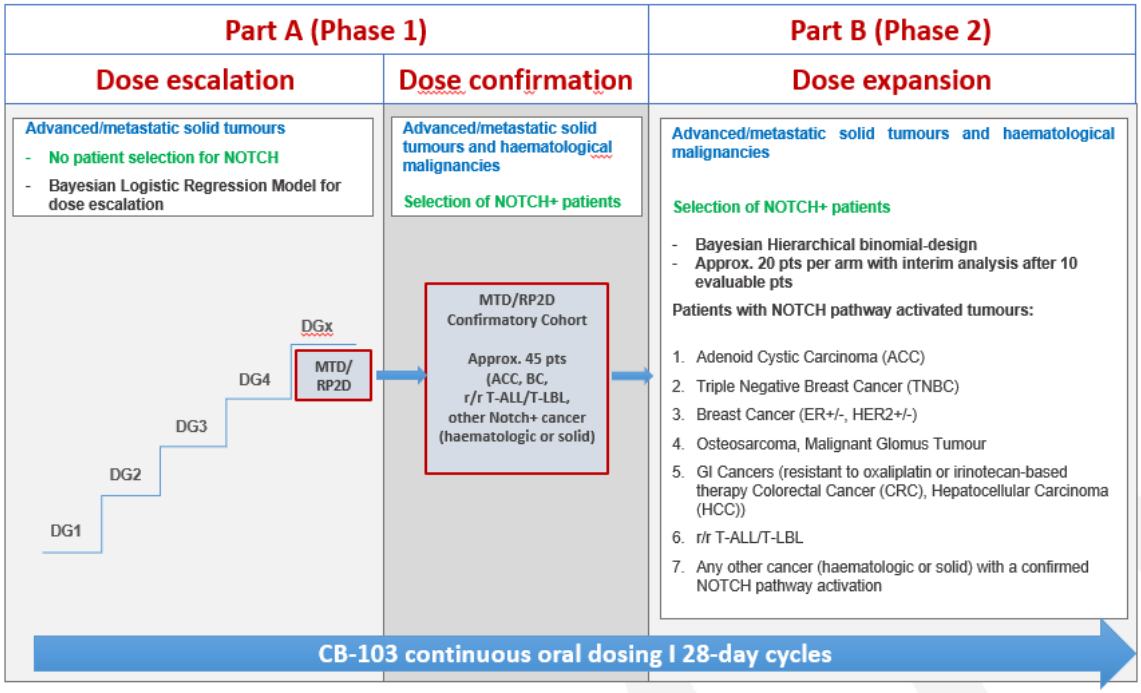
ascertain that optimal safety related to efficacy and pharmacodynamics in the tumour and in peripheral blood are achieved.

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 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 illustrated below.



Abbreviations: ACC, adenoid cystic carcinoma; DG, dose group; MTD, maximum tolerated dose; RP2D, recommended phase 2 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.

2.1.2 Study Treatment

CB-103 will be administered orally as a continuous once daily (QD) dosing during the treatment period of both Part A and Part B 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 scheduling and evaluations, a treatment cycle is defined as 28 days throughout the whole study.

2.1.3 Planned Dose-Cohorts for Dose Escalation

For Part A, the DLT period is defined as the 1st cycle of CB-103 dosing with a duration of 28 days. Eight provisional dose levels are defined for the dose escalation 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.

2.1.4 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 adjustments are permitted if it is considered 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.

Patients whose CB-103 treatment is delayed or discontinued should have at least weekly follow-ups that include a physical examination, vital signs including weight, performance status, ECGs, and assessment of adverse events and concomitant medication. Following a DLT or toxicity, haematology, renal and liver function tests should be performed as appropriate.

Guidance on dose reductions and resumption of treatment if found in protocol section 7.4.5.

2.1.5 Study Schedule

Please, find complete schedules of assessments for part A in Appendix 3.

2.2 Study Objectives

2.2.1 Primary Objective(s)

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.

2.2.2 Secondary Objective(s)

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.
- 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.

2.2.3 Exploratory Objective(s)

The exploratory objectives for part A 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:
  - in pre- and post- CB-103 dosing in **tumour tissue biopsies** as a measure of NOTCH pathway inhibition;
  - in pre- and post- CB-103 dosing in **whole blood, plasma samples and hair follicles** as a surrogate model to measure NOTCH pathway inhibition.

- To assess changes in NOTCH target genes and downstream PD markers (genes, proteins) in haematological malignancies:
  - in pre- and post- CB-103 dosing in **T-lymphocytes from blood and/or bone marrow samples**;
  - in pre- and post- CB-103 dosing in **whole blood and plasma samples**.
- To assess the changes in the percentage of mutated alleles in liquid biopsies pre- and post CB-103 dosing to determine 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 genomic studies may be performed on **tumour tissue samples or on blood and/or bone marrow samples** as a part of this study to identify gene aberrations and protein expression patterns that are associated with treatment response to CB-103, disease progression, and/or adverse events. The decision to perform such analyses would be dependent on the outcome data and sample availability.
- 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.

2.3 Sample Size and Power

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.

2.4 Interim Analyses

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.

2.5 Primary Variable(s)

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.

2.6 Secondary Variable(s)

The secondary endpoints for Part A 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.
- 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.

2.7 Exploratory Variable(s)

The exploratory endpoints for Part A 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 and NOTCH target genes expression (NOTCH1-4 receptors, NOTCH ligands, NICD1-4 and NOTCH target genes) assessed by Nanostring expression analysis 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 NOTCH genetic aberrations in pre- and post-treatment tumour tissue samples, whole blood 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 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 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

2.8 Safety Variable(s)

The safety variables of this study are as follows:

- Adverse events
- Laboratory findings
- Vital signs
- Physical examination and ECOG status
- Cardiac function

3. Analysis Populations

In accordance with ICH E3[1] and E9[2], the following analysis sets will be used for the analyses.

3.1 Safety Set

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.

3.2 Dose-Determining Set

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.

3.3 PK Set

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.

Note: 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 summarizing disposition.

4. Data Handling

4.1 Time Points and Visit Windows

4.1.1 General Definitions

All assessment days will be related to the first day of first dose of treatment.

Day 1 is defined as first dose of treatment at Cycle 1 Day 1. Relative days after Day 1 are calculated as (assessment date – Day 1 date) + 1. Relative days prior to Day 1 are calculated as (assessment date – Day 1 date). The day prior to Day 1 is Day -1. Day 0 is not defined.

The date of the first dose of treatment for each subject will be taken from the PK sampling eCRF page.

The date of the last dose of treatment for each subject will be taken from the End of Treatment eCRF page. If the date in this eCRF page is missing, alternatively the date of End of Study will be used. If the date is missing because the subject was lost to follow-up, the date of the last visit will be imputed, if appropriate.

4.1.2 Baseline Period

For all subjects, the baseline period is defined as the period from informed consent to the first dose of treatment. For some variables, data from more than one assessment within the baseline Period can be collected prior to the first dose of treatment.

The baseline value for a variable is therefore defined as the last non-missing value collected before the first dose of treatment in the baseline period.

4.1.3 Treatment Period

The Treatment Period is defined as the period from the date / time of the first dose of treatment up to and including the date / time of the last dose of treatment.

4.1.4 Visit Windows

All data will be analyzed using nominal study visit as defined in the Study Schedule and eCRF. No visit windows will be applied for summary and analysis.

4.2 Handling of Dropouts, Missing Data, and Outliers

Missing, unused and spurious data will be dealt with as such.

Due to the dose escalation design of Part A of the study no missing imputation of missing values will be done for any analysis.

Currently no drop-outs are foreseen. However, if patients in the escalation phase (Part A) do not fulfil the minimum treatment and safety evaluation requirements and discontinue for a reason other than DLT they will be replaced.

5. Statistical Methods

5.1 General Principles

All data processing, summarization and analyses will be performed using Labcorp Drug Development's SAS Environment / Version 9.4 (or later) of the SAS® statistical software package.

Baseline, safety and tolerability as well as efficacy analyses will be based on the SS.

Pharmacokinetic evaluation will be done for the PK set.

The dose-determining analyses, i.e. those to determine MTD or RP2D, will be done for the DDS.

Results will be listed and summarized using descriptive statistics overall and by cohort:

- All patients
- Cohort 1 (dosing level 1, e.g. 15mg)
- Cohort 2 (dosing level 2, e.g. 30mg)
- Etc.
- Cohort with RP2D

All summary statistics will be rounded (using the SAS® function ROUND) and presented to one more decimal place than the raw value, except for the minimum and maximum values that will be presented with the same decimal precision as the raw value.

For qualitative variables, the number (n) and percentage (%) of subjects with non-missing data per category will be the default summary presentation, and where appropriate and present, the number of missing values as a "Missing" category. Number of subjects in the analysis population will be used as denominator for percentages calculation, unless stated otherwise in TFLs mock shell(s).

When appropriate, considering number of patients within groups, Clopper-Pearson confidence intervals (CI) will be provided for rates.

For time to event type data, Kaplan-Meier estimates will be presented for dose groups with sufficiently high patient numbers.

Due to being of non-comparative nature, no inferential statistical analysis will be applied in either the escalation or the expansion part of this study to compare dose groups or arms.

The final statistical analysis will occur after all patients have discontinued treatment for any reason and completed safety FU.

All additional data collected during long-term survival FU will be separately reported in a combined FU analysis.

Notes:

- Any duration [days] = end date – onset date + 1
- All data will be listed
- All unscheduled visits will be summarized into one visit as the final visit in summary tables. In case of multiple unscheduled assessments, the first one will be considered in the summary table but will all be listed.

5.2 Subject Disposition and Data Sets Analyzed

The number and percentage of patients who were screened and have signed informed content, but did not receive any treatment, as well as patients receiving study treatment, in each analysis population, those who are ongoing on study treatment and those who discontinued study treatment together with primary reason for discontinuing treatment, those who completed and discontinued the study as well as the reasons for any premature discontinuation from the study will be summarized by cohort i.e. by dose groups in dose escalation part A. Data will be listed accordingly.

Inclusion and exclusion criteria will be listed.

5.3 Protocol Deviations or Violations

5.3.1 Violation criteria

Patients who meet any of the following criteria will be listed and presented in the study report:

- Non-compliance with inclusion criteria.
- Non-compliance with exclusion criteria.

5.3.2 Protocol deviations

All important protocol deviations occurring during the study will be reviewed, classified (as major/minor) and approved by sponsor in data review meeting prior to database lock. Minor deviation (e.g. Deviation in visit windows or time slots) may not justify exclusion of the patient. Should additional important protocol deviations, not anticipated at the time of preparing this SAP, be identified during the study, they will be documented in a separate document and included in all relevant protocol deviation reviews and approvals.

5.4 Demographic and Other Baseline Characteristics

5.4.1 Demographic Characteristics

All demographic and baseline characteristics will be summarized by cohort for both SS and PK populations and listed accordingly. The summary will include age, gender, race, height, baseline bodyweight, baseline BMI and screening and baseline ECOG. If two populations are identical, the table will be appropriately identified as representing both populations and will not be duplicated. Demographic characteristics will be also provided by subtype of cancer (solid tumours except T-ALL/T-LBL, Adenoid Cystic Carcinoma, T-ALL or T-LBL).

Patients' initial cancer history will be summarized, including tumour type (for breast cancer including ER, PR and HER2 status), Notch status as well as histological tumour grade of initial cancer, also whether or not previous systemic anti-cancer treatments, previous radiotherapies or previous surgeries had been applied and if cancer is recurrent or metastatic; the full information on primary cancer will be provided in Listings.

Active medical history (i.e. histories marked as ongoing at time of screening) will be summarized by number of active disease events, number and percentage of patients with at least one active

disease and number and percentage of patients with each disease displayed by System Organ Class (SOC) and preferred term (PT).

Prior systemic anti-cancer (AC) therapies will be summarized by number and percentage of patients previously treated with at least one systemic agent, by line of prior therapy, best response to and reason for discontinuation of prior therapy as well as number and percentage of patients who progressed under the prior therapy. These will also be summarized by number of systemic therapies, number and percentage of patients previously treated with at least one systemic agent and number and percentage of patients treated with each systemic agent displayed by type of cancer and preferred drug name and listed. Prior radiotherapy will be summarized by number and percentage of patients who received any prior radiotherapy, by body location of, setting of and best response to prior radiotherapy as well as number and percentage of patients who progressed after prior radiotherapy. Prior surgery will be summarized by number and percentage of patients with any prior surgery, by type, body location and outcome of prior surgery as well as number and percentage of patients who progressed after prior surgery.

Substance use at screening will be summarized for smoking status, alcohol use and drug abuse.

Vital signs and ECOG status at baseline will be summarized and listed.

Physical examination at baseline will be listed.

Fresh tumour biopsies collected at baseline will be listed only.

Notes:

- Age will be derived in eCRF from entered year of birth.
- Medical history will be coded according to MedDRA version will be noted in the footnote of the Tables.
- Active medical history is defined as marked as ongoing at time of screening.
- Prior systemic AC therapies will be coded according to WHO-Drug Dictionary version will be noted in the footnote of the Tables.

5.4.2 Prior and Concomitant Medications

Incidence of prior and concomitant medication will be presented by cohort, ATC class and preferred drug name and listed.

Prior medications are those that started and stopped before exposure to study medication; concomitant medications are all medications taken during the study period, including those started before but on going at first dose.

Where a medication start date is partially or fully missing, and it is unclear as to whether the medication is prior or concomitant, it will be assumed that it is concomitant.

Medications within 24 hours prior to PK sampling will be listed only.

Note:

Medications are coded using WHO Drug dictionary version will be stated in the footnote of the tables.

5.5 Measurements of Treatment Compliance and Exposure

Exposure to study drug will be summarized overall and by cohort as well as by cycle for the SS for following parameters:

- Cumulative dose (in g)
- Duration of study treatment (in months)
- Actual exposure (in months)
- Actual dose intensity (in mg/d)
- Planned dose intensity (in mg/d)
- Relative dose intensity (in %)
- Treatment compliance (in %)

All information recorded concerning study drug modifications will be listed.

Notes:

Duration of study treatment (months) is defined as:

(date of last dose of study treatment – date of first dose + 1) / 30.4375.

Actual exposure (months) is defined as:

number of days when patients actually took study medication/ 30.4375.

Actual dose intensity (mg/d) is defined as:

total actual dose taken (mg)/actual exposure (d).

Planned dose intensity (mg/d) is defined as:

total planned dose taken (mg)/planned exposure, i.e. planned days on treatment (d)

Relative dose intensity is defined as:

actual dose intensity / planned dose intensity x 100%

Treatment compliance (in %) is defined as:

total actual dose taken/ total planned dose*100

5.6 Primary Analysis

5.6.1 Dose Escalation

Each dose escalation step is considered an IA.

An adaptive BLRM guided by the EWOC principle will be used in the dose escalation.

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.

5.6.1.1 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 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.

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.

5.6.1.2 Bayesian Logistic Regression Model to Determination of MTD

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.

The model is formulated as follows:

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

where $\text{logit}(p) = \log(p/(1-p))$.

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.

$$\pi(\theta) = \varphi_1\pi_1(\theta) + \varphi_2\pi_2(\theta)$$

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 highest non-severely toxic dose (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 15mg 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 $1/10^{th}$ of the HNSTD (8.6 mg/kg/day) in (male) dogs is approximately 9000 µg*h/mL, which we would correspond to a human dose of 15*9000/600 = 225 mg, with a prior median DLT rate of 0.1%. A cautious approach was chosen again, using a median 25% DLT rate at d = 225 mg.

Table 4 Summary of prior distribution

Prior Component	Mixture Weight	Mean vector	SD 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 5. 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 5 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	SD	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.

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 is above 50%

OR

2. At least 6 patients have been treated at MTD, including the 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 of the model for Part A can be found in Appendix 2.

5.6.2 Efficacy Analysis

All efficacy endpoints will be summarized within cohort by descriptive statistics based on SS.

Tumour assessments (via CT, MRI or PET-CT, bone marrow, respectively, pending on tumour type) are scheduled for following time-points:

- At baseline
- During Cycle 2, 4, 6, etc.: on Day 15 (i.e. every 8 weeks)
- At EOT visit

Progression-free Survival (PFS) is assessed explicitly at week 24 and at EOT visit, though disease progression can be detected and recorded at any time-point.

Efficacy parameters are:

- Overall Response Rate (ORR)
- Best Overall Response (BOR)
- Time to Response (TTR)
- Duration of Response (DOR)
- Clinical Benefit Rate (CBR) at 3 months, at 6 months and at 9 months
- Progression-free Survival (PFS)
- Overall Survival (OS)

No formal hypothesis testing is planned.

All lesion and other tumour assessments will be included in the assessment of efficacy parameters.

All efficacy parameters from either the eCRF or calculated as part of statistical analysis will be listed.

In case of patients with solid tumour cancers, baseline lesion status as well as post-baseline assessments of target, non-target and new lesions will be provided. The overall response assessment as of RECIST1.1 are listed by individual cycles.

In T-ALL/T-LBL patients, baseline lesion status, tissue sites involved at baseline, post-baseline lesion status and new lesions will be listed; and so will the overall response assessments by cycle based on NCCN Guidelines on Adult Acute Lymphoblastic Leukaemia.

Patients who cannot be evaluated for response will be categorized as Not Evaluable (NE) or Unknown/Not Assessed (NA).

5.6.2.1 Best Overall Response (BOR)

BOR is defined as the best response recorded from the first day of study treatment until disease progression/recurrence, death or end of study respectively data cut-off, whatever comes first.

Patients with solid tumours are considered responders if they have a tumour assessment status of PR or CR according to RECIST, v1.1.

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence. Best is defined as the first response when all a subject's response assessments are sorted by CR, PR, SD, PD, NE/UNK. In general, the subject's best response assignment will depend on the achievement of the measurement criteria. For subjects without a post-baseline, a non-missing response assessment will have a BOR of NE assigned. Unknown (UNK) or patients with symptomatic deterioration but without any scan will also be mapped to NE.

Patients with haematologic malignancies are considered responders if they have a haematologic malignancies status CR or CRi as per NCCN guidelines.

Any response must be confirmed not less than 4 weeks after the criteria for response are first met.

Patients without a post-baseline assessment will be considered NE. Additionally, after baseline, a change in methods will result in an assessment of not evaluable.

Patients who were enrolled in study, but did not receive any study treatment will have a best overall response 'Missing' and will be included as non-responders in the analysis of BOR.

BOR for different cancer types will be summarized by cohort for patients with Solid Tumour and for those with haematologic malignancies. The BOR information will be provided in Listing.

5.6.2.2 Overall Response Rate (ORR)

Overall response rate (ORR), i.e. rate of patients with response (CR+PR for RECIST V1.1), will be presented together with corresponding Clopper-Pearson 95% CI for each dose group with at least 6 patients. 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.

For T-ALL/T-LBL patients, the overall bone marrow response rate as per local assessment, the number (n) and percentage (%) of patients with progressive disease [PD], refractory and relapsed disease will be summarized by cycle and overall for each dose group and overall, with 95 % CI. In addition to bone marrow the mediastinal response, CNS and extramedullary responses will be presented in the same way but only for subset of patients with extramedullary involvement at baseline. Swimmers plots will be generated for graphical display of response. Clopper-Pearson (exact) method will be used to derive the CI.

5.6.2.3 Time to response (TTR) and Duration of response (DOR)

TTR is defined as the time from the first day of study treatment to the first date the response criteria are met, given they were later confirmed. Patients who are not confirmed responders will be censored at the time of their last evaluable tumour assessment. Patients with no tumour assessment after the baseline visit will be censored at the time of the first day of study treatment plus 1 day.

For each dose group, estimates of the median TTR and the corresponding two-sided 95% CI will be presented along with the estimates for the 25th and 75th percentiles and the associated ranges (minimum, maximum) using the Kaplan-Meier (KM) approach.

DOR is defined only for the patients with a confirmed response according to RECIST, v1.1 for patients with solid tumours, according to NCCN guidelines for patients with haematologic malignancies.

By definition, DOR is the time interval between the date of the earliest qualifying response and the date of PD or death from any cause, whichever occurs first. For patients who are alive without progression following the qualifying response, DOR will be censored on the date of last evaluable tumour assessment or last FU for PD before the data cutoff date. Data for patients who are lost to FU prior to documented progression will be censored at the last tumour assessment date which the patient is known to be progression-free prior to the data cutoff date.

For each cohort, estimates of the median DOR and the corresponding two-sided 95% CI will be presented along with the estimates for the 25th and 75th percentiles and the associated ranges (minimum, maximum) using the Kaplan-Meier (KM) approach.

Both TTR and DOR will be provided in Listing.

5.6.2.4 Clinical Benefit Rate (CBR)

Patients with solid tumours are considered to have clinical benefit if they have a tumour assessment status of CR, PR or SD according to RECIST, v1.1.

The CBR at 3 months, 6 months and 9 months after treatment start will be presented together with corresponding Clopper-Pearson 95% CI for each dose group with at least 6 patients.

5.6.2.5 Progression Free Survival (PFS) and Overall Survival (OS)

PFS, measured in days, is defined as the time from the first day of study treatment until the first documented progression of disease or death from any cause, whichever occurs first.

PFS for patients who have neither progressed nor died will be censored on the date of last evaluable tumour assessment prior to the data cut-off date. For patients who have not died and have no recorded post-BL tumour assessment, PFS will be censored on the date of the first dose of study medication plus 1 day. Patients who die without any recorded post-baseline tumour assessment after receiving the first dose will be considered to have an event on the date of death. Data for patients who are lost to FU prior to documented progression will be censored at the last evaluable tumour assessments date which the patient is known to be progression-free prior to the data cut-off date.

For each dose group with at least 6 patients, estimates of the median PFS and the corresponding two-sided 95% CI will be presented along with the estimates for the 25th and 75th percentiles and the associated ranges (minimum, maximum) using the Kaplan-Meier (KM) approach.

OS is defined as time between the first day of study treatment and date of death of any cause. Patients for whom no death is captured on the clinical database are censored at the last date they were known to be alive. Patients with no post-BL information will be censored at the time of first study treatment plus 1 day.

For each dose group at least 6 patients, estimates of the median OS and the corresponding two-sided 95% CI will be presented along with the estimates for the 25th and 75th percentiles and the associated ranges (minimum, maximum) using the Kaplan-Meier (KM) approach.

Both PFS and OS details will be provided in Listing.

Futher survival status information from long-term FU will be listed in Listing.

5.7 Safety

The safety analysis is the primary analysis for this study.

All safety and tolerability assessments will be based on the SS and will be summarized within cohort.

The safety endpoints include the following:

- Incidence of treatment-emergent adverse events (TEAEs), including
  - All adverse events (AE)
  - Serious adverse events (SAEs)
  - Dose-limiting toxicities (DLT)
- Laboratory tests values, including
  - Biochemistry
  - Haematology
  - Urinalysis
  - Cardiac markers
- Vital signs, including
  - Systolic and diastolic arterial blood pressure (BP)
  - Weight and BMI
  - Pulse rate (PR)
  - Oral temperature
- Cardiac function testing, including
  - Electrocardiogram (ECG), including Heart Rate, PR Interval, RR Interval, QRS Interval, QT Interval, QTc Interval
  - Incidence of abnormal ECG findings
  - Left ventricular ejection fraction (LVEF) results
  - Incidence of abnormal echocardiography findings
- Physical examination, including
  - Incidence of abnormal findings

- Incidence of abnormal, clinically significant findings

5.7.1 Adverse Events

AEs and SAEs will be summarized by cohort by presenting the number and percentage of patients having any event, number of events is also presented; summaries classifying events according to severity (CTCAE) grade, relationship to study drug, outcome and action taken with study drug will be presented. Missing severity, relationship or outcome will be classed as unknown. If a patient experiences the same AE at more than one severity, or with more than one relationship to investigational product, the most severe rating or the stronger causal relationship to investigational product will be given precedence.

All AEs, related AEs, SAEs, related SAEs, AEs with CTCAE Grade ≥ 3, related AEs with CTCAE Grade ≥ 3 as well as AEs leading to premature discontinuation, interruption or discontinuation of study drug or to dose modification will be also summarized presenting the number and percentage of patients having an event in each MedDRA system organ class (SOC) and preferred term (PT) category. A patient with more than one occurrence of the same AE in a particular SOC will be counted only once in the total of those experiencing AEs in that SOC.

All AE, and SAE information collected will be listed as appropriate. A separate summary table and a listing including only DLTs will be also provided.

Only treatment emergent AEs, i.e. AEs occurring on or after day of first administration of study treatment, will be included in the event summaries. Non-treatment emergent events (starting prior to exposure to study treatment) will be included in the patient listings and flagged but not included in the summary tables. Where an AE start date is partially or fully missing, and it is unclear as to whether the AE is treatment emergent, it will be assumed that it is.

All deaths overall will be summarized and listed.

Notes:

- AEs coded using MedDRA version will be noted in the footnote of the tables and listings.
- CTCAE

5.7.2 Laboratory Evaluations

Laboratory values will be graded by NCI CTCAE version 4.03 (or higher), 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 values should be reported in SI units (if applicable), results reported in non-SI unit should be converted to SI unit. Missing values will be excluded.

Only patients with non-missing change from baseline data at the visit will be included in the post-baseline summary statistics at the visit. Baseline is defined as the last measurement prior to dosing.

Results from the following laboratory parameters will be summarized by cohort and time point:

Haematology: Haemoglobin, haematocrit, erythrocytes (RBC), reticulocyte count, platelets, leukocytes (WBC), differentials (counts): neutrophils, eosinophils, lymphocytes, monocytes, basophils.

Coagulation: Prothrombin time expressed as International normalized ratio (INR), activated partial thromboplastin time (aPTT).

Biochemistry: Total protein, albumin, alkaline phosphatase, total bilirubin, calcium, cholesterol, chloride, creatine kinase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase, C-reactive protein (CRP), lipase, pancreatic amylase, glucose, inorganic phosphorus, magnesium, potassium, sodium, triglycerides, urea/blood urea nitrogen, uric acid, creatinine (creatinine clearance estimated according to the Cockcroft-Gault formula).

Aspartate aminotransferase (AST), alanine aminotransferase (ALT), total and conjugated bilirubin, albumin, alkaline phosphatase (ALP), gamma-glutamyl-transferase (GGT), amylase, bicarbonate, calcium, chloride, total cholesterol, creatine phosphokinase (CPK), C-reactive protein (CRP), creatinine, blood urea nitrogen (BUN), glucose, phosphate, lactate dehydrogenase (LDH), lipase, magnesium, potassium, total protein, sodium, triglycerides, urate.

Urine from dipstick: Protein, glucose, ketones, red (RBC) and white blood cells (WBC), pH, specific gravity.

Detailed Urinalysis (if clinically significant positive results from the dipstick): bacteria, casts (RBC, haemoglobin, hyaline, WBC), RBC, WBC, mucus, oxalates, epithelial cells, renal and squamous epithelial cells, uric acid crystals, unspecified crystals, urate, yeast.

Cardiac markers: Serum troponin, N-terminal pro-peptide BNP

Laboratory parameters other than cardiac markers are assessed at following time points:

- At screening
- During Cycle 1 on Day 1, Day 3 (only Part A), Day 8, Day 15 and Day 22
- During other Cycles on Day 1 and Day 15
- At EOT visit

Cardiac serum markers are to be collected:

- At baseline
- During Cycle 1: on Day 22
- During other Cycles on Day 1 and Day 15
- At EOT visit

Absolute values and changes values from baseline for haematology, biochemistry and coagulation assessments will be summarized (cf. notes in section 4.1).

Shift tables for Out of Normal Range Results for haematology, biochemistry and coagulation assessments will be summarized.

Shift tables for CTCAE grades for haematology, biochemistry and coagulation assessments will be summarized.

Local dipstick urinalysis () as well as results will be summarized according to being normal or abnormal.

All laboratory results will be listed.

A separate listing for abnormal lab values (Grade 3 and higher, and low/high values) will be presented.

Notes:

- All results outside ranges will be flagged in the data listings as follows:
  - Out-of-reference-range values will be marked as high (H) or low (L).
  - Values falling outside the clinically significant reference range of the respective laboratory will be marked as clinically significant laboratory abnormalities (i.e., potentially clinically relevant) and labelled in addition by "CS". Marked laboratory abnormalities will be labeled in the subject listings as "HH" for significantly high or "LL" for significantly low.
- Repeat laboratory results within a visit will replace the original value.
- Unscheduled results will be listed only.

  Any other laboratory results will be listed only.

5.7.3 Vital Signs

Absolute as well as change from baseline results for systolic and diastolic blood pressure, pulse rate, Body Mass Index (BMI), weight and oral temperature will be summarized by cohort and visit, using standard descriptive statistics. All vital signs will be listed together with flags for outside of reference range.

Only patients with non-missing change from baseline data at the visit will be included in the post-baseline summary statistics at the visit.

Frequency of patients with notably abnormal vital signs will be provided by cohort and visit and will be defined as follows:

- Systolic blood pressure [mmHg]: >=180 mmHg or <=90 mmHg with increase or decrease from baseline of >=20 mmHg

- Diastolic blood pressure [mmHg]: >=105 mmHg or <=50 mmHg with increase or decrease from baseline of >=15 mmHg

- Pulse rate [bpm]: >=120 bpm or <=50 bpm with increase or decrease from baseline of >=15 bpm

Baseline is defined as the last measurement prior to dosing.

Systolic and diastolic blood pressure as well as pulse rate is recorded at following time points:

- At screening
- During Cycle 1: on Days 1, 2 (only **Part A)**, 3 (only **Part A)**, 8, 15 and 22
- During other Cycles on Day 1 and Day 15
- At EOT visit
- At unscheduled visits.

Oral temperature is taken at following time points:

- At baseline
- During Cycle 1: on Days 2 (only **Part A)**, 3 (only **Part A)**, 8, 15 and 22
- During other Cycles on Day 1
- At EOT visit
- At unscheduled visits.

Weight, and hence BMI, is assessed at following time points:

- At baseline
- During all Cycles other then 1: on Day 1
- At EOT visit
- At EOS visit
- At unscheduled visits.

Note:

- All results outside ranges will be flagged in the data listings as follows:
  - Out-of-reference-range values will be flagged as high (H) or low (L) where reference ranges are as follows:
    - Weight: >=7% increase or decrease from baseline weight
    - Systolic blood pressure [mmHg]: >=180 mmHg/<=90 mmHg with increase/decrease from baseline of >=20 mmHg
    - Diastolic blood pressure [mmHg]: >=105 mmHg/<=50 mmHg with increase / decrease from baseline of >=15 mmHg
    - Pulse rate [bpm]: >=120bpm/<=50 bpm with increase / decrease from baseline of >=15 bpm
  - Values falling outside the clinically significant reference range of the respective laboratory will be marked as clinically significant vital signs abnormalities (i.e., potentially clinically relevant). Marked abnormalities will be labelled in the subject listings as “HH” for significantly high or “LL” for significantly low.

5.7.4 Electrocardiograms

Cardiac function testing includes 12-lead ECG, Holter ECG and LVEF assessment

A 12-lead ECG is carried out:

- At screening
- During Cycle 1: on Days 1, 2 (only **Part A)**, 3 (only **Part A)**, 8, 15 and 22
- During other Cycles on Day 1 and Day 15

- At EOT visit
- At unscheduled visits.

A Holter ECG is done:

- At baseline

Only for **Part A:**
- During Cycle 1: on Days 1 and 8
- During Cycle 2: on Day 1
- At EOT visit

Assessment of LVEF via MUGA or ECHO is done:
- At baseline
- During Cycle 1: on Day 8
- During Cycle 3: on Day 1
- At EOT visit

Details of the ECG analyses will be covered by a separate SAP created by BMS.

Results of LVEF assessments (not done, normal, abnormal not clinically significant and abnormal clinically significant) will be summarized by cohort and time point and listed. If either result is missing for any patient, then an 'Unknown' category will be presented.

5.7.5 Physical Examination and ECOG status

A physical examination by body system (i.e. general appearance, eyes, ears and nose, skin, head, respiratory including throat, cardiovascular, renal and urinary, gastrointestinal, musculoskeletal, nervous system and other) is performed at following time points:

- At screening
- At baseline
- During Cycle 1: on Days 2 (only **Part A)**, 3 (only **Part A)**, 8, 15 and 22
- During other Cycles on Day 1 and Day 15
- At EOT visit
- At unscheduled visits.

Abnormal, clinically significant findings will be summarized by cohort and time point. All physical examination results will be listed.

ECOG performance status is assessed at screening, at baseline, during cycle 1 on days 2, 3, 8, 15 and 22, during all other cycles on days 1 and 15 as well as at EOT, at safety FU and at unscheduled visits. It will be summarized by dose group and time point and listed.

5.8 Pharmacokinetic Assessments

5.8.1 Pharmacokinetic Analysis

Samples for PK profiles is done at following timepoints:

In Part A:

- During Cycle 1:
  - on Day 1: pre-dose, 0.5h, 1h, 2h, 4h, 6h, 8h, 12h post-dose
  - on Day 2: 24h post Day 1 dose, pre-dose
  - on Day 3: pre-dose
  - on Day 8: pre-dose, 0.5h, 1h, 2h, 4h, 6h, 8h
  - on Day 9: 24h post Day 1 dose, pre-dose
  - on Day 15: pre-dose, 1h post-dose
  - on Day 22: pre-dose, 1h post-dose

  In case an oral BID dosing regimen of CB-103 is implemented, the PK sampling scheme during cycle 1 will be adjusted as follows:
  - on Day 1: pre-dose, 1st intake, 0.5h, 1h, 2h, 4h post-dose
  - on Day 1: pre-dose, 2nd intake, 0.5h, 1h, 2h, 4h post-dose
  - on Day 2: pre-dose, 1st intake
  - on Day 8: pre-dose, 1st intake, 0.5h, 1h, 2h, 4h post-dose
  - on Day 8: pre-dose, 2nd intake, 0.5h, 1h, 2h, 4h post-dose
  - on Day 9: pre-dose, 1st intake
  - on Day 15: pre-dose, 1st intake
- During Cycle 2:
  - on Day 1: pre-dose, 0.5h, 1h, 2h, 4h, 6h and 8h post-dose
  - on Day 15: pre-dose
- All further Cycles:
  - Each visit: one sample, any time

The following PK parameters will be calculated using non-compartmental methods as data permit for each dose:

- Maximum observed plasma concentration (C_{max})
- Minimum observed plasma concentration (C_{min})
- Time to maximum plasma concentration (t_{max})
- Time to last measurable plasma concentration (t_{last})
- Concentration at last measurable plasma concentration (C_{last})
- Area under the plasma concentration-time curve up to 8h ($AUC_{(0-8)}$)
- Area under the plasma concentration-time curve up to 24h ($AUC_{(0-24)}$)

- Total area under the plasma concentration-time curve from time zero to infinity ($AUC_{(0\text{-}inf)}$)
- Accumulation ratio (AR)
- Terminal-phase elimination rate constant (λ_z)
- Elimination half-life ($t_{1/2}$)
- Apparent clearance of drug after oral administration (CL/F)
- Apparent volume of distribution (V_d/F)
- Apparent volume of distribution at steady state (Vss/F)

Non-compartmental analysis will be performed using Phoenix WinNonlin version 6.3.

For each PK parameter, individual and mean data, i.e. summary statistics (including number of patients, arithmetic mean together with SD, geometric mean and CV% [except for t_{max} and t_{last}], median, Min and Max) will be presented.

Area under the plasma concentration-time curve to the last observable plasma concentration [$AUC_{(0\text{-}t)}$] will be calculated from the observed data using the linear up logarithmic down trapezoidal method. Total area under the plasma concentration-time curve from time zero to infinity [$AUC_{(0\text{-}inf)}$] will be then estimated by $AUC_{(0\text{-}inf)} = AUC_{(0\text{-}t)} + C_t/\lambda_z$, where C_t will be the observed concentration at the last quantifiable time point.

The accumulation ratio (AR) is defined as AR = $AUC_{(0\text{-}24)}$ Day 8 / $AUC_{(0\text{-}24)}$ Day 1.

The terminal-phase elimination rate constant (λ_z) will be estimated by log-linear regression of those data points visually assessed to be in the terminal phase of the profile. At least three terminal plasma concentrations after Cmax will be used for estimating λ_z. Elimination, i.e. terminal-phase, half-life ($t_{1/2}$) will be calculated as $t_{1/2} = Ln2/\lambda_z$, apparent clearance of drug after oral administration as CL/F=Dose/$AUC_{(0\text{-}inf)}$, apparent volume of distribution as V_d/F=Dose/($AUC_{(0\text{-}inf)}*\lambda_z$) and volume of distribution at steady state V_d/SS = Dose* $AUMC_{(0\text{-}inf)}/AUC_{(0\text{-}inf)}^2$, where AUMC is the area under the first moment curve.

Individual CB-103 plasma concentration-time data will be listed and graphically displayed for each patient both on linear as well as on semi-logarithmic (on concentration axis) scale for Cycle 1 Day 1, Cycle 1 Day 8 and Cycle 2 Day 1, where C1D1, C1D8 and C2D1 profiles will be overlaid for all individuals by cohort and day.

Summaries of plasma concentrations will be presented in tabular form by assessment time-point (Cycle, day within cycle and time post study drug intake). Also for Cycle 1 Day 1, Cycle 1 Day8 and Cycle 2 Day1, the mean (+/-SD) plasma concentrations will be displayed graphically over time on linear as well as on semi-logarithmic (on concentration axis) scale for each cohort and for each visit across cohorts. A graph of the pre-dose mean (+/-SD) concentrations for all days where a PK plasma sample is drawn will be provided, with both individual curves by cohort and average curves across cohorts.

Plots of key PK parameters (Cmax, $AUC_{(0\text{-}inf)}$) vs dose including all visits in one plot figure will be provided.

All PK summaries are based on the PK Set and will also be provided by indication i.e, for solid tumours or T-ALL/T-LBL and by ethnicity.

All derived PK parameters will be listed for all patients in PK set and summarized within cohort.

5.8.2 Below Limit of Quantification (BLQ)

5.8.2.1 During calculation of PK parameters:

- Any BLQ (<LLOQ (Lower Limit of Quantification)) values that occur before the first quantifiable concentration will be replaced with zero.
- If a BLQ (<LLOQ) value occurs after a quantifiable concentration in a profile and is followed by a value of LLOQ or above, then the BLQ (<LLOQ) will be replaced with LLOQ/2.
- If two BLQ (<LLOQ) values occur in succession, the profile will be deemed to have terminated at the final quantifiable concentration and subsequent LLOQ or above values will be treated as 'missing'.

5.8.2.2 For individual pharmacokinetic profiles

- A value of LLOQ/2 will be substituted for any <LLOQ irrespective of where they are in the profile and the plasma concentration-time data will be plotted as such.
- A line with a label of LLOQ in the concentration axis will be overlaid to show the level of LLOQ.

5.8.2.3 Mean or median concentration profiles

When estimating the mean or median value for the concentration at a given time point (descriptive mean or median curve), the following guidelines should be considered:

- The mean/median value at a time with one or more BLQ (<LLOQ) values will be calculated by assigning LLOQ/2. If the calculated mean/median value is less than LLOQ of the assay, then that time point will be ignored for plotting the mean/median pharmacokinetic profiles.
- It should be noted that since a high proportion of BLQ (<LLOQ) values may affect the SD; if more than 50% of values are imputed, then no mean/median be calculated for that time point.
- A line with a label of LLOQ (Lower Limit of Quantification) in the concentration axis will be overlaid to show the level of LLOQ.

5.8.2.4 Concentration summaries:

- Prior to calculation of summary statistics:
    - Any individual values less <LLOQ that occur before the first quantifiable concentration will be replaced with zero.

  - If a <LLOQ value occurs after a quantifiable concentration in a profile and is followed by a value of LLOQ or above, then the <LLOQ will be replaced with LLOQ/2.
  - After the last value above LLOQ, individual patients with values below LLOQ at the end of the plasma curve will have these values replaced with zero.
- If the calculated mean value is less than LLOQ, then the summary statistics will be left blank, with <LLOQ presented only for the mean value.
- Within the summary statistics, any minimum, median, or lower confidence values that are calculated to be <LLOQ will be presented as <LLOQ within the summary presentation.
- In listings, <LLOQ will be presented for all values of <LLOQ and a value of LLOQ added to a footnote.

Notes:

- The lower limit of quantification (LLOQ) is 3ng/mL.

Concentrations (C_{max}) will be rounded to 3 significant figures. All times (t_{max} and $t_{1/2}$) will be rounded to 2 decimal places. All AUCs, CL/F, Vd/F and Vss/F to 4 significant figures. Summary statistics will be reported to one more decimal place (or significant figure) than the data listings, except CV% which will be rounded to 2 decimal places in all instances, and minimum and maximum values which will be reported to the same precision used in the listings.

5.8.3 PK assessments in CSF in T-ALL/T-LBL patient

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.

5.9 Biomarker Analysis

Summary statistics of PD, mechanistic, and anti-tumour markers will be reported by dose group and examined for possible correlations with CT/MRI/PET-CT efficacy endpoints. Additional analyses include comparing PD modulation with exposure. Details of the biomarker analyses will be covered by a separate SAP.

6. Changes in the Conduct of the Study or Planned Analysis

There were no changes in the analysis planned in the protocol of the study at the time of preparing this SAP.

Any deviations from the approved SAP will be described and justified in the CSR.

7. Appendices

Appendix 1: Document History

Document Version, Status, Date	Summary / Reason for Changes
Version 2.0, Final, 29Apr2022	New version following Protocol Amendment
Version 1.0, Final, 28Aug2019	Initial version

Appendix 2: Statistical Details for 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** **30**	**0** **0**	**3** **3**	0.007	**60**	0.871	0.094	0.035
5	**15** **30**	**0** **1**	**3** **3**	0.121	**30**	0.602	0.277	0.121
6	**15** **30**	**0** **2**	**3** **3**	0.4	**15**	0.439	0.356	0.206
7	**15** **30**	**0** **1**	**3** **6**	0.034	**60**	0.53	0.308	0.162
8	**15** **30** **60**	**0** **0** **1**	**3** **3** **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.

Appendix 3: Schedule of Assessments for Part A

Study Period	Pre-screening*	Screening	Baseline	Six cycle treatment period (28-day cycles, until PD or toxicity)													EOT[28]	Safety follow-up[29]	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
Respiratory rate			X		X	X	X		X	X	X				X		X			
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

Study Period	Pre-screening*	Screening	Baseline	Six cycle treatment period (28-day cycles, until PD or toxicity)													EOT[28]	Safety follow-up[29]	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	
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[22]	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								
Whole blood, plasma			X								X				X					
Stool sample[15]											◄	———	———	►						
Chest X-ray [16]			X																	
Efficacy Assessment (PFS)																	X			

Study Period	Pre-screening*	Screening	Baseline	Six cycle treatment period (28-day cycles, until PD or toxicity)													EOT[28]	Safety follow-up[29]	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	
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
Tumour assessment (CT/MRI/PET-CT) [21]			X											X		X[22]	X		X[22]	X
Hair follicles [23]			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
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 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 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 of the protocol.

[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 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 of the protocol)

[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, is 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 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 of the protocol) 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 of the protocol. In the MTD/RP2D confirmatory cohort they will be collected only on selected patient groups.

[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] EOT: within 14 days after the last administration of CB-103 (within the 12 cycles period or completion of the treatment period in T-ALL/T-LBL patients). All participating patients must complete this visit even if they have had to prematurely discontinue treatment with CB-103.

[29] Safety Follow-up: within 28 days after the last dose of CB-103 (within the 6 cycles period or completion of the treatment period in T-ALL/T-LBL patients). All patients must have this visit, even if they have prematurely discontinued CB-103 treatment.

8. References

[1]ICH. *Structure and Content of Clinical Study Reports*, Guideline E3, 1995. Available at https://database.ich.org/sites/default/files/E3_Guideline.pdf

[2]ICH. *Statistical Principles for Clinical Trials*, Guideline E9, 1998. Available at https://database.ich.org/sites/default/files/E9_Guideline.pdf