Official Title of Study:

A Phase 1, Multi-center, Open-label Dose-escalation Study to Assess the Safety, Tolerability, and Pharmacokinetics of CC-122 Administered Orally to Adult Japanese Subjects With Advanced Solid Tumors or Non-Hodgkin's Lymphoma

NCT Number: NCT02509039

Document Date (Date in which document was last revised): December 13, 2016

A PHASE 1, MULTI-CENTER, OPEN-LABEL DOSE-ESCALATION STUDY TO ASSESS THE SAFETY, TOLERABILITY, AND PHARMACOKINETICS OF CC-122 ADMINISTERED ORALLY TO ADULT JAPANESE SUBJECTS WITH ADVANCED SOLID TUMORS OR NON-HODGKIN'S LYMPHOMA

INVESTIGATIONAL PRODUCT (IP):	CC-122
PROTOCOL NUMBER:	CC-122-ST-002
ORIGINAL DATE FINAL:	06 Feb 2015
AMENDMENT No. 01 DATE FINAL:	09 Apr 2015
AMENDMENT No. 02 DATE FINAL:	28 Mar 2016
AMENDMENT No. 03 DATE FINAL:	13 Dec 2016
EudraCT NUMBER:	Not applicable
IND NUMBER:	Not applicable
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CELGENE THERAPEUTIC AREA HEAD SIGNATURE PAGE

{See appended electronic signature page}	
Signature of Celgene Therapeutic Area Head	**dd mmm yyyy**
Printed Name of Celgene Therapeutic Area Head and Title By my signature, I indicate I have reviewed this protocol and find its content to be acceptable.	

SITE PRINCIPAL INVESTIGATOR SIGNATURE PAGE

Signature of Site Principal Investigator	**dd mmm yyyy**
Printed Name of Site Principal Investigator **Institution Name:** _____ By my signature, I agree to personally supervise the conduct of this study at my study site and to ensure its conduct is in compliance with the protocol, informed consent, Institutional Review Board (IRB)/Ethics Committee (EC) procedures, instructions from Celgene representatives, the Declaration of Helsinki, ICH Good Clinical Practices Guidelines, and local regulations governing the conduct of clinical studies.	

PROTOCOL SUMMARY

Study Title

A phase 1, multi-center, open-label dose-escalation study to assess the safety, tolerability, and pharmacokinetics of CC-122 administered orally to adult Japanese subjects with advanced solid tumors or non-Hodgkin's lymphoma

Indication

Advanced solid tumors or non-Hodgkin's lymphoma (NHL)

Objectives

The primary objectives of the study are:

- To determine the safety and tolerability of CC-122 when administered orally to adult Japanese subjects with advanced solid tumors or NHL and to define the maximum tolerated dose (MTD) and/or recommended phase 2 dose (RP2D)
- To determine the plasma pharmacokinetics (PK) of CC-122 in Japanese subjects with advanced solid tumors or NHL

The secondary objective of the study is:

- To make a preliminary assessment of the antitumor activity of CC-122

The exploratory objectives of the study are:

- To evaluate the plasma PK of CC-122 formulated capsules and compare results to the plasma PK of CC-122 active ingredient in capsule (AIC)
- To assess the tolerability of CC-122 formulated capsules
- [redacted]

Study Design

This is a phase 1, multicenter, open-label, dose-escalation study that will evaluate the safety, tolerability, PK, and preliminary efficacy of CC-122 in Japanese subjects with advanced solid tumors or NHL.

Subjects will receive ascending dose levels of CC-122 from Cycle 1 onwards to measure PK and to determine safety and tolerability.

An initial cohort of at least three subjects will be given CC-122 at a dose of 2.0 mg on an intermittent dosing schedule (5 continuous days out of 7 days per week) using the active ingredient in capsule (AIC) and 3-6 subjects will be enrolled in subsequent dose levels. Dose

escalation for subsequent cohorts will proceed according to a standard dose escalation design (3+3 design) (Storer, 1989) to establish initial toxicity.

The first dose level will be assessed in subjects with solid tumors or NHL, and subsequent dose levels will only be assessed in subjects with NHL.

All subjects will be treated and observed for at least 28 days (Cycle 1) after the first dose of CC-122 (dose-limiting toxicity [DLT] evaluation period) before the dose level is escalated in another cohort. The provisional dose levels to be evaluated are shown in Table 1.

A standard escalation schedule will be initiated in order to establish the MTD by assessing the occurrence of DLTs. Smaller increments and additional subjects within a dose cohort may also be evaluated as necessary to determine the MTD and RP2D more precisely.

A dose level will be considered tolerable if 0 of 3 treated subjects experiences a DLT during the DLT evaluation period for each respective group. If 1 of 3 subjects experiences a DLT, 3 additional subjects will be enrolled and treated at that dose level. A dose will be considered a non-tolerated dose (NTD) when two or more out of six evaluable subjects in a cohort experience DLTs during the DLT evaluation period. The MTD is defined as the last dose level below the NTD with zero or one out of six evaluable subjects experiencing DLTs during the DLT evaluation period. At least 6 subjects will be enrolled at the MTD/RP2D.

The decision to either evaluate a higher dose level or declare the MTD or RP2D will be determined by the Safety Review Committee (SRC), which includes the principal investigator and Celgene's medical monitor (see Section 8.2.1), each time all clinical and laboratory safety data for a given cohort are available for review.

The SRC may decide to identify an RP2D based on safety, PK, and preliminary efficacy information, which will not exceed the MTD from global CC-122 trials in various indications.

Study Population

Japanese men and women, 20 years or older, with advanced solid tumors, or NHL, including subjects who have progressed on (or were not able to tolerate) standard therapy or for whom no standard anticancer therapy exists.

Approximately 15 subjects will be enrolled and treated; however, the total number of subjects enrolled will depend on the number of dose cohorts needed to establish the MTD.

Length of Study

This study will consist of 3 periods: screening, treatment, and end of treatment & follow-up.

During the screening period, lasting up to 28 days, subjects will undergo assessments to determine their eligibility. Subjects who qualify for enrollment into the study will enter the treatment period. Each subject will be administered oral doses of CC-122 in the treatment period, which starts on Cycle 1 Day 1 where investigational product (IP) is administered on a 5 continuous days out of 7 days per week intermittent dosing schedule (Cycle = 28 days).

If subjects continue therapy with CC-122, subsequent cycles are 28 days long on a 5 continuous days out of 7 days per week intermittent dosing schedule.

Subjects may continue CC-122 without interruption for as long as they derive benefit, as assessed by the investigator. Treatment will be discontinued if there is evidence of clinically significant disease progression, unacceptable toxicity or if the subject/physician decides to stop treatment.

The follow-up period will begin at the discontinuation of IP treatment. Subjects will have an end of treatment (EOT) assessment during a visit within 21 days of the last dose of IP and a follow-up visit 28 days after the last dose of IP to obtain information regarding new or ongoing adverse events (AEs).

The End of Trial is defined as either the date of the last visit of the last subject to complete the study, or the date of receipt of the last data point from the last subject that is required for primary, secondary and/or exploratory analysis, as prespecified in the protocol and/or the Statistical Analysis Plan, whichever is the later date.

Study Treatments

The starting dose of CC-122 is a flat dose of 2.0 mg on a 5 continuous days out of 7 days per week intermittent dosing schedule using AIC.

The provisional dose-escalation levels are as follows and intermediate or lower doses of CC-122 may be evaluated as necessary.

Table 1: Provisional Dose-escalation Levels

Cohort	CC-122 dose
Assessed in subjects with solid tumors or NHL	
-1	1.0 mg (5 continuous days out of 7 days per week intermittent dosing) using the active ingredient in capsule (AIC) formulation [only used as necessary if the first dose level is not considered tolerable]
1	2.0 mg (5 continuous days out of 7 days per week intermittent dosing) AIC
Assessed only in subjects with NHL	
2	3.0 mg (5 continuous days out of 7 days per week intermittent dosing) AIC
3	4.0 mg (5 continuous days out of 7 days per week intermittent dosing) AIC
4	3.0 mg (5 continuous days out of 7 days per week intermittent dosing) using the formulated capsules

After at least 3 subjects have been enrolled in the 4 mg CC-122 AIC cohort (Cohort 3) and this dose level is determined to be tolerable, at least 6 subjects will be subsequently enrolled in the 3 mg CC-122 formulated capsules cohort (Cohort 4) to evaluate for differences in PK and tolerability.

Lower doses using CC-122 formulated capsules may be evaluated as necessary.

Intra-subject dose escalation is not permitted unless approved by the SRC.

Overview of Efficacy Assessments

Subjects will be evaluated for efficacy approximately every 2 cycles for the first 6 cycles and every 3 cycles thereafter. The primary efficacy variable is response for all tumor cohorts. Tumor response will be based on the Response Evaluation Criteria in Solid Tumors (RECIST, version 1.1) for solid tumors, and the International Workshop Group (IWG) Revised Criteria for Lymphoma (Appendix A, Section 19.1).

Overview of Safety Assessments

The safety variables for this study are adverse events, clinical laboratory assessments, 12-lead electrocardiograms (ECGs), left ventricular ejection fraction (LVEF) assessments, physical examinations and vital signs.

Overview of Pharmacokinetic Assessments

The PK of CC-122 will be determined from serial blood collections during the first treatment cycle.

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1. INTRODUCTION

1.1. Overview of CC-122

CC-122 is a pleiotropic pathway modifier (PPM), a novel class of compounds with multiple activities, which include immune modulation of several immune cell subsets including activation of T cells and natural killer (NK) cells; antiproliferative activity in multiple tumor types and antiangiogenic activity as demonstrated by inhibition of endothelial cell sprout formation and growth factor induced endothelial cell migration.

CC-122 is a nonphthalimide analog of thalidomide that retains binding affinity to a protein called cereblon (CRBN), a member of the Cullin 4-ring ligase complex.

1.1.1. Mechanism of Action

In lipopolysaccharide (LPS)-stimulated peripheral blood mononuclear cells (PBMCs) and whole blood, CC-122 inhibits tumor necrosis factor (TNF) release at nanomolar concentrations. In addition, CC-122 inhibits the release of other pro-inflammatory cytokines from LPS-stimulated PBMCs (granulocyte macrophage colony-stimulating factor [GM-CSF], interleukin-1β [IL-1β], macrophage inflammatory protein 1α [MIP1α], MIP1β, IL-6, IL-8, and macrophage-derived chemokine [MDC]) while enhancing IL-10 production. The immune modulation is further mediated by cereblon-dependent ubiquitination and subsequent degradation of aiolos and ikaros in T cells, resulting in the consequent expression of IL-2. The T cell costimulation of T cells by CC-122 also results in expression of IL-3, IL-5, IL-10, IL-13, IL-17A, interferon gamma (IFNγ), Rantes, TNFα and GM-CSF. CC-122 is also able to induce relocalization of F-actin to the membrane of PBMCs, resulting in a capping structure.

CC-122 enhances immunoglobulin G (IgG)/IL-2 stimulated NK cell production of IFNγ. This immunological modulation results in antitumor activity. For example, CC-122 enhances NK-mediated antibody-dependent cellular cytotoxicity (ADCC) with rituximab up to 30% compared with rituximab treatment alone in follicular (DoHH2), and diffuse large B cell lymphoma (DLBCL) (WSU-DLCL2, Farage, RIVA), and Burkitt's Lymphoma (Raji) cell lines. The ADCC-enhancing activity of CC-122 is concentration-dependent up to 0.1 μM. Taken together, these data suggest multiple immune modulating activities by CC-122, which have potential downstream antitumor effects.

The antiproliferative and cytotoxic effects of CC-122 have been shown in vitro in 11 cancer cell lines (Riva, U2932, TMD8, OCI-Ly10, WSU-DLCL2, SUDHL4, K1106P, Farage, Rec-1, DoHH2 and H929) and in vivo in four xenograft models (DoHH2, WSU-DLCL2, H929 and U87). The in vitro assays used five-day ^{3}H-thymidine incorporation and three-day adenosine triphosphate (ATP) production to measure effects on proliferation and cell toxicity, respectively. While CC-122 has antiproliferative effects against tumor cells, it has no activity up to 10 μM against normal primary human lung fibroblasts and aortic smooth muscle cells.

CC-122 also demonstrated potent antiangiogenic activity in several assays, including a human umbilical artery assay, human umbilical vein endothelial cell (HUVEC) proliferation, and a matrigel plug assay at low nanomolar concentrations. The data demonstrated that CC-122 was a

potent inhibitor of endothelial cell sprout formation, a measure of angiogenesis, and is comparable in potency to antiangiogenic agents AZD2171 and sunitinib.

CC-122 is inactive against a panel of 266 kinases.

1.1.2. Preclinical Toxicology

CC-122 has been evaluated in a core battery of repeat-dose (up to 28 days in rats, and 90 days in cynomolgus monkeys) and genetic toxicology studies.

In rats, the primary target organs of toxicity after 28 days of repeated administration were the kidney, lower urinary tract, and stomach. Secondary to the uremia, systemic effects consisting of vascular inflammation were present in multiple organs including the heart. Heart changes were only observed at the high dose (300 mg/kg/day); no changes were observed at the next highest dose (100 mg/kg/day) (82- to 133-fold and 38- to 59-fold safety margins based on Day 15 maximum observed concentration [C_{max}] and area under the concentration-time curve [AUC] values for the 3.0 mg dose in humans, respectively).

In a 3-month rat study, daily oral administration of CC-122 resulted in a new histologic finding of seminiferous tubule degeneration. Daily administration of CC-122 was well tolerated at all dose levels. After the 3 months of dosing, the animals underwent scheduled necropsies. Upon microscopic examination, mild to moderate seminiferous tubule degeneration was noted in 100 and 300 mg base/kg/day dose group animals. Toxicity was not observed in the reproductive organs of animals treated at the lower dose of 10 mg base/kg/day. All doses tested were at higher exposures than observed with human doses (the exposure at 10, 100 and 300 mg base/kg in rats is calculated to be 12x, 43x and 106x the observed human 3 mg dose exposure, respectively). Testicular lesions were not observed in a 28-day rat study (67x multiple to human exposure) or in 28-day and 3-month monkey studies (up to 53x multiple to human exposure). There were no histologic lesions in reproductive organs of female animals in these studies. The significance of this pre-clinical finding and the potential and relative clinical risk is unknown at this time.

In monkeys, the primary target organs of toxicity were lymphoid tissues and the lower gastrointestinal tract, resulting in systemic inflammation and early euthanasia. In the 28-day cynomolgus monkey study, minimal to moderate renal cortical inflammation was also present with variable severity across all dose groups (no blood urea nitrogen [BUN] or creatinine elevations were present). Renal cortical changes were not different from control animals in the 90-day cynomolgus monkey study. In the 90-day cynomolgus monkey study, 2 moribund and 1 terminal sacrifice animal administered 1.5 mg base/kg/day had minimal to moderate iris vascular changes (endothelial cell reactivity, and/or edema). Based upon the extent and overall severity of the inflammation present in these animals, the vascular changes in the eye were considered to be an extension of the systemic inflammatory process. Cardiovascular assessments demonstrated no test article-related cardiovascular, electrocardiogram (ECG) or vital sign changes up to the highest dose of 6.0 mg base/kg/day in males and females.

Minimal inhibition (9.6%) of human Ether-a-go-go-Related Gene (hERG) potassium ion channel was observed at 10 μM (approximately 35-fold safety margin based on Day 15 C_{max} values for the 3.0 mg dose in humans).

CC-122 was negative in a bacterial reverse mutation assay and negative in the in vitro chromosomal aberration assay in human peripheral blood lymphocytes.

There have been no reproductive and developmental toxicity studies conducted with CC-122 to date. The CC-122 Pregnancy Prevention Risk Management Plan for Celgene Clinical Trials (PPRMP) is mandated for all clinical trials.

1.1.3. Human Experience and Safety of CC-122

Human experience with CC-122 comes from three clinical pharmacology studies in healthy volunteers (CC-122-CP-001, CC-122-CP-002, and CC-122-CP-003); from one ongoing first-in-human phase 1a/1b study, CC-122-ST-001, in subjects with solid tumors and hematologic malignancies; one ongoing phase 1b study, CC-122-DLBCL-001, wherein novel combinations of CC-122, CC-223, CC-292 and rituximab are administered as doublets or triplets in subjects with DLBCL; and three additional studies in specific tumor types in adults, CC-122-HCC-001, CC-122-NHL-001, and CC-122-CLL-001.

Study CC-122-ST-001 is a study conducted in subjects with solid tumors and hematologic malignancies and was designed with two parts: dose escalation (Part A) and dose expansion (Part B). Part A was initiated with a starting dose of 0.5 mg administered orally once daily (QD) in three-subject cohorts, and increasing in 0.5 mg increments. Part B enrolled 4 parallel tumor cohorts, including non-Hodgkin's lymphoma (NHL), which includes DLBCL and mantle cell lymphoma (MCL), multiple myeloma (MM), hepatocellular carcinoma (HCC), and glioblastoma (GBM). Additional cohorts in DLBCL (DLBCL-2), GBM (GBM-2), primary central nervous system lymphoma (PCNSL), and MM (MM-2, with or without dexamethasone) are being enrolled. All data are considered preliminary.

Enrollment in Part A of the study has been completed with 34 subjects across seven dose cohorts: 0.5 (n=3), 1 (n=4), 1.5 (n=3), 2 (n=3), 2.5 (n=6), 3.0 (n=8) and 3.5 (n=7) mg QD. Dose--limiting toxicities (DLTs) were observed in two subjects and established the non-tolerated dose (NTD) at 3.5 mg QD. DLTs included Grade 3 fever, fatigue and generalized muscle weakness. No DLTs were reported for the declared maximum tolerated dose (MTD) of 3 mg QD. Diverse tumor types were enrolled, including solid tumors (n=27), lymphoma (n=5) and myeloma (n=2).

As of 13 Jan 2016, in Part A the most common treatment-emergent adverse events (TEAEs) (occurring in ≥ 20% of subjects overall) were fatigue, which was experienced by 19 (55.9%) subjects; neutropenia, 11 (32.4%) subjects; constipation, 9 (26.5%) subjects; nausea, peripheral edema and asthenia, which occurred in 8 (23.5%) subjects each; and dyspnea and vomiting, 7 (20.6%) subjects each. The system organ class (SOC) categories for which adverse events (AEs) were most frequently reported (≥ 50% of all subjects overall experienced an AE that is categorized in the respective SOC) were Gastrointestinal Disorders, with 70.6% of subjects experiencing an AE in this SOC; General Disorders and Administration Site Conditions, 67.6%; Infections and Infestations, 55.9%; and Blood and Lymphatic System Disorders, with 50.0%.

Other than decreases in white cell counts, no laboratory abnormalities showed clear treatment-related changes. ECG and left ventricular functioning monitoring were unremarkable. Seven subjects had sporadic, asymptomatic, mild troponin-T laboratory test elevations from baseline, with no associated cardiac findings, and no clear association with dose or treatment duration. The subjects continued on study treatment. Subject monitoring and troponin elevation analysis is ongoing.

Preliminary pharmacokinetic analysis of CC-122 administered to subjects with solid tumors and hematologic malignancies demonstrated that CC-122 was rapidly absorbed and eliminated with a mean terminal half-life ranging between 8.3 and 25.2 hours. Overall C_{max} and AUC increased in a linear, approximate dose proportional manner with dose after single and multiple doses. There was moderate drug accumulation (about 30% to 40%) following repeated daily dosing. In vitro studies indicate mean CC-122 plasma protein binding is approximately 38%.

The preliminary results for best overall tumor response in study CC-122-ST-001 included one complete response (CR), in a subject with follicular lymphoma in the 3 mg QD cohort, and two partial responses (PR), both in subjects with lymphoma (DLBCL and MCL) in the 3 and 3.5 mg cohorts.

Enrollment in the Part B tumor expansion cohorts is ongoing. As of 13 Jan 2016, 171 subjects had enrolled, of which 169 were enrolled in the following tumor cohorts in Part B (2 subjects had missing tumor type information at the time of the 13 Jan 2016 data cutoff date): GBM (all doses) (n=47), HCC (3 mg QD) (n=25), NHL (3 mg QD) (n=25), MM (3 mg QD) (n=27), DLBCL-2 (all doses) (n=44), and "Other" (n=1).

The most common TEAEs (occurring in ≥ 20% of 169 subjects overall) were neutropenia, which was experienced by 87 (51.5%) subjects; asthenia, 69 (40.8%); pyrexia, 51 (30.2%); anemia, 46 (27.2%); cough and peripheral edema, 38 (22.5% each), diarrhea, 37 (21.9%), and constipation, 36 (21.3%). The SOC categories for which AEs were most frequently reported (≥ 50% of all subjects experienced an AE categorized in the respective SOC) were General Disorders and Administration Site Conditions, with 131 (77.5%) subjects experiencing an AE in this SOC; Gastrointestinal Disorders, 107 (63.3%); Blood And Lymphatic System Disorders, 97 (57.4%); and Respiratory, Thoracic and Mediastinal Disorders (50.3%). Treatment-emergent AEs in the Infections and Infestations SOC occurred in 71 (42.0%) subjects.

In Part B dose expansion, there were clear trends toward increased frequency and severity of neutropenia in subjects with hematologic tumors, such as MM and NHL, versus subjects with solid tumors, such as HCC and GBM. These data suggest that subjects with hematologic tumors with marrow involvement and decreased reserve could be at increased risk for more frequent and severe neutropenia. Two intermittent dosing schedules (21 out of 28 days and 5 out of 7 days) have been evaluated in order to mitigate neutropenia while achieving similar dose intensity per cycle to 3.0 mg QD. The MTD on intermittent dosing in DLBCL subjects was established as 4 mg for 5 out of 7 days, following 2 DLTs (febrile neutropenia and interstitial pneumonitis) in 2 out of 5 subjects in the 5 mg 5 continuous days out of 7 days per week dosing schedule. Relative to the 3.0 mg QD continuous dose, the 4.0 mg 5 out of 7 day schedule was associated with less frequent and less severe neutropenia which required fewer dose interruptions, fewer dose reductions, a reduced usage of growth factor support, and improved relative dose intensity. As of 13 Jan 2016, in the Part B NHL 3 mg QD schedule cohort, 19 (76.0%) of 25 subjects experienced neutropenia, and 16 (64.0%) experienced Grade 3 or 4 neutropenia. In contrast, in the Part B DLBCL-2 cohort, 4 mg 5/7 day schedule, 17 (47.2%) of 36 subjects experienced neutropenia, and 11 (30.6%) experienced Grade 3 or 4 neutropenia.

Overall, in Part A, 11 (32.4%) out of 34 subjects experienced neutropenia, of which 10 subjects (29.4%) experienced Grade 3 or 4 neutropenia. In Part B, 87 (51.5%) out of 169 subjects have experienced neutropenia, of which 59 (34.9%) subjects experienced Grade 3 or 4 neutropenia. There were no instances of febrile neutropenia in Part A (dose escalation cohorts of the study

with doses in the range of 0.5 to 3.5 mg once daily, dosed continuously) and 11 subjects with febrile neutropenia in Part B.

Doses above the declared 3 mg QD continuous dose MTD and dosing on an intermittent schedule are being explored in subjects with GBM. The PCNSL cohort dose and schedule is 4 mg for 5 out of 7 days, and the MM-2 starting dose is 3 mg for 5 out of 7 days.

During the course of the current study, new formulations of CC-122 were developed and evaluated in healthy subjects. Study CC-122-CP-002 Part 2 was an open-label, randomized, three-period, six-sequence, three-way single-dose crossover study in healthy adult subjects to evaluate the PK of CC-122 after administration of formulated (test formulations: Formulation 4 [F4] and Formulation 6 [F6]) and non-formulated (reference AIC formulation) CC-122 capsules. The formulations have different CC-122 free base amounts compared to the CC-122 active ingredient in capsules (AIC) formulation that was employed from the beginning of the current study. CC-122 AIC 0.5, 1, and 3 mg strengths were based on CC-122 HCl and are equivalent to 0.44, 0.88, and 2.64 mg CC-122 free base, respectively. CC-122 formulated capsules of 1, 3, 3.5 and 4 mg strengths are based on CC-122 free base and are equivalent to 1.13, 3.38, 3.95 and 4.51 mg CC-122 HCl, respectively.

Following a single oral administration of CC-122 at the dose level of 3 mg from reference AIC formulation and formulated capsule F6 formulation in healthy adult subjects (N=18), the total plasma exposure (AUC_{inf}) was 16.29% higher and the peak plasma exposure (C_{max}) was 35.58% higher from the F6 formulation compared with the reference AIC formulation. The CC-122 F6 formulation has been selected for further development and within the rest of this protocol is referred to as CC-122 formulated capsules. (Data on File, 2015).

Please refer to the Investigator's Brochure for detailed information concerning the available pharmacology, toxicology, drug metabolism, clinical studies, and adverse event profile of the investigational product (IP).

1.2. Study Rationale/Purpose

CC-122 is a new investigational product that has a strong biological rationale for the treatment of subjects with advanced relapsed or refractory cancers, an unmet clinical need. Potential efficacy and toxicities associated with CC-122 have been evaluated in preclinical studies and ongoing phase 1 studies and provide the scientific rationale for starting clinical development of CC-122 in Japan.

This study is the first phase 1 study with this IP in Japan. The primary purpose is to evaluate the safety, tolerability, and pharmacokinetics (PK) of CC-122 in Japanese subjects with advanced solid tumors or NHL. Preliminary efficacy will be assessed as a secondary objective.

The selected starting dose of 2 mg on a 5 continuous days out of 7 days per week intermittent dosing in this study is approximately one-half of the intermittent dose levels (4 and 5 mg on a 5 continuous days out of 7 days per week intermittent dosing schedule) assessed in the ongoing phase 1 study, CC-122-ST-001. Observed toxicity at dose levels up to the MTD of 3 mg QD on a continuous dosing schedule and ongoing intermittent dosing schedules had been manageable and these dose levels were well tolerated in Western subjects, with fatigue, neutropenia, and diarrhea as the most common toxicities, and no DLTs being observed at these dose levels in the continuous dosing schedule.

Based on the mechanism of action of CC-122, and the observed PK and metabolism of the compound, as well as reports of no PK differences observed with other similar compounds, differences in exposure between Western and Japanese patients are not expected.

Dose levels from 2 mg QD have demonstrated pharmacodynamic effects, including decreased peripheral B cells, expansion of peripheral T cells, decreased expression of a CRBN-modulated substrate in both B and T cells, and enhanced cytokine expression. The proposed starting dose of 2 mg on a 5 continuous days out of 7 days per week intermittent dosing schedule is below the NTD of 3.5 mg QD and the MTD of 3.0 mg QD in CC-122-ST-001 and is expected to be associated with manageable toxicities that can be monitored. Thus, the selected starting dose for this study is considered appropriate based on the safety of CC-122 in the ongoing western study in subjects with advanced solid tumors and hematologic malignancies and is within the safety tolerance established in preclinical toxicology studies.

2. STUDY OBJECTIVES

2.1. Primary Objectives

The primary objectives of the study are:

- To determine the safety and tolerability of CC-122 when administered orally to adult Japanese subjects with advanced solid tumors or NHL and to define the MTD and/or recommended phase 2 dose (RP2D)
- To determine the plasma PK of CC-122 in Japanese subjects with advanced solid tumors or NHL

2.2. Secondary Objective

The secondary objective of the study is:

- To make a preliminary assessment of the antitumor activity of CC-122

2.3. Exploratory Objectives

The exploratory objectives of the study are:

- To evaluate the plasma PK of CC-122 formulated capsules and compare results to the plasma PK of CC-122 AIC
- To assess the tolerability of CC-122 formulated capsules
- [redacted]

3. STUDY ENDPOINTS

3.1. Primary Endpoint(s)

The primary endpoints of this study are:

- The following safety endpoints: DLTs, MTD, evaluated using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) criteria version 4.03
- PK parameters: C_{max}, AUC, T_{max}, $t_{1/2}$, CL/F, Vz/F and Accumulation Index of CC-122

3.2. Secondary Endpoint(s)

The secondary endpoint of this study is:

- Antitumor efficacy, determined by response rates in each tumor type using appropriate tumor response criteria, and duration of response

3.3. Exploratory Endpoint(s)

The exploratory endpoints of this study are:

- Differences in C_{max} and AUC_{inf} between CC-122 AIC and CC-122 formulated capsules
- Differences in rates of DLTs between formulations
- [redacted]

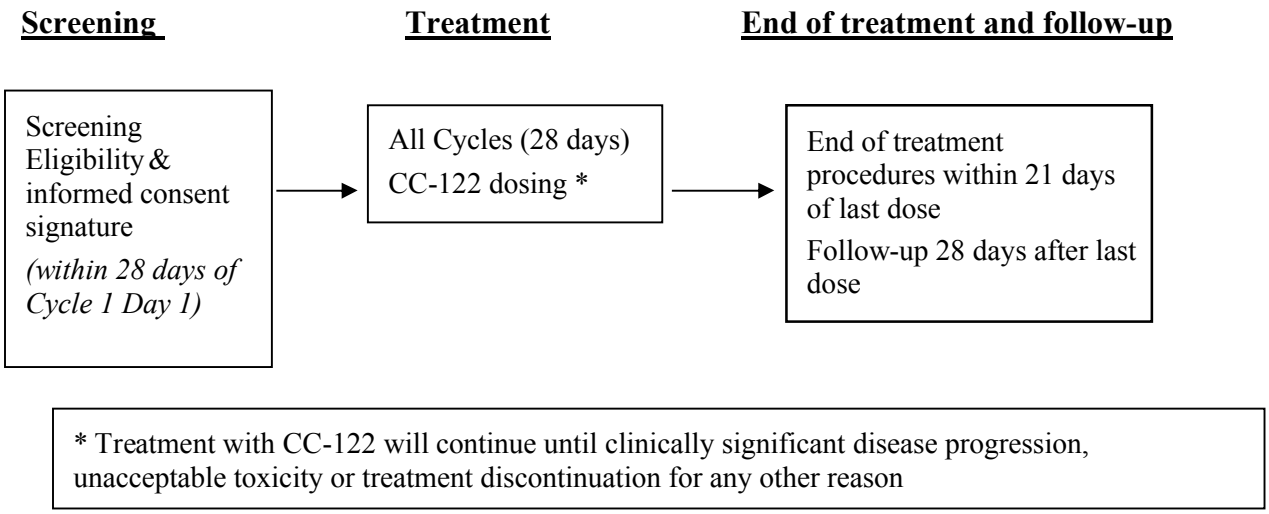
4. OVERALL STUDY DESIGN

4.1. Study Design

This is a phase 1, multicenter, open-label, dose-escalation study that will evaluate the safety, tolerability, PK, and preliminary efficacy of CC-122 in Japanese subjects with advanced solid tumors or NHL.

Subjects will receive ascending dose levels of CC-122 from Cycle 1 onwards to measure PK and to determine safety and tolerability.

Figure 1: Overall Study Design



An initial cohort of at least three subjects will be given CC-122 at a dose of 2.0 mg on a 5 continuous days out of 7 days per week intermittent dosing schedule using AIC. Dose escalation for subsequent cohorts will proceed according to a standard dose escalation design (3+3 design) (Storer, 1989) to establish initial toxicity.

The provisional dose-escalation levels to be evaluated are as follows.

Table 2: Provisional Dose-escalation Levels

Cohort	CC-122 dose
Assessed in subjects with solid tumors or NHL	
-1	1.0 mg (5 continuous days out of 7 days per week intermittent dosing) using the active ingredient in capsule (AIC) formulation [only used as necessary if the first dose level is not considered tolerable]
1	2.0 mg (5 continuous days out of 7 days per week intermittent dosing) AIC
Assessed only in subjects with NHL	
2	3.0 mg (5 continuous days out of 7 days per week intermittent dosing) AIC

Table 2: Provisional Dose-escalation Levels (Continued)

Cohort	CC-122 dose
3	4.0 mg (5 continuous days out of 7 days per week intermittent dosing) AIC
4	3.0 mg (5 continuous days out of 7 days per week intermittent dosing) using the formulated capsules

The first dose level will be assessed in subjects with solid tumors or NHL, and subsequent dose levels will only be assessed in subjects with NHL.

After at least 3 subjects have been enrolled in the 4 mg CC-122 AIC cohort (Cohort 3) and this dose level is determined to be tolerable, at least 6 subjects will be subsequently enrolled in the 3 mg CC-122 formulated capsules cohort (Cohort 4) to evaluate for differences in PK and tolerability. Lower doses using CC-122 formulated capsules may be evaluated as necessary.

4.1.1. Evaluation of Dose-limiting Toxicities

Cohorts of at least 3 subjects (to 6 subjects) will be enrolled at each dose level.

After the first dose is administered to the last subject in any cohort, subjects are observed for at least 28 days (Cycle 1) during the DLT evaluation period before the next higher, protocol-specified dose level cohort can begin.

A standard escalation schedule will be initiated in order to establish the MTD or RP2D by assessing the occurrence of DLTs. Smaller increments and additional subjects within a dose cohort may also be evaluated as necessary to determine the MTD and RP2D more precisely.

A dose level will be considered tolerable if 0 of 3 treated subjects experiences a DLT during the DLT evaluation period for each respective group. If 1 of 3 subjects experiences a DLT, 3 additional subjects will be enrolled and treated at that dose level.

A dose will be considered an NTD when two or more out of six evaluable subjects in a cohort experience DLTs during the DLT evaluation period.

The MTD is defined as the last dose level below the NTD with zero or one out of six evaluable subjects experiencing DLTs during the DLT evaluation period. At least 6 subjects will be enrolled at the MTD/RP2D.

The decision to either evaluate a higher dose level or declare the MTD or RP2D will be determined by the Safety Review Committee (SRC), which includes the principal investigator and Celgene's medical monitor (see Section 8.2.1), each time all clinical and laboratory safety data for a given cohort are available for review.

The SRC may decide to identify an RP2D based on safety, PK, and preliminary efficacy information, which will not exceed the MTD from global CC-122 trials in various indications.

4.2. Study Design Rationale

The primary objective of this study is to determine the safety, tolerability and PK of oral CC-122 and identify the MTD or RP2D in Japanese subjects with advanced solid tumors or NHL. Therefore, a standard phase 1 "3 + 3" dose-escalation design was adopted for this study. The 3 +

3 dose-escalation trial design in this patient population is standard and considered appropriate for evaluating the safety and establishing the MTD/RP2D.

Potential efficacy and toxicities associated with CC-122 have been evaluated in preclinical studies and ongoing phase 1 studies conducted outside Japan. The dose for CC-122 administered in this study was selected according to results from an ongoing phase 1 clinical study, CC-122-ST-001 (refer to Section 1.2). The dosing schedules selected are in line with schedules proven to be safe and effective in CC-122-ST-001.

4.3. Study Duration

This study will consist of 3 periods: screening, treatment and end of treatment & follow-up.

During the screening period, lasting up to 28 days, subjects will undergo assessments to determine their eligibility. Subjects who qualify for enrollment into the study will enter the treatment period. Each subject will be administered oral doses of CC-122 in the treatment period, which starts on Cycle 1 Day 1 where IP is administered on a 5 continuous days out of 7 days per week intermittent dosing schedule (Cycle = 28 days).

If subjects continue therapy with CC-122, subsequent cycles are 28 days long on a 5 continuous days out of 7 days per week intermittent dosing schedule.

Subjects may continue CC-122 without interruption for as long as they derive benefit, as assessed by the investigator. Treatment will be discontinued if there is evidence of clinical significant disease progression, unacceptable toxicity or if the subject/physician decides to stop treatment.

The follow-up period will begin at the discontinuation of IP treatment. Subjects will have an end of treatment (EOT) assessment during an evaluation within 21 days of the last dose of IP and a follow-up visit 28 days after the last dose of IP to obtain information regarding new or ongoing AEs.

4.4. End of Trial

The End of Trial is defined as either the date of the last visit of the last subject to complete the study, or the date of receipt of the last data point from the last subject that is required for primary, secondary and/or exploratory analysis, as prespecified in the protocol and/or the Statistical Analysis Plan, whichever is the later date.

5. TABLE OF EVENTS

The following table lists all of the assessments and indicates with an "X" the visits when they are performed. More frequent examinations may be performed at the investigator's discretion if medically indicated, and clinically significant results should be recorded on Unscheduled Visit case report forms (CRFs). All data obtained from these assessments must be supported in the subject's source documentation.

After completion of Cycle 1, written informed consent will be obtained again from subjects prior to the start of the second cycle of treatment.

Subjects will be hospitalized during the DLT evaluation period (Cycle 1) as a rule.

Table 3: Table of Events

Test and Observations	Reference Section	Screening		Treatment cycles (28 days)												End of treatment	Follow-up
				Cycle 1							Cycle 2 to 4				Subsequent Cycles *		
Visit (Allowable window)		Within 28 days of Cycle 1 Day 1	Within 7 days of Cycle 1 Day 1	Day 1	Day 2	Day 8 (± 2 days)	Day 10, 11 or 12	Day 11, 12 or 13	Day 15 (± 2 days)	Day 22 (± 2 days)	Day 1 (± 2 days) [a]	Day 8 (± 2 days)	Day 15 (± 2 days)	Day 22 (± 2 days)	Day 1 (± 3 days)	Within 21 days of last dose	28 days after last dose (+ 7 days)
Informed consent	6.1.1	X									X [b]						
Demography	6.1.2	X															
Inclusion/Exclusion criteria	7.2, 7.3	X															
Complete medical history	6.1.2	X															
Prior therapies	6.1.2	X															
Diagnosis and extent of cancer	6.1.2	X															
Concomitant medications & procedures	6.1.4		X														
Physical examination	6.2.1	X		X							X				X	X	
ECOG Performance status	6.2.3	X		X							X				X	X	

Table 3: Table of Events (Continued)

Test and Observations	Reference Section	Screening		Treatment cycles (28 days)												End of treatment	Follow-up
				Cycle 1							Cycle 2 to 4				Subsequent Cycles		
Visit (Allowable window)		Within 28 days of Cycle 1 Day 1	Within 7 days of Cycle 1 Day 1	Day 1	Day 2	Day 8 (± 2 days)	Day 10, 11 or 12	Day 11, 12 or 13	Day 15 (± 2 days)	Day 22 (± 2 days)	Day 1 (± 2 days) [a]	Day 8 (± 2 days)	Day 15 (± 2 days)	Day 22 (± 2 days)	Day 1 (± 3 days)	Within 21 days of last dose	28 days after last dose (+ 7 days)
Assessment of hydration status	6.2.1	X		X		X			X	X	X	X	X	X	X		
Height	6.2.1	X															
Weight	6.2.1	X		X		X			X	X	X	X	X	X	X	X	
Vital signs	6.2.2	X		X		X			X	X	X	X	X	X	X	X	
Serum β-HCG pregnancy test (for FCBP only) [c]	6.2.4	X [c]		As clinically indicated													
Urine β-HCG pregnancy test (for FCBP only) [c]	6.2.4			X		X			X	X	X				X	X	X
Amylase, lipase	6.2.6		X								X				X	X	
Cholesterol & TG	6.2.6		X								X				X	X	
TSH, fT4, LDH	6.2.6		X								X				X	X	
Immunoglobulins & T cell subsets (CD4+, CD8+)	6.2.6		X								X				X	X	
Uric acid	6.2.6		X								X				X	X	
Troponin-T, BNP	6.2.6		X	X [d]		X			X	X	X				X	X	
Hematology with differential	6.2.6		X	X [d]		X	X		X	X	X	X	X	X	X	X	
Biochemistry	6.2.6		X	X [d]		X			X	X	X	X	X	X	X	X	
Coagulation	6.2.6		X	X [d]		X			X	X	X	X	X	X	X	X	
Urinalysis	6.2.6	X		X [d]							X				X	X	
HBsAg & HCV RNA	6.2.6	X															

Table 3: Table of Events (Continued)

Test and Observations	Reference Section	Screening		Treatment cycles (28 days)												End of treatment	Follow-up
				Cycle 1							Cycle 2 to 4				Subsequent Cycles		
Visit (Allowable window)		Within 28 days of Cycle 1 Day 1	Within 7 days of Cycle 1 Day 1	Day 1	Day 2	Day 8 (± 2 days)	Day 10, 11 or 12	Day 11, 12 or 13	Day 15 (± 2 days)	Day 22 (± 2 days)	Day 1 (± 2 days) [a]	Day 8 (± 2 days)	Day 15 (± 2 days)	Day 22 (± 2 days)	Day 1 (± 3 days)	Within 21 days of last dose	28 days after last dose (+ 7 days)
12-lead ECG [e]	6.2.7.1	X		X		X	X		X	X	X	X	X	X	X	X	
LVEF (MUGA or ECHO) [f]	6.2.7.2	X									X [f]				X [f]	X	
Ophthalmologic examination [g]	6.2.8	X															
Tumor assessments [h]	6.3	X											X [h]		Day 15 instead of Day 1 X [h]	X	
PK sampling [i]	6.4			X	X		X	X									
[redacted]																	
CC-122 contraceptive risk counseling and education	6.2.5	To be completed prior to each dispensing of IP as per PPRMP														X	
Dispense CC-122	8.1, 8.2			X							X				X		
Drug accountability/compliance	8.5, 8.6										X				X	X	
CC-122 administration (5 out of 7 day dosing) [j]	8.2			X	X	X	X	X [k]	X	X	X	X	X	X	X		
AE monitoring	11		X [l]														

AE = adverse event; BNP = brain natriuretic peptide; C = cycle; CD = cluster of differentiation; CT = computed tomography; D = day; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; FCBP = females of childbearing potential; fT4 = free thyroxine 4; HBsAg = Hepatitis B surface antigen; HCG = Human chorionic gonadotropin; HCV = Hepatitis C virus; IP = investigational product; LDH = lactate dehydrogenase; LVEF = left ventricular ejection fraction; MRI = magnetic resonance imaging; MUGA = multiple gated acquisition scan; PK = pharmacokinetic; PPRMP = Pregnancy Prevention Risk Management Plan (Appendix B, Section 19.2); RNA = ribonucleic acid; TG = triglycerides; TSH = thyroid stimulating hormone.

* With Protocol Amendment 03, Day 8 and 22 visits from Cycle 5 onwards and Day 15 visits from Cycle 5 onwards were eliminated, with the exception of Day 15 of Cycle 6 and every 3 cycles thereafter for tumor assessments. Subjects enrolled prior to this protocol amendment may have data at these visits prior to the approval of protocol amendment 03.

[a] The ±2 day allowable window does not apply to Cycle 2 Day 1.
[b] After completion of Cycle 1, written informed consent will be obtained again from subjects prior to the start of the second cycle of treatment.
[c] As per the PPRMP, screening pregnancy tests must be performed within 10 to 14 days prior to starting dosing. FCBP with regular or no menstrual cycles will undergo postdose pregnancy tests as noted on this table, every week for the first 28 days and every 28 days thereafter until the end of treatment, and 28 days after the last dose of CC-122. However, FCBP with irregular menstrual cycles will undergo weekly assessments for the first 28 days, every 14 days thereafter until the end of treatment and the end of treatment pregnancy test must be performed 14 and 28 days after discontinuing treatment.
[d] If screening assessments are performed within 2 days of Cycle 1 Day 1 these assessments do not need to be repeated on Cycle 1 Day 1.
[e] Triplicate ECGs (3 recordings within 2±1 minute intervals) will be performed only at screening. Single ECGs will be collected for all other visits.
[f] During the study, LVEF assessments should be repeated on Day 1 after every three cycles starting with Cycle 3 and when clinically indicated (for example, for decreased cardiac output) using the same modality at screening.
[g] Ophthalmology examinations will be performed for all subjects at screening and during the study if clinically indicated.
[h] Tumor assessments include imaging studies (via CT/MRI) and may include brain scans, and/or bone marrow aspirate/biopsy depending on tumor type and involvement. After screening, tumor assessments will be performed on Day 15 of Cycle 2, 4, 6 and every 3 cycles thereafter (Cycles 9, 12, 15, etc.), with an allowable window of ±7 days. Tumor assessments at the end of treatment visit may be omitted if performed within the previous 28 days.
[i] Refer to Section 6.4 for details on PK sampling time points.
[j] Starting from Cycle 1 Day 1, CC-122 is administered once a day for 5 continuous days out of 7 days per week.
[k] If performed on Day 13, a dose of CC-122 will not be administered.
[l] AE monitoring will be performed according to Section 11 and AEs will be followed for up to 28 days after the last dose of IP. However, AE monitoring for non-serious AEs may be halted once other anticancer treatments are started even if the full 28 days of follow-up has not been completed.

6. PROCEDURES

Procedures will be performed at the visits listed in Table 3.

6.1. Screening Assessments

6.1.1. Informed Consent

The screening period begins on the date the Informed Consent Form (ICF) is signed and should be within 28 days of Cycle 1 Day 1. The ICF must be signed and dated by the subject and the administering staff prior to the start of any study procedures solely for the purpose of this study and completion documented in source documents and the CRF. Standard of care assessments performed prior to signing the ICF may be used for this study, assuming these assessments meet the protocol requirements. Recording of Adverse AEs/Serious adverse events (SAEs) will begin once the subject has signed the ICF.

Written informed consent will be obtained again from subjects prior to the start of the second cycle of treatment.

6.1.2. Patient Demographics/Medical History/Diagnosis and Extent of Cancer/Prior Therapies

Medical, surgical and oncologic histories, diagnosis and extent of cancer, along with demographic data, including each subject's date of birth, gender, race, and ethnicity will be collected during screening as consistent with local regulations. The medical history will be general enough to document common co-morbid conditions as well as specific enough to reveal any conditions listed as participation exclusion criteria, and will document whether the identified conditions are active or inactive at the time of enrollment. All prior anticancer treatments (for example, chemotherapy, surgeries) and medical history, including approximate dates of treatment or diagnosis, must be recorded during screening. This should be recorded in source documents and the CRF.

6.1.3. Assessment of Inclusion/Exclusion Criteria

Inclusion and exclusion criteria will be assessed at screening and recorded in source documents and the CRF.

6.1.4. Concomitant Medications and Procedures

All concomitant medications and procedures taken or performed beginning 28 days prior to the administration of IP until 28 days after the last dose of IP will be recorded in the source documents and the CRF.

6.1.5. Information to be Collected on Screen Failures and Non-treated Subjects

The following are minimum data requirements to be entered in CRFs for screen failures and other subjects who did not start treatment.

- Subject number

- Date of informed consent
- Demography
- Screening visit date
- Eligibility criteria – specific inclusion and/or exclusion criteria not met by the subject, as applicable
- All AEs/SAEs from the time of signing the ICF until discontinuation from study
- Disposition – the date when it was determined that the subject would not continue further in the study, and specification of the reason for termination from the study ("Screen Failure" for subjects who do not meet all of the eligibility criteria, or the applicable reason for other non-treated subjects)

6.2. Safety Assessments

6.2.1. Physical Examination, Height and Weight, Assessment of Hydration Status

Complete physical examinations, assessments of hydration status, and measurements of height and weight will be performed at the visits listed in Table 3. Assessments of hydration status should be performed and recommendations for per os (PO) or intravenous (IV) hydration given as applicable.

Results of physical examinations and assessment of hydration status will be recorded in source documents and height and weight recorded on source documents and the CRF.

6.2.2. Vital Signs

Vital signs include body temperature, blood pressure, pulse rate, and respiration rate. Recorded measurements will be captured in the source documents and the CRF.

Vital signs should be measured after the subject has rested for at least 5 minutes. Vital sign measurements should be repeated for confirmation if clinically significant observations or changes from baseline occur. All confirmed, clinically significant vital sign measurements must be recorded as AEs.

6.2.3. Eastern Cooperative Oncology Group Performance Status

Performance status will be assessed using the following scale. Data will be captured in the source documents and the CRF.

Table 4: ECOG Performance Status Scale

Score	Description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, for example, 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

Table 4: ECOG Performance status Scale (Continued)

Score	Description
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

6.2.4. Pregnancy Test

A female of child bearing potential (FCBP) is defined as a female who has:

1. Achieved menarche at some point
2. Not undergone a hysterectomy or bilateral oophorectomy, or
3. Not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (has had menses at any time in the preceding 24 consecutive months).

The investigator will classify a female subject as an FCBP according to this definition. Pregnancy testing is not required for non-FCBP subjects but justification must be recorded in the CRF and source documents. Pregnancy testing will be conducted by the local laboratory.

For an FCBP, pregnancy testing will be conducted at the visits listed in Table 3:

- A serum pregnancy test with sensitivity of at least 25 mIU/mL is to be obtained at screening.
- A urine pregnancy test (minimum test sensitivity [25 mIU/mL]) should be performed at subsequent visits; however, a serum pregnancy test may be performed as clinically indicated.
- The subject may not receive IP until the investigator has verified the screening pregnancy tests to be negative.
- An FCBP must avoid activities that could lead to conception for 28 days after the last dose of any IP or a male subject whose partner is an FCBP must avoid activities that could lead to conception within 3 months after the last dose of CC-122.

Note: FCBP receiving CC-122 will undergo pregnancy testing according to the schedule described in the CC-122 Pregnancy Prevention Risk Management Plan and CC-122 Information Sheet.

Results for pregnancy tests will be recorded in source documents and CRFs.

6.2.5. Contraceptive Counseling

Subjects will be counseled about appropriate contraception during screening (refer also to the previous section). Double contraceptive methods (one of which must be a barrier method) for females (such as oral, injectable, or implantable hormonal contraceptives; intra-uterine devices; barrier contraceptives with spermicide approved or certified in Japan; or a vasectomized partner)

and a single contraceptive method for males (complete abstinence or a condom) must be used from the time the ICF is signed, throughout the study by fertile subjects, and for 28 days after the last dose of IP for FCBP and for 3 months after the last dose of CC-122 for male subjects whose partner is an FCBP. FCBP must confirm that they have been using appropriate contraception for at least 28 days prior to starting CC-122 as per the PPRMP. Counseling should be documented in source documents.

The CC-122 PPRMP for Celgene Clinical Trials applies to all subjects receiving CC-122 therapy and will be given to sites as a separate document.

CC-122 will be dispensed through a qualified healthcare professional (including but not limited to nurses, pharmacists and physicians). These healthcare professionals will be trained by Celgene, or designee, in requirements specific to counseling of subjects. Once trained, these healthcare staff will counsel subjects prior to the administration of CC-122 to ensure that the subject has complied with all requirements, including use of birth control, and that the subject understands the risks associated with CC-122. This step will be documented with a completed Education and Counseling Guidance Document, and CC-122 will not be administered until this step occurs.

A CC-122 Information Sheet will be provided to each subject before IP is dispensed.

Females of childbearing potential and fertile males, other than the subject, should not handle or administer CC-122 unless they are wearing gloves.

6.2.6. Clinical Laboratory Tests

The following clinical laboratory tests will be assessed. All samples should be drawn predose unless otherwise specified. Data will be captured in the source documents and the CRF.

Table 5: Clinical Laboratory Test Parameters

Laboratory test	Parameters
Amylase, lipase	Amylase, lipase
Cholesterol and triglycerides	Cholesterol and triglycerides
Thyroid stimulating hormone (TSH), free thyroxine 4 (fT4), and lactate dehydrogenase (LDH)	TSH, fT4, and LDH
Immunoglobulins (Ig) and T cell subsets	Immunoglobulins = IgG, IgM and IgA only T cell subsets = CD4+ and CD8+
Uric acid	Uric acid
Troponin-T, brain natriuretic peptide (BNP)	Troponin-T, BNP

Table 5: Clinical Laboratory Test Parameters (Continued)

Laboratory test	Parameters
Hematology	Complete blood count consisting of red blood cells (RBCs), a total white blood cell count with differentials (including total neutrophil [including bands], lymphocyte, monocyte, eosinophil, and basophil counts), hemoglobin, hematocrit and platelet count
Biochemistry	Sodium, potassium, chloride, calcium, glucose, magnesium, phosphorus, serum blood urea nitrogen (BUN), serum creatinine, total bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, albumin, and total protein
Coagulation	Prothrombin time (PT), international normalized ratio (INR) and, partial thromboplastin time (PTT)
Urinalysis	Dipstick test, with microscopy in event of positive (1+ or greater) blood or protein and 24-hour collection for creatinine clearance and protein quantification in the event of 2+ or greater protein
HBsAg and HCV RNA	Hepatitis B surface antigen (HBsAg) & Hepatitis C virus (HCV) ribonucleic acid (RNA) If Hepatitis B core antibody (HBcAb) and/or Hepatitis B surface antibody (HBsAb) is positive even if HBs antigen is negative, measurement of hepatitis B viral load (HBV DNA quantitated by PCR) should be performed and, if positive, the subject will be excluded from the study

6.2.7. Cardiac Imaging

6.2.7.1. 12-lead Electrocardiograms

Triplicate or single standard 12-lead electrocardiograms (ECGs) will be recorded. The 12-lead ECGs (12-lead at 25 mm/sec reporting rhythm, ventricular rate, PR-interval, QRS complex, QT interval, and corrected QT [QTc] interval) will be performed after the subject has been in the supine position for at least 5 minutes. Data will be captured in the source documents and the CRF.

Whenever vital signs, ECGs and/or blood draws are scheduled for the same nominal time, the ECG will be obtained first, followed by vital signs and then blood draw(s).

6.2.7.2. Left Ventricular Ejection Fraction

LVEF will be measured via multiple gated acquisition scan (MUGA), or echocardiogram (ECHO) for all subjects. Follow-up assessments should use the same procedure used at the screening assessment. Data will be captured in the source documents and the CRF.

6.2.8. Ophthalmologic Examination

An ophthalmologic examination will be performed by a qualified ophthalmologist at screening as described below in all subjects. The screening ophthalmologic exam will include:

- Visual acuity

- Slit-lamp examination with fluorescein staining following pupillary dilation (unless fluorescein and pupillary dilatation are contraindicated)
- Ophthalmologic examination focusing on the anterior chamber, iris and anterior vitreous

Subsequent ophthalmologic examinations will be performed as clinically indicated. If there are any clinically significant findings, a full ophthalmologic exam will be conducted by a qualified ophthalmologist.

6.3. Efficacy Assessments

Tumor assessments will be performed as follows:

Table 6: Tumor Assessments

Visit	Assessments
Screening	Tumor assessments via imaging studies, including computed tomography (CT) and/or magnetic resonance imaging (MRI), of the chest and abdomen and pelvis (including other sites, as appropriate) [or fludeoxyglucose positron emission tomography (FDG-PET) as necessary] will be performed. A brain scan (CT or MRI) will be performed for subjects with known brain lesions. Bone marrow aspirate and biopsy (with cytogenetic analysis, as appropriate depending on cancer type) should be performed for subjects with known or suspected bone marrow involvement. Note: Efficacy assessments (scans, aspirates, and biopsies) obtained within 8 weeks of the first dose of IP and prior to obtaining informed consent as part of standard of care assessments may be used, assuming these assessments meet the protocol requirements.
Day 15 of Cycle 2, 4, 6 and every 3 cycles thereafter (Cycles 9, 12, 15, etc.) Allowable window: (± 7 days)	Tumor assessments via imaging studies, including CT and/or MRI, of the chest and abdomen and pelvis (including other sites, as appropriate) [or FDG-PET as necessary] will be performed. A brain scan (CT or MRI) will be performed for subjects with known brain lesions. Bone marrow aspirate and biopsy (with cytogenetic analysis, as appropriate depending on cancer type) should be performed for subjects with known or suspected bone marrow involvement.
End of treatment (may be omitted if performed within the previous 28 days)	Tumor assessments via imaging studies, including CT and/or MRI, of the chest and abdomen and pelvis (including other sites, as appropriate) [or FDG-PET as necessary] will be performed. A brain scan (CT or MRI) will be performed for subjects with known brain lesions. Bone marrow aspirate and biopsy (with cytogenetic analysis, as appropriate depending on cancer type) should be performed for subjects with known or suspected bone marrow involvement.

After screening, tumor assessments thereafter should be performed using the same CT/MRI scanning modalities used at screening, as permissible.

6.4. Pharmacokinetic Assessments

The schedule for PK assessments is described below:

Table 7: PK Sampling Time Points

Visit	Nominal time point	Allowable window
Cycle 1 Day 1	Predose	<15 min prior to dosing
	0.5 hours postdose	± 5 minutes
	0.75 hours postdose	± 5 minutes
	1 hour postdose	± 5 minutes
	1.5 hours postdose	± 5 minutes
	3 hours postdose	± 10 minutes
	5 hours postdose	± 10 minutes
	8 hours postdose	± 10 minutes
Cycle 1 Day 2	24 hours after dose administered on Cycle 1 Day 1 and predose of dosing on Cycle 1 Day 2	<15 min prior to dosing
Cycle 1 Day 10, 11 or 12	Predose	<15 min prior to dosing
	0.5 hours postdose	± 5 minutes
	0.75 hours postdose	± 5 minutes
	1 hour postdose	± 5 minutes
	1.5 hours postdose	± 5 minutes
	3 hours postdose	± 10 minutes
	5 hours postdose	± 10 minutes
	8 hours postdose	± 10 minutes
Cycle 1 Day 11, 12 or 13	24 hours after dose administered on Cycle 1 Day 10, 11 or 12 and predose of dosing on Cycle 1 Day 11, 12 or 13	± 1 hour

Should dose administration CC-122 be interrupted for > 72 hours before the Cycle 1 Day 10, 11 or 12 sampling, serial PK samples will not be collected until ≥ 2 days of CC-122 continuous treatment has been reestablished.

Intra-subject dose escalation:

The following additional PK samples will only be collected for subjects who were dose escalated from their initial assigned dose (see Sections 8.2.1 and 8.2.9.2):

- After at least 2 days of continuous dosing of CC-122, PK samples should be collected at the following time points:
  - At predose (<15 min prior to dosing), and at 0.5, 0.75, 1, 1.5, 3, 5, 8, and 24 hours postdose

Sample collection kits and detailed instructions for PK sample collection, processing, storage, shipping and handling will be provided to the sites by the central laboratory upon study initiation.

[redacted]

7. STUDY POPULATION

7.1. Number of Subjects and Sites

Approximately 15 subjects will be enrolled and treated in approximately 3 sites in Japan. However, the total number of subjects enrolled will depend on the number of dose cohorts needed to establish the MTD/RP2D.

7.2. Inclusion Criteria

Subjects must satisfy the following criteria to be enrolled in the study:

1. Understand and voluntarily sign an informed consent document prior to any study-related assessments/procedures are conducted
2. Men and women, 20 years or older, with histological or cytological confirmation of advanced solid tumors or NHL, including those who have progressed on (or are not able to tolerate) standard anticancer therapy or for whom no other conventional therapy exists ***(Note: subjects with solid tumors or NHL will be enrolled for the first dose level and only subjects with NHL will be enrolled in subsequent dose levels)***
3. ECOG Performance Status ≤ 2 for all tumors
4. Subjects must have the following laboratory values:
   - Absolute Neutrophil Count (ANC) ≥ 1.5 x 10^9/L
   - Hemoglobin (Hgb) ≥ 9 g/dL, drawn at least 7 days after the last RBC transfusion
   - Platelets (Plt) ≥ 100 x 10^9/L, drawn at least 7 days after the last platelet transfusion
   - Potassium within normal limits or correctable with supplements
   - AST and ALT ≤ 3 x upper limit of normal (ULN) or ≤ 5.0 x ULN if liver tumors are present
   - Serum bilirubin ≤ 1.5 x ULN; subjects with serum bilirubin >1.5 x ULN and ≤ 2 x ULN may be enrolled if agreed to by the sponsor
   - Serum creatinine ≤ ULN or 24-hour clearance ≥ 50 mL/min
   - Negative serum pregnancy test in females of childbearing potential as per the CC-122 PPRMP (Appendix B, Section 19.2)
5. Able to adhere to the study visit schedule and other protocol requirements
6. Must adhere to the PPRMP
   a. Females of childbearing potential must undergo pregnancy testing based on the frequency outlined in PPRMP and pregnancy results must be negative

b. Unless practicing complete abstinence from heterosexual intercourse, sexually active FCBP must agree to use adequate contraceptive methods as specified in the PPRMP
   - Complete abstinence is only acceptable in cases where this is the preferred and usual lifestyle of the subject.
   - Periodic abstinence (calendar ovulation, symptothermal, post-ovulation methods) and withdrawal are **not acceptable**

c. Males (including those who have had a vasectomy) must practice complete abstinence or use barrier contraception (condoms) when engaging in sexual activity with FCBP as specified in the PPRMP
d. Males must agree not to donate semen or sperm for the duration specified in the PPRMP
e. All subjects must:
   - Understand that the IP could have a potential teratogenic risk.
   - Agree to abstain from donating blood while taking IP and following discontinuation of investigational product.
   - Agree not to share IP with another person.
f. Other than the subject, FCBP and males able to father a child should not handle the IP or touch the capsules, unless gloves are worn
g. Be counseled about pregnancy precautions and risks of fetal exposure

7.3. Exclusion Criteria

The presence of any of the following will exclude a subject from enrollment:

1. Subjects with primary central nervous system (CNS) malignancies or symptomatic central nervous system metastases. Subjects with brain metastases that have been previously treated and are stable for 6 weeks are allowed
2. Known acute or chronic pancreatitis
3. Any peripheral neuropathy ≥ NCI CTCAE Grade 2
4. Persistent diarrhea or malabsorption ≥ NCI CTCAE Grade 2, despite medical management
5. Impaired cardiac function or clinically significant cardiac diseases, including any of the following:
   - LVEF < 45% as determined by MUGA scan or ECHO
   - Complete left bundle branch, or bifascicular block
   - Congenital long QT syndrome
   - Persistent or uncontrolled ventricular arrhythmias or atrial fibrillation
   - QTcF > 460 msec on screening ECG (mean of triplicate recordings)
   - Unstable angina pectoris or myocardial infarction ≤ 3 months prior to starting CC-122

- Troponin-T value >0.4 ng/mL or BNP >300 pg/mL
  Subjects with baseline troponin-T >ULN or BNP >100 pg/mL are eligible but must have cardiologist evaluation prior to enrollment in the trial for baseline assessment and optimization of cardioprotective therapy.
- Other clinically significant heart disease such as congestive heart failure requiring treatment or uncontrolled hypertension (blood pressure ≥ 160/95 mmHg)

6. Prior systemic cancer-directed treatments or investigational modalities ≤ 5 half lives or 4 weeks, whichever is shorter, prior to starting CC-122 or who have not recovered from side effects of such therapy. Luteinizing hormone-releasing hormone (LHRH) agonists will be allowed for subjects with metastatic prostate cancer
7. Major surgery ≤ 2 weeks prior to starting CC-122 or still recovering from post operative side effects
8. Women who are pregnant or breast feeding. Adults of reproductive potential not employing two forms of birth control as per PPRMP
9. Known human immunodeficiency virus (HIV) infection *
10. Known acute or chronic hepatitis B or C virus infection **
11. Status post solid organ transplant
12. Less than 100 days for subjects receiving autologous hematologic stem cell transplant (HSCT); or 6 months for subjects receiving allogeneic HSCT, or if otherwise not fully recovered from HSCT-related toxicity
    a. The 6-month exclusionary period for recovery from HSCT-associated toxicity, applies regardless of whether an autologous or allogeneic transplant was performed
13. Known hypersensitivity to any component of the formulation of CC-122
14. Any significant medical condition (including active or controlled infection or renal disease), laboratory abnormality, or psychiatric illness that would prevent the subject from participating in the study
15. Any condition, including the presence of laboratory abnormalities, which places the subject at unacceptable risk if he/she were to participate in the study
16. Any condition that confounds the ability to interpret data from the study

* HIV testing is not required at screening.

** Refer to Table 5 for exclusion based on hepatitis testing results.

8. DESCRIPTION OF STUDY TREATMENTS

8.1. Description of Investigational Product(s)

Please refer to the CC-122 Investigator's Brochure for detailed information concerning the physical properties of CC-122.

CC-122 will be supplied in two distinct formulations as follows: CC-122 AIC in 0.5, 1 and 3-mg strengths (equivalent to 0.44, 0.88, and 2.64 mg free base CC-122, respectively) and as CC-122 formulated capsules in 1, 3, 3.5 and 4-mg strengths (equivalent to 1.13, 3.38, 3.95 and 4.51 mg CC-122 HCl, respectively).

CC-122 AIC will be provided in white/white opaque gelatin capsules in strengths of 0.5 mg (size 4), 1 mg (size 3), and 3 mg (size 2). There are no excipients in the capsules.

The formulated capsules will be provided in reddish brown gelatin capsules in strengths of 1 mg (size 3), 3 (size 3), 3.5 mg (size 2) and 4 mg (size 2), containing the following excipients: Avicel PH 102, spray dried mannitol, crospovidone, areosil, and stearic acid.

The IP will be labeled per local regulations. Store as directed on the package label.

8.2. Treatment Administration and Schedule

CC-122 is administered orally, on a 5 continuous days out of 7 days per week intermittent dosing schedule.

Each dose will be taken in the morning, with the subject having fasted overnight (minimum of 6 hours) and for one hour after dosing. Every effort should be made to ensure that subjects are adequately hydrated prior to dosing, such as ensuring that capsules are swallowed with at least 8 ounces of water (approximately 240 mL), and hydration levels should be adjusted according to age and clinical status.

Breakfast will be delayed until at least one hour after dosing. The site will record the time of the first meal after dosing for clinic visits with PK collection time points.

Doses will be administered in an escalating manner following satisfactory review of safety data from the lower doses. Within each cohort, enrollment will be staggered 24 hours or more between Cycle 1 Day 1 visits for each subject.

8.2.1. Safety Review Committee

The SRC will review the safety and available PK data at the end of the DLT evaluation period for each cohort to determine whether dose escalation can occur, to confirm the dose level to be used in a subsequent cohort, and to determine the MTD/RP2D. The SRC will also review and approve intra-subject dose escalations.

SRC members will include the study investigators, the sponsor's medical monitor, safety physician or designee, clinical research scientist, and study manager. In addition, the study pharmacokineticist, statistician, and other relevant study team members may attend, if needed, and both internal and external experts may be consulted by the SRC, as necessary. The outcomes of SRC meetings will be documented, and the minutes distributed for SRC approval.

8.2.2. Definition of a Treatment Cycle

Each subject will be administered oral doses of CC-122 starting from Cycle Day 1 on a 5 continuous days out of 7 days per week intermittent dosing schedule in 28-day cycles (DLT evaluation period = at least 28 days).

Subjects may continue to receive CC-122 for as long as they derive benefit from treatment as assessed by the investigator. In subsequent cycles, subjects are treated in 28-day cycles on a 5 continuous days out of 7 days per week intermittent dosing schedule.

8.2.3. Starting Dose Level and Provisional Dose Levels

The starting dose is a flat dose of 2.0 mg administered on a 5 continuous days out of 7 days per week intermittent dosing schedule. Provisional dose-escalation levels are listed in Table 2.

8.2.4. Definition of Evaluable Subjects

A subject evaluable for DLT evaluation is defined as one whom, in the DLT evaluation period, either:

a. Received at least 85% of the planned doses of CC-122 at the cohort-specified dose in Cycle 1 (at least 17 out of 20 doses for the 5 continuous days out of 7 days per week intermittent dosing cohorts), has sufficient data for safety evaluation by the SRC and has not experienced a treatment-related DLT, or
b. Received at least one dose of CC-122 and experienced a DLT

Non-evaluable subjects will be replaced in the dosing cohort. An additional subject may be enrolled in each dosing cohort to allow for early drop-outs and to avoid study delays after consultation with the sponsor.

Subjects for whom >20% of PK samples were not collected will also be replaced in order to collect sufficient data for PK analysis.

8.2.5. Definition of Maximum Tolerated Dose and Non-tolerated Dose

The non-tolerated dose is defined as the dose level at which 2 or more out of 6 evaluable subjects in any dose cohort experience a DLT.

Once the NTD is identified, dose escalation will be halted.

The MTD is defined as the last dose level below the NTD with zero or one (out of 6) evaluable subject experiencing DLTs during the DLT evaluation period. An intermediate dose (for example, one between the NTD and the last dose level before the NTD) or additional subjects within a dose cohort may be evaluated in order to determine the MTD more precisely.

8.2.6. Definition of Dose-limiting Toxicities

National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.03 will be used to grade adverse events. Events described below will be classified as DLTs.

Table 8: DLT Criteria

Toxicity	
Non-hematologic AEs	A clinically relevant non-hematologic AE that is suspected to be related to CC-122 and that commences during the DLT evaluation period and is ≥ Grade 3 EXCEPT for: • Grade 3 rash of the acneiform or maculopapular type lasting ≤ 4 days (with optimal medical management) • Grade 3 diarrhea or vomiting lasting less than 72 hours (with optimal medical management)
Laboratory abnormalities	A clinically relevant laboratory abnormality that is suspected to be related to CC-122 and that commences during the DLT evaluation period and is ≥ Grade 3
Hematologic	Any febrile neutropenia
	Grade 4 neutropenia lasting > 7 days
	Grade 4 thrombocytopenia lasting > 24 hours or thrombocytopenia of any grade requiring platelet transfusions
	Any Grade 3/4 thrombocytopenia with clinically significant bleeding
Hepatic	Grade 4 liver function tests (LFTs) or Grade 3 ALT with Grade 2 or higher bilirubin will be considered a DLT, irrespective of underlying attribution However, other Grade 3 LFTs due to disease progression in the liver will not be considered DLTs
Other adverse events	Any adverse event suspected to be related to CC-122 and necessitating a dose reduction during the DLT evaluation period

Toxicities will be considered treatment-related unless clearly attributed to an alternative etiology (for example, tumor progression) by the investigator. Toxicities must be clearly not related to disease progression, medical procedures or intercurrent illnesses in order to be considered dose-limiting.

Isolated laboratory changes without associated clinical signs or symptoms will not be included in this definition. These findings will be discussed and reviewed by the SRC.

8.2.7. Criteria for Dose Escalation in the Next Cohort of Subjects

Cohorts will consist of at least 3 or at least 6 evaluable subjects. The decision criteria for dose escalation in any cohort are:

- If no DLT is observed in at least 3 evaluable subjects during the first cycle, the dose will be considered a well-tolerated dose and dose escalation will continue to the next dose level.
- If any DLT is observed in 2 or more of 6 evaluable subjects in the cohort, this dose is considered a non-tolerated dose and dose escalation will discontinue.

- If any DLT is observed in one evaluable subject during the DLT evaluation period, additional subjects will be enrolled to expand the cohort to up to at least 6 evaluable subjects.

The number of cohorts depends on the incidence of DLTs. A subject may experience more than one DLT. Dose-escalation decisions are based on the number of subjects experiencing DLTs.

8.2.8. Definition of Stopping Criteria for Dose Escalation

Dose escalation stops when 2 or more of 6 evaluable subjects at a dose level experience DLTs or the MTD in global CC-122 studies in various indications has been reached.

8.2.9. Permitted Dosing Adjustments

No dose reduction is allowed during the DLT evaluation period, except for subjects who experience DLTs. Subjects who experience DLTs during the DLT evaluation period will be allowed to resume CC-122 at a reduced dose once their toxicity recovers to Grade 1 or baseline, provided recovery occurs within 28 days of interrupting dosing. Dose reductions for non-dose-limiting toxicities are allowed after the DLT evaluation period after consultation with the sponsor.

Those continuing to take CC-122 beyond Cycle 1 may, following approval by the SRC, have their dose level increased, provided that the alternative dose level has been shown to be well-tolerated in at least one cohort of other subjects in this study. In these instances, additional PK evaluations at the higher dose level will be collected.

If a dose reduction is indicated, the next lower dose level will be selected. Two dose reductions are allowed, with the exception of the starting dose for which only one dose reduction is allowed. If any subject continues to experience unacceptable toxicity after 2 dose reductions, CC-122 will be discontinued permanently.

8.2.9.1. Criteria for Dose Reduction

Dose reductions are not allowed during the DLT evaluation period, except for subjects who experience DLTs. Subjects who experience toxicities during the DLT evaluation period that do not meet the protocol specified definition for DLTs (Section 8.2.6) may either continue at their assigned dose or withdraw from the study at the discretion of the investigator and/or the subject. If a subject withdraws for any reason other than DLTs prior to the completion of the DLT evaluation period, that subject will be considered non-evaluable and will be replaced.

Once the dosage has been reduced for toxicity for a subject, future escalation will not be permitted.

Any of the AEs listed in Table 10 after the DLT evaluation period will require a dose interruption and/or reduction.

Dose reductions may be considered for AEs occurring after the DLT evaluation period that do not meet the criteria listed in Table 10 after discussion between the investigator and the sponsor.

Guidance for dose reduction is as follows:

- Subjects requiring dose reductions for toxicities occurring on or BEFORE Cycle 1 Day 28 (such as subjects who have experienced DLTs and recovered) should be reduced to the next lowest dose level that has been shown to be tolerated by at least 3/3 or 5/6 subjects.
- Subjects requiring dose reduction for toxicities occurring AFTER Cycle 1 Day 28 may be reduced to the next lowest dose level that has been shown to be tolerated by at least 3/3 or 5/6 subjects.

Table 9: Example of Dose Reduction Steps

Current Dose	**2.0 mg intermittent 5/7 days**	**3.0 mg intermittent 5/7 days**	**4.0 mg intermittent 5/7 days**
Dose reduction -1	1.0 mg intermittent 5/7 days	2.0 mg intermittent 5/7 days	3.0 mg intermittent 5/7 days
Dose reduction -2	Discontinue	1.0 mg intermittent 5/7 days	2.0 mg intermittent 5/7 days
Dose reduction -3	-	Discontinue	Discontinue

8.2.9.2. Intra-subject Escalation

Intra-subject dose escalation beyond the dose initially assigned to a subject is not permitted during the DLT evaluation period. Those continuing to take CC-122 longer term may, following approval by the SRC, have their dose level increased, provided that the alternative dose level has been shown to be well-tolerated in at least one cohort of other subjects in this study.

To be considered for intra-subject dose escalation, a subject must not have experienced ≥ Grade 3 toxicities at their assigned dose level.

8.2.9.3. Treatment Delay

Treatment may be delayed up to 4 weeks until treatment-related toxicities (excluding alopecia) resolve to either ≤ Grade 1 or baseline levels. Treatment may restart either at the same, or a reduced dose level, at the investigator's discretion or as described in Section 8.2.9.1.

During the DLT evaluation period, a treatment interruption that causes a subject to miss 3 doses (need not be consecutive) for reasons other than DLTs will make a subject non-evaluable for DLTs and will necessitate the replacement of that subject in the dosing cohort.

8.2.9.4. Dose Modification and Management of Toxicities

Guidelines for dose modification are listed below.

Table 10: Guidelines for Dose Modifications of CC-122 Related Toxicities

Toxicity	Modification
Hematologic toxicities	
Grade 2 thrombocytopenia	• No action
Grade 3 thrombocytopenia	• Hold dosing until resolution to Grade ≤ 1 or baseline • Follow complete blood count (CBC) at least every 7 days • If resolution to Grade ≤ 1 or baseline occurs in ≤ 8 days, reintroduce CC-122 at the same dose level • If AE resolution occurs after > 8 days, or event reoccurs within the same cycle, reintroduce CC-122 at a lower dose level, if available
Grade 4 thrombocytopenia	• Hold dosing until recovery to Grade ≤ 1 or baseline • Repeat CBC within 24 to 48 hours • Follow CBC at least every 7 days • Reintroduce CC-122 at a lower dose level, if available
Grade 3 neutropenia	• Hold dosing until resolution to Grade ≤ 1 • Follow CBC at least every 7 days • If AE resolution to Grade ≤ 1 occurs in ≤ 8 days, reintroduce CC-122 at the same dose level • If AE resolution occurs after > 8 days, or event reoccurs within the same cycle, reintroduce CC-122 at one dose level lower, if available
Grade 4 neutropenia	• Hold dosing until recovery to Grade ≤ 1 • Follow CBC at least every 5 days • Reintroduce CC-122 at a lower dose level, if available • Use of growth factors (granulocyte-colony stimulating factor [G-CSF], granulocyte macrophage-colony stimulating factor [GM-CSF]) is permitted at the discretion of the investigator
Febrile neutropenia	• Hold further dosing until recovery to Grade ≤ 1 then resume dosing at one dose level lower, if available • Use of growth factors (G-CSF, GM-CSF) is permitted at the discretion of the investigator
Any hematological toxicity requiring interruption for > 4 weeks	• Discontinue CC-122
Non-hematologic toxicities	
Any Grade 4 non-hematologic toxicity, including LFT elevations	• Hold dosing until recovery to Grade ≤ 1 (or baseline LFT if liver tumors are present) • Reintroduce CC-122 at a lower dose level, if available

Table 10: Guidelines for Dose Modifications of CC-122 Related Toxicities (Continued)

Toxicity	Modification
Grade 3 or 4 clinical liver failure	• Discontinue CC-122
Troponin-T > ULN with associated 20% increase in BNP over baseline with an absolute value > 100 pg/mL (confirmed on repeated measurements) without associated cardiac symptoms or findings	• Hold dosing • Perform a cardiology evaluation, notify the sponsor • Follow troponin-T, BNP, and ECG at least every 7 days • If troponin-T returns to normal levels in ≤ 7 days and there are no other significant cardiac findings, restart CC-122 at the next lower dose level or the same dose • If troponin-T elevation persists beyond 7 days or recurs upon rechallenge, permanently discontinue CC-122
Troponin-T > ULN with cardiac symptoms or significant changes in ECG or LVEF	• Permanently discontinue CC-122, notify the sponsor
Rash ≥ Grade 3	• If Grade 3, hold dosing until recovery to Grade ≤ 1. • If AE resolution to Grade ≤ 1 occurs in ≤ 8 days, reintroduce CC-122 at the same dose level • If AE resolution to Grade ≤ 2 or resolution after > 8 days, reintroduce CC-122 at the next lower dose level, if available • Discontinue CC-122 for 2nd occurrence of ≥ Grade 3 rash • For desquamating (blistering) Grade 3 or any Grade 4 rash, discontinue CC-122 • For maculopapular, acneiform, or pustular rashes lasting ≤ 7 days medical management is warranted
Pneumonitis ≥ Grade 3	• Discontinue CC-122
Grade 1 or 2 Tumor Flare Reaction (TFR)* * assessed according to NCI CTCAE Version 3.0	• Continue CC-122, maintain dose level • Nonsteroidal antiinflammatory drugs (NSAIDs) and/or narcotics may also be used as per the investigator's discretion • Initiate therapy with corticosteroids as per the investigator's discretion
Grade 3 or 4 TFR*	• Hold CC-122 dosing • Initiate therapy with corticosteroids • NSAIDs and/or narcotics may also be used as per the investigator's discretion • When symptoms resolve to < Grade 1, restart CC-122 at the same dose level

Table 10: Guidelines for Dose Modifications of CC-122 Related Toxicities (Continued)

Toxicity	Modification
Peripheral neuropathy (neuropathies which begin or worsen while on study) ≥ Grade 3	• Hold dosing at investigator's discretion • When the toxicity resolves to ≤ Grade 2 or to baseline, restart CC-122 at the next lower dose level
Allergic reaction or hypersensitivity ≥ Grade 3	• Discontinue CC-122
Venous thrombosis/embolism ≥ Grade 3	• Hold dosing and start anticoagulation therapy; restart CC-122 at the investigator's discretion (maintain dose level)
Other ≥ Grade 3 non-hematologic toxicity	• Hold dosing at the investigator's discretion • When the toxicity resolves to ≤ Grade 2, restart CC-122 at the same dose level or at the next lower dose level at the investigator´s discretion
Any non-hematologic toxicity requiring interruption for > 4 weeks	• Discontinue CC-122
Recurrence of Grade 3 non-hematologic toxicity after dose reduction	• Reduce dose to the next lower dose level, if available. If a lower dose is not available, discontinue CC-122
Recurrence of Grade 4 non-hematologic toxicity after dose reduction	• Discontinue CC-122

8.2.9.4.1. Dose Modification and Management of Cardiac Laboratory Abnormalities

In addition to routine ECG monitoring, additional monitoring for potential cardiac toxicity is included for subjects treated with CC-122. This includes routine monitoring of troponin-T and BNP, as well as monitoring of LVEF as described in Section 6. Elevations of troponin-T or BNP warrant further investigation, including assessment of the subject for signs and symptoms of cardiac injury, consideration of a cardiology consultation, other cardiac evaluations (such as an exercise stress test, additional evaluation of LVEF, or other cardiac tests recommended by a cardiologist), and the addition of cardioprotective therapy (for example, beta blockers), as appropriate. Laboratory evaluation to assess for assay interference may also be warranted.

Isolated asymptomatic elevations of troponin-T or BNP without associated ECG or LVEF changes or other cardiac findings do not require that dosing be held. For any elevation of troponin-T > ULN associated with either significant elevation of BNP (20% increase from baseline with an absolute value > 100 pg/mL) or associated cardiac symptoms or findings, CC-122 dosing should be held and the sponsor should be notified. Additional cardiac monitoring should be performed as described in the table above and as medically indicated. CC-122 may be restarted, in consultation with the sponsor, based on troponin-T/BNP guidelines in Table 10 and general guidelines provided in Sections 8.2.9.1 and 8.2.9.3. For troponin-T elevations that either persist, recur with CC-122 rechallenge and/or are associated with cardiac symptoms or significant changes in ECG or LVEF, CC-122 should be permanently discontinued.

8.2.9.4.2. Dose Modification and Management of Pneumonitis

Pneumonitis has been reported with CC-122. The diagnosis should be considered in subjects presenting with nonspecific respiratory signs and symptoms such as hypoxia, pleural effusion, cough, dyspnea, or interstitial pulmonary infiltrates, and in whom infectious, neoplastic and other causes are excluded by appropriate investigations. Subjects should be specifically advised to promptly report any new or worsening respiratory symptoms they experience.

CC-122 dosing for those with radiological features suggestive of noninfectious pneumonitis but with minimal (Grade 1) symptoms may be interrupted per the investigator's discretion. For drug-related Grade 2 pneumonitis, CC-122 treatment should be interrupted and corticosteroids may be indicated. Once symptoms have resolved completely, CC-122 may be reintroduced at the next lower dose level. For drug-related Grade 3 or 4 pneumonitis, CC-122 must be permanently discontinued and corticosteroids used until clinical symptoms have resolved.

8.2.9.4.3. Dose Modification and Management of Tumor Flare Reaction

Subjects in this study should be monitored for tumor flare. Tumor flare reaction (TFR) is defined as a sudden and tender increase in the size of the disease bearing sites, including the lymph nodes, spleen and/or the liver often accompanied by low-grade fever, nonpruritic diffuse rash and in some cases increase in the peripheral blood lymphocyte counts. Tumor flare usually occurs within the first cycle of treatment. Tumor flare reaction may mimic progression of disease (PD); however, the TFR will generally subside over time. Therefore, careful monitoring and evaluation is important prior to discontinuing a study subject for PD in the initial cycles of CC-122 therapy.

There are currently no laboratory or radiological tests that distinguish TFR from PD. The distinction should be made on clinical grounds, incorporating observations such as associated physical findings, laboratory findings, and pace of disease before and after institution of treatment. Tumor flare will be recorded as an AE (graded using the NCI CTCAE 3.0 criteria) and not as PD.

Treatment of the TFR is up to the discretion of the investigator, depending on the severity and clinical situation. Recommendations for treatment are outlined in Table 10. Refer to Table 10 for further instructions and dose modifications for Grades 3 and 4 TFR. In mild to moderate cases, it is suggested that CC-122 be continued along with symptomatic treatment as outlined above. In more severe cases, CC-122 should be interrupted, as indicated in Table 10.

8.2.9.5. Overdose

An overdose, as defined for this protocol, refers to CC-122 dosing only.

On a per dose basis, an overdose is defined as the following amount over the protocol-specified dose of CC-122 assigned to a given subject, regardless of any associated adverse events or sequelae.

- PO any amount over the protocol-specified dose

On a schedule or frequency basis, an overdose is defined as anything more frequent than the protocol required schedule or frequency.

Complete data about drug administration, including any overdose, regardless of whether the overdose was accidental or intentional, should be reported in the case report form. See Section 11.1 for the reporting of adverse events associated with overdose.

In the event of overdose, the subject should be monitored as appropriate and should receive supportive measures as necessary. There is no known specific antidote for CC-122 overdose. Actual treatment should depend on the severity of the clinical situation and the judgment and experience of the treating physician.

8.3. Method of Treatment Assignment

All subjects enrolled on this study will receive treatment with CC-122.

The investigators must explain the study to prospective patients, using the informed consent form and obtain the written consent from patients who wish to participate in the study prior to screening assessments. After the confirmation of the inclusion and exclusion criteria, the investigators will fax an enrollment form (if subject is eligible) to the registration center. After receiving confirmation from the registration center, dosing should be started within 7 days of receiving the confirmation of registration.

As this is a dose-escalation trial, the assignment of a subject to a particular dose level will be coordinated by the sponsor and the investigator.

8.4. Packaging and Labeling

The label(s) for IP will include sponsor name, address and telephone number, the protocol number, IP name, dosage form and strength (where applicable), amount of IP per container, lot number, expiry date (where applicable), medication identification/kit number, dosing instructions, storage conditions, and required caution statements and/or regulatory statements, as applicable. Additional information may be included on the label as applicable per local regulations.

8.5. Investigational Product Accountability and Disposal

Celgene (or designee) will review with the investigator and relevant site personnel the process for Investigational Product return, disposal, and/or destruction including responsibilities for the site vs. Celgene (or designee).

The sponsor (or its designee) will deliver IP with the “Investigational Product Delivery Form” to the IP storage manager at the study site at the start of the study and thereafter as necessary. The IP storage manager will confirm the amount of IP received and submit the “Investigational Product Receipt Form” to the sponsor.

At the end of the study and when needed, the IP storage manager will return all of the unused IP, partially used IP, and empty bottles with the “Investigational Product Return Form” to the sponsor. The sponsor (or designee) will deliver the “Investigational Product Collection Form” to the IP storage manager. If any IP is missing or damaged, the sponsor should be notified immediately. The IP storage manager will document this in the “Investigational Product Return Form,” and the investigator will record this information in the source documents.

8.6. Investigational Product Compliance

The IP storage manager will manage the IPs following the instructions in the "Operating Procedure for Handling and Management of IPs" provided by the sponsor.

The IP storage manager will record receipt of IP from the sponsor, stock of IP at the study site, usage of IP by each subject, and return of unused drug to the sponsor or the disposition of IP. These records include the date, IP names/codes, quantity, lot numbers, and the subject number. The IP storage manager will also record whether the subject received IP at the dose specified in the protocol and whether IP supplied by the sponsor was appropriately managed and stored. Following completion of the study, the IP storage manager will sign and date these records verifying their accuracy. The IP storage manager will retain the original records, and copies of the records are to be submitted to the sponsor.

The investigator is responsible for accounting for all IPs that are issued to and returned by the subject during the course of the study. The investigators will instruct the subjects to manage IP by themselves, and return all unused drugs, if any due to missed doses or other reasons, including empty bottles to the study site.

9. CONCOMITANT MEDICATIONS AND PROCEDURES

9.1. Permitted Concomitant Medications and Procedures

In general, the use of any concomitant medication/therapies deemed necessary for the care of the subject is permitted.

Prophylactic antiemetics will be withheld until the subject has experienced ≥ Grade 1 nausea or vomiting. The subject may then receive prophylactic antiemetics at the discretion of the treating physician.

Stable, therapeutic doses of anticoagulants are permitted. However, subjects on warfarin should have PT/INR/PTT monitored according to Table 3 and as clinically indicated.

Subjects receiving recombinant erythropoietin or darbepoetin alfa for at least 4 weeks prior to starting IP treatment may continue their pretreatment doses throughout the study. However, as of April 2015, note that recombinant erythropoietin and darbepoetin alfa are not approved for the treatment of cancer chemotherapy associated anemia in Japan.

G-CSF may be used to mitigate the duration of neutropenia in the following situations:

- During Cycle 1: Grade 4 neutropenia lasting > 7 days or associated with fever (such as after experiencing a DLT of neutropenia)
- After Cycle 1: ≥ Grade 3 neutropenia

Note: G-CSF should not be administered concurrently (within 24 hours) with CC-122.

Flu vaccination is permitted.

Routine infectious disease prophylaxis is not recommended. However, antibiotic, antiviral, antipneumocystis, antifungal, or other prophylaxis may be implemented during the study at the discretion of the investigator.

Pneumocystis pneumonia (PCP) prophylaxis may be initiated with two consecutive confirmed CD4 measurements < 200 / mm^3.

Treatment with bisphosphonates (such as pamidronate, zolendronate), or other agents (such as denosumab) to prevent or delay progression of bone metastases are permitted. Maintenance of a stable dosing regimen throughout the study is recommended.

Subjects may receive physiologic replacement doses of glucocorticoids (up to the equivalent of 10 mg daily prednisone) as maintenance therapy for adrenal insufficiency.

Caution is recommended with the use of valproic acid due to the potential for drug interaction.

CC-122 absorbs ultraviolet (UV) light between the frequencies of 290 and 700 nm and has been shown to distribute to the skin and eyes in preclinical animal studies. As a precautionary measure, it is recommended that subjects avoid prolonged exposure to UV light, wear protective clothing and sunglasses, and use UV-blocking topical preparations while taking CC-122.

Subjects receiving CC-122 have developed venous thromboembolism/thromboembolism events reported as serious adverse events. Subjects and physicians are advised to be observant for the

signs and symptoms of thromboembolism. Subjects should be instructed to seek medical care if they develop symptoms, such as shortness of breath, chest pain, or arm or leg swelling. It is recommended that the investigator carefully assess an individual subject's underlying risk for thromboembolism and bleeding and consider prophylactic measures with anticoagulation or antiplatelet agents.

9.2. Prohibited Concomitant Medications and Procedures

Other investigational therapies must not be used while the subject is on the study.

Anticancer therapy (chemotherapy, biologic or investigational therapy, and surgery) other than the study treatments must not be given to subjects during the study. If such treatment is required, the subject must be discontinued from the study.

However, focal palliative radiotherapy for treatment of cancer-related symptoms is allowed during study treatment at the discretion of the investigator.

9.3. Required Concomitant Medications and Procedures

Every effort should be made to ensure that subjects are adequately hydrated prior to dosing.

Subjects who develop asymptomatic rises in TSH $\geq$ 10 mIU/L or symptomatic rises > 5 mIU/L should receive supplementation with thyroxine according to local standard practice.

10. STATISTICAL ANALYSES

10.1. Overview

The primary objectives of the study are to determine the safety and tolerability of CC-122, to define the MTD and/or RP2D, and to determine the plasma PK of CC-122 when administered orally to adult Japanese subjects with advanced solid tumors or NHL. The secondary objective of the study is to make a preliminary assessment of the antitumor activity of CC-122. The exploratory objectives of the study include evaluating the plasma PK of CC-122 formulated capsules and compare results to the plasma PK of CC-122 AIC, assessing the tolerability of CC-122 formulated capsules, [redacted]

In the following, statistical analyses will be performed by dose level, visit cycle and tumor type as needed or applicable.

10.2. Study Population Definitions

The study population definitions are as follows:

- Enrolled Population – includes all subjects enrolled, such as all subjects who are assigned an enrollment number.
- Treated Population – all enrolled subjects who take at least one dose of CC-122.
- Efficacy Population – all subjects who complete at least one cycle of their assigned treatment regimen, and have a baseline and at least one post-baseline efficacy assessment.

10.3. Sample Size and Power Considerations

A standard 3+3 design (Storer, 1989) will be used for dose escalation as described in Section 4.1, and approximately 15 subjects will be enrolled. Sample sizes are not based on statistical calculation but rather on clinical empirical and practical considerations traditionally used for phase 1 studies of this kind.

10.4. Background and Demographic Characteristics

Subjects' age, height, weight, and baseline characteristics will be summarized using descriptive statistics, while gender, race and other categorical variables will be provided using frequency tabulations. Medical history data will be summarized using frequency tabulations by system organ class and preferred term. The treated population will be used to summarize background and demographic characteristics.

10.5. Subject Disposition

Subject disposition (analysis population allocation, entered, discontinued, along with primary reason for discontinuation) will be summarized using frequency and percent for both treatment and follow-up periods. A summary of subjects enrolled by site will be provided. Protocol

deviations will be summarized using frequency tabulations. The enrolled population will be used to summarize subject disposition.

10.6. Efficacy Analysis

The efficacy population will be used for efficacy analysis. The efficacy variables of primary interest are tumor response. Tumor response (Appendix A, Section 19.1) will be based on investigator assessment using the Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1 for solid tumors, and the International Workshop Group (IWG) Revised Criteria for Lymphoma. Subjects will be evaluated for tumor response on Day 15 of Cycle 2, 4, 6, and every 3 cycles thereafter. A descriptive analysis of evidence of antitumor activity will be provided based on clinical, laboratory and radiographic assessments performed by the investigator, which includes assessments of target lesions, non-target lesions, new lesions and overall response. Both confirmed and unconfirmed responses by RECIST version 1.1 will be assessed.

The efficacy variable of focus will be best overall response. Duration of response will also be assessed. The data analyses of other preliminary efficacy variables will be detailed in the Statistical analysis plan (SAP).

10.7. Safety Analysis

All subjects who receive at least one dose of study medication will be included in the safety analyses. Adverse events, vital sign measurements, physical examination findings, clinical laboratory information, ECG interpretations, LVEF assessments and concomitant medications will be tabulated and summarized by dose level, visit cycle, and tumor type, as appropriate.

DLTs and all available safety information will be reviewed on an ongoing basis by the investigators and sponsor and summarized at the conclusion of each dose level. After completion of each dose cohort, the SRC will review the summarized data to determine the next step. Complete safety data for the DLT evaluation period will be summarized when all subjects have completed the DLT evaluation period.

Adverse events observed will be classified using the MedDRA classification system. The severity of toxicities will be graded according to NCI CTCAE version 4.03 whenever possible.

The frequency of adverse events will be tabulated by MedDRA System Organ Class and Preferred Term. In the by-subject analysis, a subject experiencing the same event more than once will only be counted once. Adverse events will be summarized by NCI CTCAE grade. Adverse events leading to discontinuation from treatment, events classified as Grade 3 or higher, treatment-related events, serious adverse events, and deaths will be tabulated and listed separately. Subject listings of all adverse events, serious adverse events, and their attributes will be provided.

Clinical laboratory data will be summarized. Lab data will be graded according to NCI CTCAE version 4.03 whenever possible. The frequencies of the worst severity grade observed during treatment will be displayed in cross-tabulations by screening status.

Vital signs, ECG data and LVEF data will be summarized by cross-tabulations presenting normal and abnormal values by number of subjects at pre- and post-IP initiation.

Graphical displays will be provided where useful in the interpretation of results.

10.8. Interim Analysis

No formal interim analysis is planned.

10.9. Assessment of Pharmacokinetics

Pharmacokinetic measures are incorporated into the study to assess the extent of systemic exposure, provided data is sufficient. Blood samples for PK will be collected at selected visits from all subjects. The following PK measurements will be determined for CC-122 after doses of CC-122 are given:

- Area under the plasma concentration time-curve (AUC).
- Peak (maximum) plasma concentration (C_{max}).
- Terminal half-life of ($t_{1/2}$).
- Time to maximum plasma concentration (T_{max}).
- Apparent clearance (CL/F).
- Apparent volume of distribution (Vz/F).

Descriptive statistics (N, mean, standard deviation [SD], coefficient of variation [CV%], standard error [SE], geometric mean, geometric CV%, median, min, and max) will be provided for all data. Results will be presented in tabular and graphic forms as appropriate.

[redacted]

[redacted]

11. ADVERSE EVENTS

11.1. Monitoring, Recording and Reporting of Adverse Events

An adverse event is any noxious, unintended, or untoward medical occurrence that may appear or worsen in a subject during the course of a study. It may be a new intercurrent illness, a worsening concomitant illness, an injury, or any concomitant impairment of the subject's health, including laboratory test values (as specified by the criteria in Section 11.3), regardless of etiology. Any worsening (such as any clinically significant adverse change in the frequency or intensity of a preexisting condition) should be considered an AE. A diagnosis or syndrome should be recorded on the AE page of the CRF rather than the individual signs or symptoms of the diagnosis or syndrome.

Abuse, withdrawal, sensitivity or toxicity to an investigational product should be reported as an AE. Overdose, accidental or intentional, whether or not it is associated with an AE should be reported on the overdose CRF. (See Section 8.2.9.5 for the definition of overdose.) Any sequela of an accidental or intentional overdose of an investigational product should be reported as an AE on the AE CRF. If the sequela of an overdose is an SAE, then the sequelae must be reported on an SAE report form and on the AE CRF. The overdose resulting in the SAE should be identified as the cause of the event on the SAE report form and CRF but should not be reported as an SAE itself.

All subjects will be monitored for AEs during the study. Assessments may include monitoring of any or all of the following parameters: the subject's clinical symptoms, laboratory, pathological, radiological or surgical findings, physical examination findings, or findings from other tests and/or procedures.

All AEs will be recorded by the investigator from the time the subject signs informed consent until 28 days after the last dose of IP and those SAEs made known to the investigator at any time thereafter that are suspected of being related to IP. AEs and serious adverse events will be recorded on the AE page of the CRF and in the subject's source documents. All SAEs must be reported to Celgene Drug Safety within 24 hours of the investigator's knowledge of the event by facsimile, or other appropriate method, using the SAE Report Form, or approved equivalent form.

11.2. Evaluation of Adverse Events

A qualified investigator will evaluate all adverse events as to:

11.2.1. Seriousness

An SAE is any AE occurring at any dose that:

- Results in death;
- Is life-threatening (in the opinion of the investigator, the subject is at immediate risk of death from the AE);

- Requires inpatient hospitalization or prolongation of existing hospitalization (hospitalization is defined as an inpatient admission, regardless of length of stay);
- Results in persistent or significant disability/incapacity (a substantial disruption of the subject's ability to conduct normal life functions);
- Is a congenital anomaly/birth defect;
- Constitutes an important medical event.

Important medical events are defined as those occurrences that may not be immediately life threatening or result in death, hospitalization, or disability, but may jeopardize the subject or require medical or surgical intervention to prevent one of the other outcomes listed above. Medical and scientific judgment should be exercised in deciding whether such an AE should be considered serious.

Events **not considered** to be SAEs are hospitalizations for:

- A standard procedure for protocol therapy administration. However, hospitalization or prolonged hospitalization for a complication of therapy administration will be reported as an SAE.
- Routine treatment or monitoring of the studied indication not associated with any deterioration in condition.
- The administration of blood or platelet transfusion as routine treatment of studied indication. However, hospitalization or prolonged hospitalization for a complication of such transfusion remains a reportable SAE.
- A procedure for protocol/disease-related investigations (such as surgery, scans, endoscopy, sampling for laboratory tests, bone marrow sampling). However, hospitalization or prolonged hospitalization for a complication of such procedures remains a reportable SAE.
- Hospitalization or prolongation of hospitalization for technical, practical, or social reasons, in absence of an AE.
- A procedure that is planned (planned prior to starting of treatment on study); must be documented in the source document and the CRF. Hospitalization or prolonged hospitalization for a complication remains a reportable SAE.
- An elective treatment of or an elective procedure for a preexisting condition unrelated to the studied indication.
- Emergency outpatient treatment or observation that does not result in admission, unless fulfilling other seriousness criteria above.

If an AE is considered serious, both the AE page/screen of the CRF and the SAE Report Form must be completed.

For each SAE, the investigator will provide information on severity, start and stop dates, relationship to IP, action taken regarding IP, and outcome.

11.2.2. Severity/Intensity

For both AEs and SAEs, the investigator must assess the severity/intensity of the event.

The severity/intensity of AEs will be graded based upon the subject's symptoms according to the current active minor version of CTCAE version 4.03.

http://www.jcog.jp/doctor/tool/CTCAEv4J_20111217.pdf

AEs that are not defined in the CTCAE should be evaluated for severity/intensity according to the following scale:

- Grade 1 = Mild – transient or mild discomfort; no limitation in activity; no medical intervention/therapy required
- Grade 2 = Moderate – mild to moderate limitation in activity, some assistance may be needed; no or minimal medical intervention/therapy required
- Grade 3 = Severe – marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalization is possible
- Grade 4 = Life-threatening – extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable
- Grade 5 = Death - the event results in death

The term "severe" is often used to describe the intensity of a specific event (as in mild, moderate or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This criterion is *not* the same as "serious," which is based on subject/event *outcome* or *action* criteria associated with events that pose a threat to a subject's life or functioning.

Seriousness, not severity, serves as a guide for defining regulatory obligations.

11.2.3. Causality

The investigator must determine the relationship between the administration of IP and the occurrence of an AE/SAE as Not Suspected or Suspected as defined below:

Not suspected:	Means a causal relationship of the adverse event to IP administration is **unlikely or remote**, or other medications, therapeutic interventions, or underlying conditions provide a sufficient explanation for the observed event.
Suspected:	Means there is a **reasonable possibility** that the administration of IP caused the adverse event. 'Reasonable possibility' means there is evidence to suggest a causal relationship between the IP and the adverse event.

Causality should be assessed and provided for every AE/SAE based on currently available information. Causality is to be reassessed and provided as additional information becomes available.

If an event is assessed as suspected of being related to a comparator, ancillary or additional IP that has not been manufactured or provided by Celgene, please provide the name of the manufacturer when reporting the event.

11.2.4. Duration

For both AEs and SAEs, the investigator will provide a record of the start and stop dates of the event.

11.2.5. Action Taken

The investigator will report the action taken with IP as a result of an AE or SAE, as applicable (for example, discontinuation, interruption, or reduction of IP, as appropriate) and report if concomitant and/or additional treatments were given for the event.

11.2.6. Outcome

The investigator will report the outcome of the event for both AEs and SAEs.

All SAEs that have not resolved upon discontinuation of the subject's participation in the study must be followed until these events have recovered, recovered with sequelae, not recovered or have resulted in death (due to the SAE).

11.3. Abnormal Laboratory Values

An abnormal laboratory value is considered to be an AE if the abnormality:

- results in discontinuation from the study;
- requires treatment, modification/interruption of IP dose, or any other therapeutic intervention; or
- is judged to be of significant clinical importance.

Regardless of severity grade, only laboratory abnormalities that fulfill a seriousness criterion need to be documented as a serious adverse event.

If a laboratory abnormality is one component of a diagnosis or syndrome, then only the diagnosis or syndrome should be recorded on the AE page/screen of the CRF. If the abnormality was not a part of a diagnosis or syndrome, then the laboratory abnormality should be recorded as the AE. If possible, the laboratory abnormality should be recorded as a medical term and not simply as an abnormal laboratory result (for example, record thrombocytopenia rather than decreased platelets).

11.4. Pregnancy

All pregnancies or suspected pregnancies occurring in either a female subject or partner of a male subject are immediately reportable events.

11.4.1. Females of Childbearing Potential

Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a female subject occurring while the subject is on IP, or within 28 days of the

subject's last dose of IP, are considered immediately reportable events. IP is to be discontinued immediately and the subject instructed to return any unused portion of the IP to the investigator. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to Celgene Drug Safety immediately by facsimile, or other appropriate method, using the Pregnancy Initial Report Form, or approved equivalent form.

The exposure of any pregnant female (for example, caregiver or pharmacist) to CC-122 is also an immediately reportable event.

The female subject should be referred to an obstetrician-gynecologist, preferably one experienced in reproductive toxicity for further evaluation and counseling. Female subjects must avoid breastfeeding for at least 28 days after the last dose of CC-122.

The investigator will follow the female subject until completion of the pregnancy, and must notify Celgene Drug Safety immediately about the outcome of the pregnancy (either normal or abnormal outcome) using the Pregnancy Follow-up Report Form, or approved equivalent form.

If the outcome of the pregnancy was abnormal (for example, spontaneous abortion), the investigator should report the abnormal outcome as an AE. If the abnormal outcome meets any of the serious criteria, it must be reported as an SAE to Celgene Drug Safety by facsimile, or other appropriate method, within 24 hours of the investigator's knowledge of the event using the SAE Report Form, or approved equivalent form.

All neonatal deaths that occur within 28 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 28 days that the investigator suspects is related to the in utero exposure to the IP should also be reported to Celgene Drug Safety by facsimile, or other appropriate method, within 24 hours of the investigator's knowledge of the event using the SAE Report Form, or approved equivalent form.

11.4.2. Male Subjects

If a female partner of a male subject taking investigational product becomes pregnant, the male subject taking IP should notify the investigator, and the pregnant female partner should be advised to call their healthcare provider immediately.

11.5. Reporting of Serious Adverse Events

Any AE that meets any criterion for an SAE requires the completion of an SAE Report Form in addition to being recorded on the AE page/screen of the CRF. All SAEs must be reported to Celgene Drug Safety within 24 hours of the investigator's knowledge of the event by facsimile, or other appropriate method, using the SAE Report Form, or approved equivalent form. This instruction pertains to initial SAE reports as well as any follow-up reports.

The investigator is required to ensure that the data on these forms is accurate and consistent. This requirement applies to all SAEs (regardless of relationship to IP) that occur during the study (from the time the subject signs informed consent until 28 days after the last dose of IP) or any SAE made known to the investigator at any time thereafter that are suspected of being related to IP. SAEs occurring prior to treatment (after signing the ICF) will be captured.

The SAE report should provide a detailed description of the SAE and include a concise summary of hospital records and other relevant documents. If a subject died and an autopsy has been

performed, copies of the autopsy report and death certificate are to be sent to Celgene Drug Safety as soon as these become available. Any follow-up data should be detailed in a subsequent SAE Report Form, or approved equivalent form, and sent to Celgene Drug Safety.

Where required by local legislation, the investigator is responsible for informing the Head of the Institution and the institutional review board (IRB) of the SAE and providing them with all relevant initial and follow-up information about the event. The investigator must keep copies of all SAE information on file including correspondence with Celgene and the IRB.

11.5.1. Safety Queries

Queries pertaining to SAEs will be communicated from Celgene Drug Safety to the site via facsimile or electronic mail. The response time is expected to be no more than five (5) business days. Urgent queries (for example, missing causality assessment) may be handled by phone.

11.6. Expedited Reporting of Adverse Events

For the purpose of regulatory reporting, Celgene Drug Safety will determine the expectedness of events suspected of being related to CC-122 based on the Investigator Brochure.

Celgene or its authorized representative shall notify the investigators and the Heads of the Institutions of the following information

- Any AE suspected of being related to the use of IP in this study or in other studies that is both serious and unexpected (Suspected Unexpected Serious Adverse Reactions [SUSARs]);
- Any finding from tests in laboratory animals that suggests a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity.
- In Japan, measures taken in foreign countries to ensure patient safety, study reports that indicates potential risk of cancer, etc., or biannual SAE report according to the local regulations.

Where required by local legislation, the investigator shall notify his/her IRB and the Head of the Institution promptly of these new serious and unexpected AE(s) or significant risks to subjects.

The investigator must keep copies of all pertinent safety information on file including correspondence with Celgene and the IRB. (See Section 15.3 for record retention information.)

Celgene Drug Safety Contact Information:

For Celgene Drug Safety contact information, please refer to the Serious Adverse Event Report Form Completion Guidelines or to the Pregnancy Report Form Completion Guidelines.

12. DISCONTINUATIONS

The following events are considered sufficient reasons for discontinuing a subject from the investigational product and/or from the study:

- Adverse Event
- Disease progression
- Withdrawal by subject
- Death
- Lost to follow-up
- Protocol violation
- Physician decision

The reason for discontinuation should be recorded in the CRF and in the source documents.

The decision to discontinue a subject remains the responsibility of the treating physician, which will not be delayed or refused by the sponsor. However, prior to discontinuing a subject, the investigator may contact the sponsor and forward appropriate supporting documents for review and discussion.

13. EMERGENCY PROCEDURES

13.1. Emergency Contact

In emergency situations, the investigator should contact the responsible Clinical Research Physician/Medical Monitor or designee by telephone at the number(s) listed on the Emergency Contact Information page of the protocol (after title page).

In the unlikely event that the Clinical Research Physician/Medical Monitor or designee cannot be reached, please contact the global Emergency Call Center by telephone at the number listed on the Emergency Contact Information page of the protocol (after title page). This global Emergency Call Center is available 24 hours a day and 7 days a week. The representatives are responsible for obtaining your call-back information and contacting the on-call Celgene/Contract research organization (CRO) Medical Monitor, who will then contact you promptly.

Note: The back-up 24 hour global emergency contact call center should only be used if you are not able to reach the Clinical Research Physician(s) or Medical Monitor or designee for emergency calls.

13.2. Emergency Identification of Investigational Products

This is an open-label study. Therefore, IP will be identified on the package labeling.

14. REGULATORY CONSIDERATIONS

14.1. Good Clinical Practice

The procedures set out in this study protocol pertaining to the conduct, evaluation, and documentation of this study are designed to ensure that Celgene, its authorized representative, and investigator abide by Good Clinical Practice (GCP), as described in International Conference on Harmonization (ICH) Guideline E6 and in accordance with the general ethical principles outlined in the Declaration of Helsinki. The study will receive approval from an IRB prior to commencement. The investigator will conduct all aspects of this study in accordance with applicable national, state, and local laws of the pertinent regulatory authorities.

14.2. Investigator Responsibilities

Investigator responsibilities are set out in the ICH Guideline for Good Clinical Practice and in the local regulations. Celgene staff or an authorized representative will evaluate and approve all investigators who in turn will select their staff.

The investigator should ensure that all persons assisting with the study are adequately informed about the protocol, amendments, study treatments, as well as study-related duties and functions. The investigator should maintain a list of sub-investigators and other appropriately qualified persons to whom he or she has delegated significant study-related duties.

The investigator is responsible for keeping a record of all subjects who sign an informed consent document and are screened for entry into the study. Subjects who fail screening must have the reason(s) recorded in the subject's source documents and the CRF.

The investigator, or a designated member of the investigator's staff, must be available during monitoring visits to review data, resolve queries and allow direct access to subject records (such as medical records, office charts, hospital charts, and study-related charts) for source data verification. The investigator must ensure timely and accurate completion of CRF and queries.

14.3. Subject Information and Informed Consent

The investigator must obtain informed consent of a subject and/or a subject's legal representative prior to any study related procedures.

Documentation that informed consent occurred prior to the study subject's entry into the study and of the informed consent process should be recorded in the study subject's source documents, including the date. The original informed consent document signed and dated by the study subject and by the person consenting the study subject prior to the study subject's entry into the study must be maintained in the investigator's study files and a copy given to the study subject. In addition, if a protocol is amended and it impacts on the content of the informed consent, the informed consent document must be revised. Study subjects participating in the study when the amended protocol is implemented must be reconsented with the revised version of the informed consent document. The revised informed consent document signed and dated by the study subject and by the person consenting for the study subject must be maintained in the investigator's study files and a copy given to the study subject.

14.4. Confidentiality

Celgene affirms the subject's right to protection against invasion of privacy and to be in compliance with ICH and other local regulations (whichever is most stringent). Celgene requires the investigator to permit Celgene's representatives and, when necessary, representatives from regulatory authorities, to review and/or copy any medical records relevant to the study in accordance with local laws.

Should direct access to medical records require a waiver or authorization separate from the subject's signed informed consent document, it is the responsibility of the investigator to obtain such permission in writing from the appropriate individual.

14.5. Protocol Amendments

Any amendment to this protocol must be approved by the Celgene Clinical Research Physician/Medical Monitor. Amendments will be submitted to the IRB for written approval. Written approval must be obtained before implementation of the amended version occurs. The written signed approval from the IRB should specifically reference the investigator name, protocol number, study title and amendment number(s) that is applicable. Amendments that are administrative in nature do not require IRB approval but will be submitted to the IRB for information purposes.

14.6. Institutional Review Board/Independent Ethics Committee Review and Approval

Before the start of the study, the study protocol, informed consent document, and any other appropriate documents will be submitted to the IRB with a cover letter or a form listing the documents submitted, their dates of issue, and the site (or region or area of jurisdiction, as applicable) for which approval is sought. If applicable, the documents will also be submitted to the authorities in accordance with local legal requirements.

IP can only be supplied to an investigator by Celgene or its authorized representative after documentation on all ethical and legal requirements for starting the study has been received by Celgene or its authorized representative. This documentation must also include a list of the members of the IRB and their occupation and qualifications. If the IRB will not disclose the names, occupations and qualifications of the committee members, it should be asked to issue a statement confirming that the composition of the committee is in accordance with GCP. For example, the IRB General Assurance Number may be accepted as a substitute for this list. Formal approval by the IRB should mention the protocol title, number, amendment number (if applicable), study site (or region or area of jurisdiction, as applicable), and any other documents reviewed. It must mention the date on which the decision was made and must be officially signed by a committee member. Before the first subject is enrolled in the study, all ethical and legal requirements must be met.

The IRB and, if applicable, the authorities, must be informed of all subsequent protocol amendments in accordance with local legal requirements. Amendments must be evaluated to determine whether formal approval must be sought and whether the informed consent document should also be revised.

The investigator must keep a record of all communication with the IRB and, if applicable, between a Coordinating investigator and the IRB. This statement also applies to any communication between the investigator (or Coordinating investigator, if applicable) and regulatory authorities.

Any advertisements used to recruit subjects for the study must be reviewed by Celgene and the IRB prior to use.

14.7. Ongoing Information for Institutional Review Board/Ethics Committee

If required by legislation or the IRB, the investigator must submit to the IRB:

- Information on serious or unexpected adverse events as soon as possible;
- Periodic reports on the progress of the study;
- Deviations from the protocol or anything that may involve added risk to subjects.

14.8. Closure of the Study

Celgene reserves the right to terminate this study at any time for reasonable medical or administrative reasons. Any premature discontinuation will be appropriately documented according to local requirements (for example, for the IRB, regulatory authorities, etc.).

In addition, the investigator or Celgene has the right to discontinue a single site at any time during the study for medical or administrative reasons such as:

- Unsatisfactory enrollment;
- GCP noncompliance;
- Inaccurate or incomplete data collection;
- Falsification of records;
- Failure to adhere to the study protocol.

14.9. Compensation for Injured Subjects

Celgene is prepared to compensate for the costs of medical care and others losses associated with study-related injuries.

The compensation for injured subjects and the payment to them will be specified in the informed consent document.

15. DATA HANDLING AND RECORDKEEPING

15.1. Data/Documents

The investigator must ensure that the records and documents pertaining to the conduct of the study and the distribution of the investigational product are complete, accurate, filed and retained. Examples of source documents include: hospital records; clinic and office charts; laboratory notes; memoranda; subject's diaries or evaluation checklists; dispensing records; recorded data from automated instruments; copies or transcriptions certified after verification as being accurate copies; microfiche; x-ray film and reports; and records kept at the pharmacy, and the laboratories, as well as copies of the CRFs or compact disc read-only memory (CD-ROM).

15.2. Data Management

Data will be collected via electronic CRFs/an electronic data capture (EDC) system. This data will be electronically verified through use of programmed edit checks specified by the clinical team. Discrepancies in the data will be brought to the attention of the clinical team, and investigational site personnel, if necessary. Resolutions to these issues will be reflected in the electronic CRFs/EDC system. An audit trail within the system will track all changes made to the data.

15.3. Record Retention

Essential documents must be retained by the Head of the Institution and investigator for a minimum of the time period listed below or according to local laws or requirements, whichever is longer:

- Two years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region
- At least two years have elapsed since the formal discontinuation of clinical development of the IP
- Until the marketing application of the IP is approved in Japan
- Three years have elapsed since the formal completion (discontinuation) of the clinical trial in Japan

Essential documents include, but are not limited to, the following:

- Signed informed consent documents for all subjects;
- Subject identification code list, screening log (if applicable), and enrollment log;
- Record of all communications between the investigator, the Head of the Institution and the IRB;
- Composition of the IRB;
- Record of all communications between the investigator, Celgene, and their authorized representative(s);

- List of sub-investigators and other appropriately qualified persons to whom the investigator has delegated significant study-related duties, together with their roles in the study, curriculum vitae, and their signatures;
- Copies of CRFs (if paper) and of documentation of corrections for all subjects;
- IP accountability records;
- Record of any body fluids or tissue samples retained;
- All other source documents (subject records, hospital records, laboratory records, etc.);
- All other documents as listed in Section 8 of the ICH consolidated guideline on GCP (Essential Documents for the Conduct of a Clinical Trial).

The Head of the Institution and the investigator must notify Celgene if they wish to assign the essential documents to someone else, remove them to another location or is unable to retain them for a specified period. The Head of the Institution and the investigator must obtain approval in writing from Celgene prior to destruction of any records. If the Head of the Institution and the investigator are unable to meet this obligation, they must ask Celgene for permission to make alternative arrangements. Details of these arrangements should be documented.

All study documents should be made available if required by relevant health authorities. The Head of the Institution and the investigator/institution should take measures to prevent accidental or premature destruction of these documents.

16. QUALITY CONTROL AND QUALITY ASSURANCE

All aspects of the study will be carefully monitored by Celgene or its authorized representative for compliance with applicable government regulations with respect to current GCP and standard operating procedures.

16.1. Study Monitoring and Source Data Verification

Celgene ensures that appropriate monitoring procedures are performed before, during and after the study. All aspects of the study are reviewed with the investigator and the staff at a study initiation visit and/or at an investigator meeting. Prior to enrolling subjects into the study, a Celgene representative will review the protocol, CRFs, procedures for obtaining informed consent, record-keeping, and reporting of AEs/SAEs with the investigator. Monitoring will include on-site visits with the investigator and his/her staff as well as any appropriate communications by mail, email, fax, or telephone. During monitoring visits, the facilities, investigational product storage area, CRFs, subject's source documents, and all other study documentation will be inspected/reviewed by the Celgene representative in accordance with the Study Monitoring Plan.

Accuracy will be checked by performing source data verification that is a direct comparison of the entries made onto the CRFs against the appropriate source documentation. Any resulting discrepancies will be reviewed with the investigator and/or his/her staff. Any necessary corrections will be made directly to the CRFs or via queries by the investigator and/or his/her staff. Monitoring procedures require that informed consents, adherence to inclusion/exclusion criteria and documentation of SAEs and their proper recording be verified. Additional monitoring activities may be outlined in a study-specific monitoring plan.

16.2. Audits and Inspections

In addition to the routine monitoring procedures, a Good Clinical Practice Quality Assurance unit exists within Celgene. Representatives of this unit will conduct audits of clinical research activities in accordance with Celgene SOPs to evaluate compliance with Good Clinical Practice guidelines and regulations.

The Head of the Institution and the investigator are required to permit direct access to the facilities where the study took place, source documents, CRFs and applicable supporting records of study subject participation for audits and inspections by IRBs, regulatory authorities (for example, Food & Drug Administration [FDA], European Medicines Agency [EMA], Health Canada) and company authorized representatives. The Head of the Institution and the investigator should make every effort to be available for the audits and/or inspections. If the Head of the Institution or the investigator is contacted by any regulatory authority regarding an inspection, he/she should contact Celgene immediately.

17. PUBLICATIONS

The results of this study may be published in a medical publication, journal, or may be used for teaching purposes. Additionally, this study and its results may be submitted for inclusion in all appropriate health authority study registries, as well as publication on health authority study registry websites, as required by local health authority regulations. Selection of first authorship will be based on several considerations, including, but not limited to study participation, contribution to the protocol development, and analysis and input into the manuscript, related abstracts, and presentations in a study.

18. REFERENCES

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Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). European J Cancer 2009; (45) 228–247.

Lenz G, Wright G, Dave SS, et al. Stromal gene signatures in large-B-cell lymphomas. N Engl J Med. 2008; 359(22): 2313-23.

Storer B. Design and Analysis of Phase I Clinical Trials. Biometrics 1989; 45: 925-937.

19. APPENDICES

19.1. Appendix A

19.1.1. Guidelines for Tumor Response Evaluation

19.1.1.1. Solid Tumors

The Guidelines for the New Response Evaluation Criteria in Solid Tumors (RECIST, [Eisenhauer, 2009]) can be accessed online at:

www.eortc.be/recist/documents/RECISTGuidelines.pdf

19.1.1.2. Lymphoma

The International Working Group Revised Response Criteria for Malignant Lymphoma (Cheson, 2007) can be accessed online at the following address:

http://jco.ascopubs.org/cgi/reprint/25/5/579

(click on “manual download for full text PDF of manuscript)

19.2. Appendix B

19.2.1. CC-122 Pregnancy Prevention Risk Management Plan

Specific details regarding the CC-122 Pregnancy Prevention Risk Management Plan will be provided via a separate, stand-alone document.

Celgene Signing Page

This is a representation of an electronic record that was signed electronically in Livelink. This page is the manifestation of the electronic signature(s) used in compliance with the organizations electronic signature policies and procedures.

UserName: [redacted]
Title: [redacted]
Date: [redacted]
Meaning: Approved, no changes necessary.
==========

1. JUSTIFICATION FOR AMENDMENT

The primary purpose of protocol amendment 03 is to adjust the visit schedule for Cycle 5 onwards and to clarify that dose escalation will stop if the MTD in global CC-122 studies in various indications is reached.

Given that safety has been confirmed in the 2, 3, and 4 mg active ingredient in capsule (AIC) dose levels (dose levels 1-3) as documented in the Safety Review Committee (SRC) dose-escalation meeting minutes and given that several patients have remained on study for as long as 12 cycles with no major safety issues, the visit schedule from Cycle 5 onwards is being changed to allow for less frequent study visits to ease the burden on patients having to visit the study site for study assessments.

The clarification regarding stopping dose escalation if the MTD in global studies in various indications is reached was added to allow flexible decision-making based on other ongoing studies being conducted globally and not just the CC-122-ST-001 study.

The changes to the protocol are as follows:

- The study design section of the protocol summary was updated to include language regarding stopping dose escalation if the MTD in global CC-122 studies in various indications is reached.
- Section 4.1.1 was also revised to include the revised wording stated in the bullet above.
- The table of events (Table 3) in Section 5 has been updated to allow for once monthly visits from Cycle 5 onwards (with the exception of Cycles with tumor assessments, e.g. Cycle 6 and every 3 cycles thereafter, wherein a Day 15 visit is necessary) instead of weekly visits.
- A footnote under the table of events was updated to more accurately reflect the pregnancy prevention risk management plan.
- Section 8.2.8 was also revised to include the revised wording regarding stopping dose escalation if the MTD in global CC-122 studies in various indications is reached.

The amendment also includes a few minor formatting and editing changes for added clarity.

1. JUSTIFICATION FOR AMENDMENT

The primary purpose of protocol amendment 02 is to introduce the evaluation of a formulated capsule of CC-122.

The current active ingredient in capsule (AIC) and the new CC-122 formulated capsules were evaluated in healthy adult subjects in a separate study (CC-122-CP-002 Part 2, which is clinically completed). The CC-122 formulated capsules have different CC-122 free base (the active moiety) amounts compared with CC-122 AIC capsules that were employed from the beginning of the current study. CC-122 AIC 0.5, 1, and 3 mg strengths were based on CC-122 HCl (the salt form) and are equivalent to 0.44, 0.88, and 2.64 mg CC-122 free base, respectively. CC-122 formulated capsules of 1, 3, 3.5 and 4 mg strengths are based on CC-122 free base and are equivalent to 1.13, 3.38, 3.95 and 4.51 mg CC-122 HCl, respectively.

Following a single oral administration of CC-122 at the dose level of 3 mg, the drug exposure (AUC_{inf} and C_{max}) was higher in subjects administered CC-122 formulated capsules than in subjects administered CC-122 AIC (16.29% and 35.58%, respectively). Given the increased exposure in healthy adults, pharmacokinetic (PK) and safety evaluations of the CC-122 formulated capsules will be performed in subjects with cancer within the current CC-122-ST-002 study.

[redacted]

The changes to the protocol are as follows:

- the addition of updated information from ongoing studies in Section 1.1.3
- the addition of exploratory objectives and endpoints to assess the PK and tolerability of the formulated capsules to the Protocol Summary and Sections 2 and 3
- [redacted]
- the addition of a provisional dose cohort using formulated capsules to the Protocol Summary and Section 4
- the addition of information on previous clinical experience with the formulated capsules to Section 1
- [redacted]
- the revision of the expected number of subjects from 12 to 15 in the Protocol Summary and Sections 7 and 10 in line with the addition of a provisional cohort
- the addition of information on the formulated capsules to Section 8
- [redacted]

The amendment also includes a change in the responsible medical monitor, as well as a few minor language and formatting changes for added clarity.

1. JUSTIFICATION FOR AMENDMENT

The primary purpose of this protocol amendment is to include the following changes [redacted]

- changing the duration of recommendation for hospitalization during Cycle 1 from 2 weeks to the entire DLT evaluation period (Cycle 1) in Section 5
- the addition of language stating that contraception methods should be approved or certified in Japan in Section 6.2.5
- the addition of thrombocytopenia requiring platelet transfusions as a dose-limiting toxicity in Section 8.2.6
- the addition of language stating that recombinant erythropoietin and darbepoetin alfa are not approved for the treatment of cancer chemotherapy associated anemia in Japan in Section 9.1
- the addition of language stating that female subjects must avoid breastfeeding for at least 28 days after the last dose of CC-122 to Section 11.4.1

[redacted]

The amendment also includes a change in the responsible medical monitor, as well as the deletion of a sentence in Section 14.9 as a result of changes to the Japanese protocol template language and minor formatting changes.