Official Title of Study:

A Phase 1, Open-Label, Dose Finding Study to Assess the Safety, Tolerability, Pharmacokinetics and Preliminary Efficacy of CC-90011 in Subjects with Relapsed and/or Refractory Solid Tumors and Non-Hodgkin's Lymphomas

NCT Number: NCT02875223

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A PHASE 1, OPEN-LABEL, DOSE FINDING STUDY TO ASSESS THE SAFETY, TOLERABILITY, PHARMACOKINETICS AND PRELIMINARY EFFICACY OF CC-90011 IN SUBJECTS WITH RELAPSED AND/OR REFRACTORY SOLID TUMORS AND NON-HODGKIN'S LYMPHOMAS

INVESTIGATIONAL PRODUCT (IP):	**CC-90011 (also known as BMS-986363)**
PROTOCOL NUMBER:	**CC-90011-ST-001**
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SPONSOR NAME/ ADDRESS:	Celgene Corporation 86 Morris Avenue Summit, NJ 07901

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{See appended electronic signature page}
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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, International Council for Harmonisation (ICH) Good Clinical Practices Guidelines, and local regulations governing the conduct of clinical studies.	

COORDINATING PRINCIPAL INVESTIGATOR SIGNATURE PAGE

Signature of Coordinating Principal Investigator	**dd mmm yyyy**
Printed Name of Coordinating Principal Investigator **Institution Name:**_____ By my signature, I agree the protocol has been written to comply with ICH Good Clinical Practices guidelines and agree to offer guidance throughout the study as needed.	

PROTOCOL SUMMARY

Study Title

A Phase 1, Open-label, Dose Finding Study to Assess the Safety, Tolerability, Pharmacokinetics and Preliminary Efficacy of CC-90011 in Subjects with Relapsed and/or Refractory Solid Tumors and Non-Hodgkin's Lymphomas.

Indication

Relapsed and/or refractory advanced unresectable solid tumors (enriched for grade 2 neuroendocrine neoplasms [NEN] and grade 2 [G2] neuroendocrine tumors [NETs] and neuroendocrine carcinomas [NEC]) and relapsed and/or refractory (R/R) advanced Non-Hodgkin's lymphomas (NHLs) (ie, diffuse large B-cell lymphoma [DLBCL] and follicular lymphoma [FL] and marginal zone lymphoma [MZL]).

Part B will enroll relapsed and/or refractory advanced unresectable low/intermediate-grade lung NETs (typical and atypical carcinoid), prostate NECs (NEPCs) and R/R NHL.

Parts C and D will enroll subjects with advanced unresectable solid tumors.

Objectives Part A and Part B

Primary Objectives:

- To determine the safety and tolerability of CC-90011
- To define the maximum tolerated dose (MTD) and/or the recommended Phase 2 dose (RP2D) of CC-90011

Secondary Objectives:

- To provide information on the preliminary efficacy of CC-90011
- To characterize the pharmacokinetics (PK) of CC-90011

Objectives Part C and Part D

Primary Objectives:

- To evaluate the effect of rifampicin, a strong cytochrome P450 (CYP) 3A and P-glycoprotein (P-gp) inducer, on the PK of CC-90011 (Part C)
- To evaluate the effect of itraconazole, a strong CYP3A and P-gp inhibitor on the PK of CC-90011 (Part D)

Secondary Objectives:

- To characterize the PK parameters of a single dose of CC-90011 alone and in combination with rifampicin (Part C) or itraconazole (Part D)
- To assess the safety and tolerability of a single dose of CC-90011 alone and in combination with rifampicin (Part C) or itraconazole (Part D)

Exploratory Objectives

All exploratory objectives are outlined in Section 2.

Study Design

Study CC-90011-ST-001 is an open-label, Phase 1, dose escalation and expansion, First-In-Human (FIH) clinical study of CC-90011 in subjects with advanced unresectable solid tumors (enriched for grade 2 NENs, grade 2 NETs and NECs) and R/R NHL (MZL, including extranodal MZL [EMZL], splenic MZL [SMZL], nodal MZL [NMZL], and histologic transformation of MZL). The dose escalation part (Part A) of the study will explore escalating oral doses of CC-90011 to estimate the MTD of CC-90011. A Bayesian logistic regression model (BLRM) utilizing escalation with overdose control (EWOC) (Babb, 1998; Neuenschwander, 2008) will help guide CC-90011 dose escalation and dose frequency decisions, with the final decisions made by a safety review committee (SRC). The expansion part (Part B) will further evaluate the safety and efficacy of CC-90011 administered at or below the MTD in 3 selected expansion cohorts of approximately 10-20 evaluable subjects each, in order to further define the RP2D. The Drug-Drug Interaction (DDI) cohorts will evaluate the effect of multiple doses of rifampicin (Part C) and itraconazole (Part D) on CC-90011 by comparison of the PK parameters of a single dose of CC-90011 alone and in combination with rifampicin or itraconazole. Parts A and B will consist of 3 periods: Screening, Treatment, and Follow-up periods (refer to Figure 2). Part C and D will consist of 4 periods: Screening, DDI evaluation, Treatment and Follow-up periods (refer to Figure 3).

Screening Period

The Screening Period starts 28 days (± 3 days) prior to first dose of CC-90011. The informed consent form (ICF) must be signed and dated by the subject and the administering staff prior to the start of any other study procedures. All screening tests and procedures must be completed within the 28 days (± 3 days) prior to the first dose of CC-90011.

Treatment Period

Parts A and B

During the Treatment Period, CC-90011 will initially be administered orally once weekly in each 4-week (28-day) Cycle in Part A. Alternative dosing schedules (eg, once every other week or twice weekly) may be evaluated based on the review of available safety, PK, PD, and efficacy data by the SRC. Once the MTD has been established for a once weekly schedule, and if the pharmacokinetics and clinical safety data in man suggest more frequent dosing might be appropriate, and if the SRC is supportive, alternative more frequent dosing schedules may be explored. In Part A, the window for evaluation of dose-limiting toxicity (DLT) will be 28 days (4 weeks) during Cycle 1.

In September 2018, after completion of Part A, the SRC determined the RP2D to be 60 mg CC-90011 once weekly (QW) in each 28-day cycle. In Part B, 3 cohorts, of approximately 10-20 (MZL, including EMZL, SMZL, NMZL and histologic transformation of MZL) evaluable subjects each, with advanced low/intermediate-grade lung NETs, NEPCs, R/R NHL will receive the RP2D to further evaluate safety, PK, PD and preliminary efficacy.

The enrollment of subjects with bronchial NET, prostate NEC and MZL was closed due to Company's strategic decisions and not due to any safety concern. The RP2D established during Part A, was confirmed to be safe and tolerable during Part B.

Parts C and D

The DDI cohorts will consist of a nonrandomized, fixed-sequence, crossover, two-period design that will evaluate the effect of multiple doses of rifampicin (Part C) and itraconazole (Part D) on CC-90011 PK parameters in approximately 16 subjects with advanced unresectable solid tumors. The DDI evaluation for both Parts C and D will be conducted across 2 study periods (hereafter referred to as Period 1 and Period 2) followed by a CC-90011 treatment period in which subjects will receive CC-90011 at the RP2D of 60 mg QW in 28-day cycles. Both Part C and Part D will have a 14-day washout interval between Period 1 and Period 2 and the total duration of the DDI evaluation period (Period 1 + Period 2) will be 40 days. Overnight stay for subjects can be arranged or subjects can be hospitalized at any time point due to study procedures, without this constituting a serious adverse event (SAE), if the treating physician considers this appropriate for an individual subject. Blood samples and urine will be collected at prespecified time points for PK analyses. Blood samples will also be collected at prespecified time points for PD analyses.

Follow-up Period

In the Follow-up Period, all subjects will be followed for 28 days (± 3 days) after the last dose of CC-90011 (in Parts A and B) and after the last dose of any study treatment, whichever is the latest (in Parts C and D) for safety.

Subjects who discontinue treatment for reasons other than disease progression, start of a new anticancer therapy, or withdrawal of consent from the entire study will have disease assessments performed according to the specified tumor assessment schedule until progression and/or initiation of new systemic anticancer therapies. This does not apply to subjects who discontinue during the DDI evaluation period in Part C and Part D.

After the Safety Follow-up visit, subjects will be followed every subsequent 3 months, (± 2 weeks) for survival follow-up, for up until 2 years or until death, lost to follow-up, or the End of Trial, whichever occurs first. This does not apply to subjects who discontinue during the DDI evaluation period in Part C and Part D.

Subjects who discontinue treatment during the DDI evaluation in Parts C and D may be replaced if not DDI evaluable.

Part A-Dose Escalation

A minimum of 3 subjects will be enrolled at each dose level. The initial CC-90011 dose was 1.25 mg once per week. The BLRM with EWOC will incorporate available prior safety information and update the model parameters after each new cohort of subjects completes Cycle 1. The decision for the next dose will be made by the SRC based on a calculation of risk assessment using the BLRM, and available safety (ie, DLT and non-DLT safety data), PK, PD, and preliminary efficacy information. In addition, relevant non-clinical data (eg, GLP (good laboratory practice) toxicity studies, in vivo pharmacology from xenograft models, etc) may be utilized in the assessment. Details of the statistical methodology are provided in Appendix E.

At all decision time points, the BLRM permits alterations in the dose increments based on the observed DLTs; however, the dose for the next cohort will not exceed a 100% increase from the

prior dose. The MTD is the highest dose for which less than 33% of the population (not sample from the population) treated with CC-90011 suffer a DLT in the first cycle with at least 6 evaluable subjects having been treated at this dose. The SRC will make the final decision regarding the CC-90011 dose for each cohort.

During dose escalation, a CC-90011 dose can be declared the MTD after meeting the following conditions:

- at least 6 evaluable subjects have been treated at the dose,
- the posterior probability that the DLT rate lying in the target interval (16-33%) at the dose exceeds 60% or a sufficient number of subjects have been entered into the study to ensure the precision of the MTD estimate, as the posterior probability approaches but fails to exceed 60%, and
- the dose is recommended according to the BLRM and is approved by SRC.

Dose escalation may be terminated by SRC at any time based on emerging safety concerns without establishing the MTD. The SRC will include Investigators (and/or designated representatives), the Sponsor's study physician, safety physician, study statistician, and the study manager. Ad hoc attendees may include the study pharmacokineticist, the study biomarker scientist, and the study clinical scientist. Other internal and external experts may be consulted by the SRC, as necessary.

All decisions made at the SRC meetings will be formally documented (via SRC meeting minutes) and circulated to all sites in writing. No dose escalation, de-escalation, change to dosing schedule, or expansion of existing dose cohorts will commence prior to a written notification being sent to all participating sites of the respective SRC decision.

The decision to evaluate additional subjects within a dose cohort, a higher dose cohort, intermediate dose cohorts, smaller dose increments, alternative dosing schedules (eg, once every other week or twice weekly), or declare a MTD will also be determined by the SRC, based on the BLRM assessment and their review of available safety (ie, DLT and non-DLT data), PK, PD, and preliminary efficacy information. The final decision will be made by the SRC.

After the first dose is administered in any cohort during dose escalation, subjects in each cohort are observed for 28 days (Cycle 1, DLT window) before the next dose cohort can begin. A subject evaluable for DLT is defined as one that:

- Has received ≥ 75% of the total planned dose amount of CC-90011 during Cycle 1 without experiencing a DLT,

or

- Experienced a DLT after receiving at least one dose of CC-90011.

Subjects non-evaluable for DLT will be replaced.

During the initial dose levels, subjects with relapsed and/or refractory advanced unresectable solid tumors and R/R NHL will be enrolled until the 2nd occurrence of a Grade ≥ 2, study drug-related toxicity in Cycle 1 which fall under the adverse event terms of thrombocytopenia/platelet count decrease, anaemia/red blood cell count decrease, neutropenia/white blood cell count decrease, and/ or gastrointestinal tract toxicities. Then, enrollment in Part A will be restricted to

subjects with grade 2 (G2) neuroendocrine neoplasms (NEN)/neuroendocrine tumors (NETs), small cell lung cancer (SCLC), and other neuroendocrine carcinomas (NEC) which may secrete neuroendocrine markers such as Pro-GRP, CgA, or calcitonin (only in Part A).

Intra-subject dose escalation will not be allowed during the DLT assessment period; however, in Cycles ≥ 3, subjects without evidence of disease progression who are tolerating their assigned dose of CC-90011 may (at the Investigator's discretion and in consultation and agreement with the Sponsor's study physician) escalate to the highest dose level shown to be adequately tolerated by at least one cohort of subjects in this study (ie, overdose risk is less than 25% based on the BLRM assessment).

Part B-Cohort Expansion

Following completion of dose escalation (Part A), Part B (expansion) will enroll 3 cohorts, of approximately 10-20 evaluable subjects each, with advanced low/intermediate-grade lung NETs, NEPCs and R/R NHL (MZL, including EMZL, SMZL, NMZL and histologic transformation of MZL) will receive the RP2D to further evaluate the safety, PK, PD and preliminary efficacy. Expansion may occur at the MTD and schedule established in the dose escalation phase, and/or at an alternative tolerable dose and schedule, based on review of available safety, PK, PD, and efficacy data from Part A. The SRC will select the doses and schedules of interest for cohort expansion. One or more dosing regimens may be selected for cohort expansion. The SRC will continue to review safety data regularly throughout the study and make recommendations about study continuation and dose modification, as appropriate. The study will be conducted in compliance with International Council for Harmonisation (ICH)/Good Clinical Practices (GCPs).

In Part B of the study, SRC meetings will be held after at least 6 subjects have been recruited with at least 2 months of follow up; or after the number of subjects specified in the futility analyses has been reached; and/or ad-hoc as advised by emerging safety/efficacy data.

Part C and Part D- DDI Cohorts

Approximately 8 DDI evaluable subjects with advanced unresectable solid tumors will be enrolled in each part, leading to a total of up to 16 DDI evaluable subjects for Parts C and D. DDI evaluable population is described in Section 9.2. Following confirmation of eligibility during screening, subjects will be alternatively enrolled in Part C or Part D. The DDI evaluation will be conducted across 2 study periods (Period 1 and Period 2), followed by a CC-90011 treatment period in which subjects will receive CC-90011 at the RP2D of 60 mg QW of 28-day cycles. Overnight stay for subjects can be arranged or subjects can be hospitalized at any time point due to study procedures, without this constituting a serious adverse event (SAE), if the treating physician considers appropriate for an individual subject. Treatment in Part C and Part D are as described below. Both parts will have a 14-day washout interval between Period 1 and Period 2 and the total duration of the DDI evaluation period (Period 1 + Period 2) will be 40 days:

- **Part C:** Period 1 (Day 1 - Day 14) will consist of a single oral 60 mg CC-90011 dose administered on Day 1, followed by a washout interval of 14 days.

  Period 2 (Day 15 - Day 40) will consist of a total of 21 oral doses of rifampicin 600 mg administered daily from Day 15 until Day 35, and a single oral 60 mg CC-90011

dose administered on Day 22, followed by a washout interval from Day 36 until Day 39 (both included).

- **Part D:** Period 1 (Day 1 - Day 14) will consist of single oral 20 mg CC-90011 dose administered on Day 1, followed by a washout interval of 14 days.

  Period 2 (Day 15 - Day 40) will consist of a total of 17 oral doses of itraconazole 200 mg administered daily from Day 15 until Day 31, and a single oral 20 mg CC-90011 dose administered on Day 18, followed by a washout interval from Day 32 until Day 39 (both included).

Following completion of DDI evaluation period, including a washout period of 5 days after the last dose of rifampicin (Part C) or 9 days following last dose of itraconazole (Part D), subjects will start CC-90011 dosing on Study Day 40 at the RP2D of 60 mg QW with 28-day cycles.

Study Population

Men and women, 18 years or older, with relapsed and/or refractory advanced unresectable solid tumors (enriched for G2 NENs/NET, SCLC, and other NECs) and R/R NHL (including DLBCL and FL or MZL) will be enrolled in the study for Part A.

In Part B, 3 cohorts, of approximately 10-20 evaluable subjects each, with advanced low/intermediate-grade lung NETs, NEPCs and R/R NHL (MZL, including EMZL, SMZL, NMZL and histologic transformation of MZL) will receive the RP2D to further evaluate safety, PK, PD and preliminary efficacy.

In Parts C and D, approximately 16 DDI evaluable subjects with advanced unresectable solid tumors will be enrolled.

Length of Study

Enrollment is expected to take approximately 67 months to complete (24 months for dose escalation and 24 to 43 months for expansion). Completion of active treatment and post-treatment follow-up is expected to take an additional 4 to 28 months. Enrollment and DDI evaluation in Parts C and D is expected to take 12 to 15 months. Completion of treatment and post-treatment follow-up is expected to take an additional 6 to 24 months. The entire study is expected to last approximately 9-10 years.

The End of Trial is defined as either the date of the last visit of the last subject to complete the post-treatment follow-up, 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, whichever is the later date.

Study Treatments

Part A and Part B

Celgene Corporation (Celgene) will supply the investigational product (IP), CC-90011 in Parts A and B (containing only the active pharmaceutical ingredient at dosage strengths of 0.50 mg, 0.75 mg, and 2.00 mg, 5.00 mg, and 15 mg) capsules for oral administration, labeled appropriately for investigational use as per the regulations of the relevant country health authority.

Study treatment may be discontinued if there is evidence of clinically significant disease progression, unacceptable toxicity or subject/physician decision to withdraw.

Part C and Part D

Celgene Corporation (Celgene) will supply the IP, CC-90011 capsules [available as Blend in Capsule (BIC, Gen 2) with 20 mg, 40 mg or 60 mg strengths] for oral administration. Rifampicin and itraconazole may be obtained through the local hospital pharmacy at the sites or licensed distributor in Spain, where both drugs are commercially available. All study drugs supplied by Celgene will be labeled appropriately for investigational use as per the regulations of the relevant country health authorities.

During the DDI evaluation periods:

CC-90011 will be given orally on Days 1 and 22 at a dose of 60 mg (Part C) or on Days 1 and 18 at a dose of 20 mg (Part D).

Rifampicin will be orally administered, once daily, at a dose of 600 mg (2 tablets of 300 mg) from Day 15 until Day 35 (21 doses in total).

Itraconazole will be orally administered, once daily, at a dose of 200 mg (2 capsules of 100 mg) from Day 15 until Day 31 (17 doses in total).

Dose modifications or interruptions are not allowed during the DDI evaluation period. It is highly recommended to consult with the Sponsor Study Physician prior to interrupting doses for DDI cohorts. In case of safety concerns, the physician may interrupt treatment to protect the safety of the subject. Such subjects will become non-evaluable for DDI assessment and will need to be replaced.

During the CC-90011 Treatment period:

CC-90011 will be given orally at the RP2D of 60 mg once weekly in 28 -days cycles. Dose modifications or interruptions are allowed, after discussion and agreement by the Study Sponsor Physician.

Study treatment may be discontinued if there is evidence of clinically significant disease progression, unacceptable toxicity or subject/physician decision to withdraw.

Overview of Key Efficacy Assessments

Subjects will be evaluated for efficacy after every 2 cycles through Cycle 6, and then every 3 cycles thereafter. All subjects who discontinue treatment for reasons other than disease progression, start of a new anticancer therapy, or withdrawal of consent from the entire study will be followed until progression and/or initiation of new systemic anticancer therapies.

Tumor response will be determined by the Investigator. For solid tumors, assessment will be based on Response Evaluation Criteria in Solid Tumors (RECIST 1.1) (Eisenhauer, 2009). For NHLs, assessment will be based on the Lugano Classification (Cheson, 2014). [18F]fluorodeoxyglucose (FDG) positron emission tomography (PET) or FDG PET/CT imaging is required to confirm a complete response in subjects with FDG-avid tumors. For prostate cancer (PC) and neuroendocrine prostate carcinoma (NEPC), response assessment will be based on the PCWG3 criteria (Scher, 2016). For hepatotocellular carcinoma (HCC) and neuroendocrine hepatocellular carcinoma (NEHCC), response will be based on the mRECIST criteria (Lencioni, 2010). Neuroendocrine neoplasms G2, G2 NETs and neuroendocrine carcinomas will additionally have levels of neuroendocrine markers assessed at baseline and on study.

In Parts C and D, a CT/MRI will be performed at the end of the DDI evaluation period, before starting CC-90011 treatment period, that will be considered as the baseline.

Overview of Key Safety Assessments

The safety variables for this study include adverse events, safety clinical laboratory variables, 12-lead electrocardiograms, Eastern Cooperative Oncology Group Performance Status, left ventricular ejection fraction assessments, physical examinations, vital signs, exposure to study treatment, assessment of concomitant medications, and pregnancy testing for females of child bearing potential. The PK profiles of CC-90011 will be determined from serial blood collections.

Overview of Pharmacokinetic Assessments

For Parts A and B, the plasma PK parameters determined for CC-90011 will be maximum observed plasma concentration (C_{max}), area under the plasma concentration time-curve (AUC), time to maximum plasma concentration (T_{max}), terminal half-life ($t_{1/2}$), apparent clearance (CL/F), and apparent volume of distribution (Vz/F). Exposure-response analyses may be conducted, as appropriate, to assist in identification of the dosing regimen for Part B or Phase 2 studies.

For Parts C and D, plasma PK parameters for CC-90011 will be determined as described above, in Period 1 (CC-90011 single dose administration) and Period 2 [CC-90011 in combination with rifampicin (Part C) or itraconazole (Part D)].

Additionally, in Parts C and D, PK parameters will also be determined for CC-90011 in urine, and for metabolite CC7108272 (M1) and possibly other metabolites in plasma and urine, as exploratory assessments, described in Section 9.9.2.

Overview of Exploratory Pharmacodynamic Assessments

Pharmacodynamic assessments are described in Section 0.

Statistical Methods for Part A

Part A and Part B Adverse Events

The primary objectives of this study are to evaluate the safety and tolerability of treatment with CC-90011, including the determination of the MTD. The analysis method for estimating the MTD is the BLRM guided by the EWOC principle (Babb, 1998; Neuenschwander, 2008).

Statistical analyses will be performed by dose level (Part A) and tumor cohort (Part B) as needed or applicable. All analyses will be descriptive in nature. All summaries of safety data will be conducted using subjects receiving any CC-90011 (the Treated Population).

Study data will be summarized for disposition, demographic and baseline characteristics, exposure, efficacy, safety, PK, and PD. Categorical data will be summarized by frequency distributions (number and percentages of subjects) and continuous data will be summarized by descriptive statistics (mean, standard deviation, median, minimum, and maximum).

Treatment-emergent adverse events (TEAEs) will be summarized by National Cancer Institute Common Terminology Criteria for Adverse Event (CTCAE) version 4.03 grades. The frequency of TEAEs will be tabulated by Medical Dictionary for Regulatory Activities system organ class and preferred term. Grade 3 or 4 TEAEs, TEAEs leading to discontinuation of CC-90011, study drug-related TEAEs, and SAEs will be tabulated separately. Changes from baseline in selected

laboratory analytes, vital signs, 12-lead ECGs, and ECHO/MUGA scans will be summarized. All data will be presented in by-subject listings.

Part C and Part D Adverse Events

TEAEs will be summarized by CTCAE version 4.03 grades. The frequency of TEAEs will be tabulated by Medical Dictionary for Regulatory Activities system organ class and preferred term. Grade 3 or 4 TEAEs, TEAEs leading to discontinuation of subjects during the DDI evaluation period, CC-90011-related TEAEs, rifampicin-related TEAEs, itraconazole-related TEAEs, TEAEs leading to discontinuation of CC-90011 during the treatment period, and SAEs will be tabulated separately. Changes from baseline in selected laboratory analytes and vital signs will be summarized. All data will be presented in by-subject listings.

Part A Efficacy

The primary efficacy variable for Part A is clinical benefit rate (CBR). CBR is defined as tumor responses (as assessed by the Investigators) of complete response (CR), partial response (PR) and durable stable disease (SD) (SD of $\geq$ 4 months duration). Point estimates and 95% confidence intervals of CBR will be reported. Objective response rate (defined as the percentage of subjects whose best response is complete response or partial response), duration of response/stable disease, progression-free survival, and overall survival will be summarized using frequency tabulations for categorical variables, or descriptive statistics for time to event variables. Efficacy analysis will be repeated for the Treated Population and Efficacy Evaluable Population (subjects who received a baseline disease assessment evaluation, at least 75% of assigned doses in Cycle 1, and one on study disease assessment evaluation), with the result using the Treated Population considered primary.

Number of Subjects

During the Part A dose escalation, 50 subjects were enrolled. During the Part B dose expansion, 17 subjects were enrolled. In Parts C and D, approximately 16 DDI evaluable subjects with advanced unresectable solid tumors will be enrolled, with approximately 8 subjects evaluable for each DDI assessment. The subjects may be replaced if not DDI evaluable.

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1. INTRODUCTION

Epigenetic dysregulation is an important mechanism in the initiation and progression of cancer (Mohammad, 2015). Mechanisms that control DNA and histone modifications have become a major focus for targeted therapy. CC-90011 is a reversible, potent, and selective inhibitor of the epigenetic target, lysine-specific demethylase 1A (LSD1/KDM1A). LSD1 is a histone-modifying enzyme that removes methyl groups and hence regulates the expression of many genes important in cancer progression and cell proliferation (Scoumane, 2007; Hoffmann, 2012; Lynch, 2012). It also plays a part in cellular differentiation, regulation of epithelial-to-mesenchymal transition, and stem cell maintenance (Adamo, 2011; McDonald, 2011).

Inhibition of LSD1 reduces cell proliferation and stem cell maintenance and promotes cell differentiation (Harris, 2012), as well as delaying or inhibiting tumor growth, in a range of human solid tumor xenografts (Maes, 2010; Mohammad, 2015; DC QC6688 2015; Sankar, 2014; Thiesen, 2014).

1.1. Disease Background

The epigenetic code determines if, when, and where specific genes are expressed. It is a dynamic and reversible process written, erased, and read by families of enzymes. Initiation and progression of cancer has increasingly been linked to misreading, miswriting or miserasing of histone modifications (Chi, 2010).

LSD1 is an eraser of the epigenetic code. It is a member of the flavin adenine dinucleotide (FAD) dependent amine oxidase family of demethylases and has substrate affinity for mono- and dimethylated lysines (Shi, 2004; Lynch, 2012). LSD1 is typically found associated with protein complexes that act as transcription repressors. For example, it catalyses the demethylation of monomethyl and dimethyl histone H3 lysine 4 (H3K4), which are marks of active transcription states (Lynch, 2012). However, it associates with different complexes and can function as a co-activator or co-repressor in a target-specific manner (Amente, 2013). For example, LSD1 binds to hormone receptors such as the estrogen or androgen receptors and catalyses the demethylation of both monomethyl and dimethyl histone H3 lysine 9 (H3K9). Monomethyl H3K9 is associated with active transcription states whereas dimethyl H3K9 is associated with repressed transcription states (Barski, 2007). LSD1 also demethylates other non-histone proteins such as p53 (Huang, 2007), DNA methytransferase 1 (DNMT1) (Wang, 2009), and E2F1 (Helen, 2013), and has been reported to bind the oncogene MYC (Amente, 2010).

LSD1 knockout mice are embryonically lethal and LSD1 is essential for mammalian development (Wang, 2007). LSD1 is involved in many biological processes, including proliferation, differentiation, gene activation and repression and regulation of epithelial-to-mesenchymal transition (Scoumane, 2007; Wang, 2007; Adamo, 2011; Lv, 2012). Additionally, LSD1 has been shown to be an essential regulator of leukemia stem cell potential (Harris, 2012) and stem cell maintenance (Adamo, 2011).

[redacted] Studies involving knock down of LSD1 have suggested that loss of LSD1 expression reduces the growth of cancer cells as well as their potential for migration and invasion (Mohammad, 2015). Inhibition of LSD1 also significantly delayed or inhibited tumor growth in a number of solid tumor xenografts, including colon cancer, endometrial carcinoma, Ewing's sarcoma, and SCLC (Maes, 2010; Mohammad, 2015, DC QC6688 2015; Sankar, 2014; Thiesen, 2014).

LSD1 expression is observed in approximately 25.5% of mature B-cell non-Hodgkin's lymphoma (B-NHL) cases and it is highly expressed in germinal centers (Neibel 2014), however, the role of LSD1 in germinal center formation has only recently been elucidated (Haines, 2018; Hatzi, 2019).

Hence, LSD1 appears to play a significant role in the development and progression of malignancy and investigation of the LSD1 inhibitor CC-90011 is warranted.

1.2. Compound Background

Please refer to the Investigator's Brochure (IB version V6.0, dated 15 Feb 2021) for detailed information concerning the available pharmacology, toxicology, pharmacokinetics, and drug metabolism profile of the investigational product (IP).

1.2.1. Overview of CC-90011 Mechanism of Action and In vitro and In vivo Nonclinical Pharmacology

LSD1 was the first lysine demethylase to be discovered and, unlike the Jumonji class of demethylases, belongs to the broad family of monoamine oxidases that uses FAD as a cofactor in its enzymatic demethylase activity (DC QC6688, 2015).

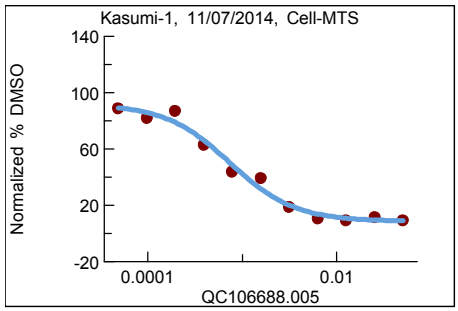
The importance of LSD1 in development is exemplified by the embryonic lethality seen in knockout mice (Wang, 2007). shRNA knockdown experiments in human embryonic stem (ES) cell lines show that suppression of LSD1 activity decreases the proliferation and self-renewal ability of ES cells while promoting differentiation towards endoderm and mesoderm lineages (DC QC6688, 2015). In the adult setting, LSD1 is necessary for normal hematopoiesis through interaction and modulation of GFI1b transcriptional programs and loss of LSD1 results in impaired hematopoiesis through a block in differentiation (Mohammad, 2015). The importance of LSD1 in normal differentiation suggests that aberrant gene expression resulting from dysregulation of LSD1 may result in alterations in pathways associated with a stem-cell like phenotype.

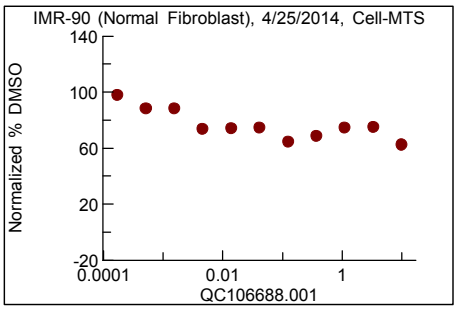
In prior studies, proliferation screens of cell lines representing a number of tumor types indicated that SCLC is sensitive to LSD1 inhibition (Mohammad, 2015). In SCLC, LSD1 and H3K4 methylation are associated with regions of chromatin that are implicated in the regulation of cell state. Inhibition of LSD1 increases methylation and LSD1 enrichment at these sites. While differentiation of SCLC is not well understood, LSD1 positioning at genes associated with neuronal differentiation and transcriptional regulation may suggest that inhibition of LSD1 will promote alterations in expression programs associated with differentiation of this tumor type (Mohammad, 2015).

CC-90011, previously known as QC6688, is an extremely potent and selective inhibitor of LSD1 (DC QC6688, 2015). The inhibitory mechanism of CC-90011 against LSD1 was studied at various concentrations, and the linear correlation between the IC_{50} and S/Km indicates that CC-90011 is a competitive inhibitor of LSD1. The selectivity of CC-90011 for LSD1 over other FAD containing enzymes (LSD2, MAO-A, and MAO-B) is greater than 60,000-fold.

CC-90011 demonstrated potent anti-proliferative activity in a Kasumi-1 cell line model of acute myeloid leukemia (AML), with an IC_{50} of 0.0024 µM and showed no effect (IC_{50} of >10 µM) in a normal human fibroblast cell model (Figure 1).

Figure 1: CC-90011 Dose Responsive CellTiter 96® Aqueous Assay Results





[redacted]

Many growth modulatory factors are expressed by SCLC, and are felt to contribute to the aggressive nature of the tumor. One such peptide growth factor is gastrin-releasing peptide (GRP), which functions as an autocrine growth factor in SCLC (Campbell, 2002). Prior work with another LSD1 inhibitor showed loss of expression of GRP in SCLC xenografts (Mohammad, 2015), which being a neuroendocrine marker may be suggestive of a change in the cell state, similar to the pro-differentiation effect seen in leukaemia with LSD1 inhibition (Harris, 2012). [redacted]

1.2.1.1. Overview of Nonclinical Pharmacokinetics

In preclinical species, CC-90011 demonstrated moderate (mouse, dog, and monkey) to high (rat) systemic clearance and extensive (12- to 43-fold of total body water) volume of distribution. Terminal half-lives were considerably different between rodents (2 to 4 hours) and non-rodents (12 to 20 hours). Upon oral dosing, CC-90011 was well absorbed with oral bioavailability ranging from 28% to 74% in rodents and from 82% to 100% in dogs and monkeys. In vitro data indicate that CC-90011 is a P-glycoprotein (P-gp) substrate, and a weak breast cancer resistance protein (BCRP) substrate, but these properties have not limited its oral availability or absorption. Due to the disparate half-lives between mice and dogs, repeat-dose toxicity studies were conducted using different dosing regimens in either mice (5 days on/2 days off [QDx5/week] for 4 weeks, and QD for up to 3 months) or dogs (QW, BIW, or once every 2 weeks [Q2W] for 4 weeks, and QW for 3 months). In the 3-month toxicology studies, systemic exposure to CC-90011 in mice increased in a greater than dose-proportional manner from 1 to 3 mg base/kg/day and in an approximately dose-proportional manner from 3 to 10 mg base/kg/day, while in dogs the increase in exposure was approximately dose-proportional in the dose range 0.10 to 0.25 mg

base/kg/week. No consistent sex differences and no accumulation in toxicokinetics (TK) were noted.

CC-90011 was moderately to highly bound to plasma protein binding (approximately 83% to 92%) in preclinical species and humans with no notable differences in free fraction among species.

After oral administration of [^{14}C]CC-90011 to mice, radioactivity was widely distributed and then rapidly eliminated from most tissues by 48 hours. Distribution of radioactivity in the uveal tract and pigmented skin in CB63F1 (pigmented) mice, as compared to CD-1 (non-pigmented) mice, suggest an affinity for melanin-containing tissues.

The in vitro metabolism of CC-90011 was characterized using hepatocytes from various species (mouse, rat, rabbit, dog, monkey, and human). In hepatocytes, CC-90011 showed minimal turnover in human, dog, monkey, and mouse, moderate metabolism in female rabbit, and was extensively metabolized in rats. In hepatocytes, the biotransformation pathways of CC-90011 across all species included oxidative deamination, piperidine hydroxylation and subsequent ring-opened carboxylation, demethylation as well as glucuronidation and sulfation of oxidized species and a combination of these pathways. No unique human metabolites were found. All metabolites observed in humans were also found in mouse and dog, supporting the use of these species for toxicology testing.

The absorption, metabolism, and excretion of [^{14}C]CC-90011 following oral administration has been studied in mice and dogs. Metabolic pathways were qualitatively similar in mice and dogs, with no major sex differences in metabolism observed. The primary metabolic pathways in mice and dogs were similar to those observed in vitro and included deamination, dealkylation followed by glucuronidation (or sulfation, in dogs only), oxidations/carboxylation, hydrolysis and combinations of these pathways. In mouse and dog plasma, CC-90011 was the predominant drug-related component and M1 (CC7108272, a deamination product) was a prominent circulating metabolite

A study was conducted to profile and identify CC-90011 metabolites in human plasma samples and to estimate exposure coverage of any major metabolites in the toxicity species (CC-90011-DMPK-3367). After oral administration of unlabeled CC-90011 to human patients, parent drug and metabolite CC7108272 were the prominent drug-related components in human plasma. Other metabolites were only detectable at trace levels and no unique human metabolites were found in human plasma. Based on an exploratory quantitative assessment, the weekly exposure of CC7108272 in mice at a dose of 3 mg/kg/day QD and dogs at a dose of 0.25 mg/kg QW (the NOAEL doses in the 3 month toxicology studies), was approximately 2.9- to 3.4-fold and 0.27- to 0.28-fold, respectively of the human exposure at a dose of 60 mg QW.

In rats, CC-90011 may be eliminated primarily via metabolism, since following an IV bolus dose, the amount of intact drug excreted in bile and urine was 17.8% and 8.5%, respectively.

Following oral administration of [^{14}C]CC-90011 to mice and dogs, feces was the primary route for excretion of radioactivity. Approximately 29% and 54% of the [^{14}C]CC-90011 dose was absorbed in bile duct-cannulated (BDC) mouse and dog, respectively. The absorbed CC-90011 was primarily eliminated by direct urinary excretion and metabolism in mouse, and by metabolism and direct biliary excretion in dog.

In vitro studies suggest that CC-90011 does not inhibit or induce major CYP enzymes and is not an inhibitor of major uptake and efflux drug transporters at clinically relevant concentrations and thus CC-90011 has minimal potential to cause drug-drug interactions with co-administered drugs that are CYP or transporter substrates. CC-90011 was not a substrate of organic anion transporting polypeptide (OATP)1B1 and OATP1B3, multi-drug resistance protein (MRP)2, organic anion transporter (OAT)1 and OAT3, and organic cation transporter (OCT)2, and therefore, interactions with drugs that are inhibitors of these transporters are not expected. However, the metabolism of CC-90011 is governed primarily by cytochrome P450 (CYP) 3A4/5 and it was also an in vitro substrate of P-gp and BCRP transporters. Therefore, the exposure of CC-90011 may be affected when co-administered with drugs that are inhibitors or inducers of CYP3A and/or P-gp and BCRP.

1.2.1.2. Overview of Nonclinical Toxicology

A series of exploratory and pivotal Good Laboratory Practice (GLP)-compliant toxicity studies in mice and dogs of up to 3 months, and 2 in vitro genetic toxicity studies were conducted to characterize the toxicity profile of CC-90011. In vivo studies were conducted using the oral route as it is the intended route of administration in clinical trials. Pivotal toxicity studies were conducted using a QD, QDx5/week, or every other day (QOD) 3 days per week (QODx3/week) dosing schedule in mice, and QW, BIW, or Q2W dosing in dogs. Pivotal toxicity studies were conducted in accordance with the requirements of the United States Food and Drug Administration (FDA) GLP Regulations for Nonclinical Laboratory Studies (21 CFR Part 58), the Organisation for Economic Cooperation and Development (OECD) Principles of GLP, ENV/MC/CHEM(98)17 (revised in 1997, issued January 1998), and the International Council on Harmonisation (ICH) S9 guideline, 2009.

The doses and schedules for the pivotal toxicity studies were selected based on data from pharmacology studies and exploratory repeat-dose toxicity studies in mice and dogs. The pivotal toxicity studies were conducted in Crl:CD1(ICR) mice and Beagle dogs. Dose levels were 0, 5, 15, or 45 mg base/kg/dose QDx5/week or 25 mg base/kg/dose QODx3/week in the mouse pivotal 4-week oral toxicity study with a 4-week recovery period, and 0, 1, 3, or 10 mg/kg/day QD in the mouse 3-month study. Dose levels in the initial dog pivotal 4-week oral toxicity study (with a 4-week recovery period) were 0, 0.375, 0.75, or 1.5 mg base/kg/dose QW, or 0.375 mg base/kg/dose BIW. Since a QW nonseverely toxic dose was not identified in this study, a second pivotal dog study at lower dose levels of 0, 0.125 or 0.25 mg base/kg/dose QW, or 0.5 mg base/kg/dose Q2W was conducted (no recovery period). A study was also conducted in dogs using doses of 0, 0.10, and 0.25 mg/kg QW for 3 months (total of 14 doses).

In 4-week toxicity studies, treatment-related mortality was observed at 45 mg base/kg/dose in mice following a QDx5/week dose schedule; and at $\geq$ 0.375 mg base/kg/dose in dogs following a QW dose schedule. The cause of mortality in mice was not determined; the moribund condition of dogs was due to CC-90011-related gastrointestinal (GI) toxicity and ensuing septicemia.

In mice dosed at up to 45 mg base/kg/dose for 4 weeks, there was dose-proportional marrow toxicity, evidenced by a myeloid shift and/or marrow hypocellularity. The marrow space was replaced by fibrosis in the sternum and/or femur, with hyperostosis of endosteal, periosteal, and trabecular bone surfaces of affected sternebrae. Collectively, these changes persisted through a recovery period at the highest dose only. Some increase in marrow megakaryocytes (without

peripheral correlate) was noted at all doses, also persisting at the highest dose. Marrow toxicity occurred in concert with declines in peripheral red cell mass (red blood cell [RBC] count, hemoglobin, and hematocrit), and declines in platelet, reticulocyte and/or leukocyte counts along with significant increases in splenic extramedullary hematopoiesis at all doses (a reactive change to which mice are particularly sensitive). Depletion of splenic marginal zone lymphocytes was observed in all but the lowest dose groups but did not persist through a recovery period.

In dogs dosed for 4 weeks, findings were more clearly inflammatory in nature. The predominant finding centered on GI inflammation which in some instances was ulcerative and associated with secondary septicemia and mortality at higher doses. Changes in the bone marrow reflected peripheral demand, with myeloid hypercellularity and variable evidence of marrow toxicity reflected in the peripheral blood as either a decrease or increase in peripheral leukocyte numbers; unlike mice, no reactive bone alterations were noted.

In one 4-week dog study, there was mortality at ≥ 0.375 mg base/kg/dose, with morbidity generally attributed to gastric inflammation and/or ulceration. Slight to marked, acute to subacute inflammation was observed variably in the esophagus, stomach, small and/or large intestines, and/or rectum of dogs dying early. Findings that correlated with these microscopic changes included dehydration, abnormal feces (liquid, red), red vomitus, decreased food consumption and body weight, hypoactivity, fever, and/or GI tract discomfort. Related clinical pathology findings included decreased albumin, albumin:globulin ratio, calcium, and inorganic phosphorous; increased monocytes, large unstained cells, and neutrophils; and decreased red cell mass, platelets, reticulocytes, and eosinophils. Other findings in these animals were attributed to generalized inflammation and/or septicemia secondary to mucosal ulceration in the GI tract (inflammation in multiple lymph nodes, subcutaneous edema, acute inflammation in the heart or liver), and/or physiologic stress, including extramedullary hematopoiesis in the spleen and an increased myeloid:erythroid ratio in the sternal marrow. In surviving animals, only minimal to moderate acute inflammation of the intestines and/or rectum was observed at ≤ 0.75 mg/kg/dose, with complete recoverability following a 4-week non-dosing interval.

In a 4-week study at lower doses (0.125 or 0.25 mg base/kg/dose QW or 0.5 mg/kg/dose Q2W), there was no mortality, and findings were of lower severity, with acute inflammation in the cecum, ileum, and/or gut-associated lymphoid tissue of dogs from the highest dose-groups from each dosing-interval. Changes were minimal when dosed Q2W, becoming marked when dosed QW. Other findings included minimal extramedullary hematopoiesis in animals from the highest dose groups of either dosing regimen.

All CC-90011-related findings in mice and dogs treated for 4 weeks demonstrated evidence of partial to complete reversibility following a 4-week treatment-free period.

In mice dosed daily for up to 3 months at up to 10 mg/kg/dose, further evidence of CC-90011-related systemic inflammation was observed. Inflammation affected multiple tissues, with instances of mortality (10 mg/kg/dose level) being associated with more severe inflammatory foci. Specifically, scattered neutrophilic inflammatory cell infiltrates occurred at 10 mg/kg/day in the heart valve, epididymides, eye sclera, and/or periocular tissue. Some instances of periocular inflammation were clearly an extension of peripheral glandular inflammation and, in general, the interior of the eye was unaffected. At 3 mg/kg/day, such infiltrates became minimal and were restricted to the periocular tissues; no such findings were seen at the 1 mg/kg/day. At the nontolerated dose level, ophthalmology examination revealed hyporeflection and reduced pallor

in the fundus of the eye. Also, at 10 mg/kg/day, mortality was associated with focal abscessation in the Harderian glands and/or skin/subcutis. Reactive alterations in affected dose groups included increased (myeloid) marrow cellularity, and extramedullary hematopoiesis in the liver (with some necrosis at the highest dose), spleen and/or adrenal glands.

In dogs dosed QW for 3 months, CC-90011 was well tolerated up to 0.25 mg/kg/dose, the highest dose level administered, with no signs of toxicity.

CC-90011 was not mutagenic based on the negative results from the in vitro mutagenicity assays.

Overall, CC-90011 exhibits an acceptable safety profile in preclinical species for a clinical drug candidate in an advanced oncology setting and the toxicology program for CC-90011 adequately supports the conduct of clinical trials in oncology subjects.

1.2.1.3. Summary of Clinical Data

As of 11 Sep 2020, 50 subjects were enrolled in Part A of the study and received escalating oral doses of CC 90011 QW at 9 dose levels from 1.25 mg to 120 mg/dose and 17 subjects (14 subjects with low/intermediate-grade lung NETs [typical and atypical carcinoid], 2 subjects with prostate NEC and 1 subject with MZL) were enrolled in Part B of the study and received oral CC-90011 QW at 60 mg. The Part A of the study has been completed and the primary objectives were met. The nontolerated dose (NTD) was determined to be 120 mg, the MTD was 80 mg, and the RP2D was 60 mg, QW of 28-day cycles. Thrombocytopenia, an on target effect, was the only dose limiting toxicity (DLT); these events occurred mainly at the highest dose levels and were successfully managed with dose interruption for a week and/or dose reduction. CC-90011 has been generally well tolerated with the majority of treatment-emergent adverse events (TEAEs) being reversible and manageable by dose adjustments and/or supportive treatments.

In Part A of the study (N = 50), the most frequently reported TEAEs (in at least 10% of subjects) were thrombocytopenia (46.0%), anemia and vomiting (28.0% each), fatigue (26.0%), nausea, constipation and asthenia (22.0% each), diarrhea, pyrexia, and decreased appetite (20.0% each), musculoskeletal pain (16.0%), back pain (14.0%), neutropenia, abdominal pain, increased alanine aminotransferase (ALT), increased aspartate aminotransferase (AST)and cough (12.0% each), and tumor pain, headache, and dyspnea (10.0% each). Overall, 24 (48.0%) subjects experienced at least one Grade 3 or 4 TEAE and the most frequently reported Grade 3 or 4 TEAEs (in at least 2 subjects) were thrombocytopenia (24.0%), neutropenia (8.0%), anemia (6.0%), and general physical health deterioration, increased ALT, increased blood bilirubin, increased lipase, and hypophosphatemia (4.0% each). Grade 3 or 4 thrombocytopenia occurred from the dose level of 40 mg and Grade 3 or 4 neutropenia occurred from the dose level of 80 mg and only after clinically significant thrombocytopenia. Overall, 34 (68.0%) subjects experienced at least one TEAE assessed as related to the study treatment by the investigator and the most frequently reported treatment-related TEAEs (in at least 5% of subjects) were thrombocytopenia (40.0%), neutropenia (12.0%), fatigue (10.0%), and vomiting and asthenia (6.0% each). No death due to drug-related toxicity occurred during the study. Overall, 23 (46.0%) subjects experienced at least one serious TEAE, and the most frequently reported serious TEAEs (in at least 2 subjects) were thrombocytopenia (8.0%) and general physical health deterioration (4.0%).

CC-90011 demonstrated preliminary evidence of antitumor activity in this difficult-to-treat patient population with very few treatment options. Among 27 NEN subjects, 7 subjects have demonstrated prolonged stabilization of disease (stable disease [SD] > 4 months). Notably, 3 subjects with bronchial NEN had prolonged SD of > 6 months and 2 subjects with prostate NEN remained on study treatment for over 6 months due to clinical benefit. The R/R NHL subject (transformed MZL) experienced a complete metabolic response (see IB version V6.0, dated 15 Feb 2021) and currently is on-going in Cycle 49.

In Part B of the study (N = 17), the most frequently reported TEAEs (in at least 10% of subjects) were thrombocytopenia (70.6%), asthenia (41.2%), anemia (35.3%), constipation, diarrhea, and nausea (29.4% each), neutropenia and dysgeusia (23.5% each), decreased appetite, arthralgia, musculoskeletal pain, cough and epistaxis (17.6% each), and leucopenia, stomatitis, vomiting, fatigue, hepatic pain, bronchitis, lipase increased, hypokalemia, bone pain, neck pain, dizziness, peripheral sensory neuropathy, sciatica, confusional state, dyspnea and pruritus (11.8% each). Overall, 13 (76.5%) subjects experienced at least one Grade 3 or 4 TEAE and the most frequently reported Grade 3 or 4 TEAEs (in at least 2 subjects) were thrombocytopenia (35.3%), and neutropenia (17.6%) and asthenia (11.8%). Overall, 16 (94.1%) subjects experienced at least one TEAE assessed as related to the study treatment by the investigator, and the most frequently reported treatment-related TEAEs (in at least 2 subjects) were thrombocytopenia (70.6%), asthenia (29.4%), anemia and neutropenia (23.5% each), diarrhea, and nausea (17.6% each), and leucopenia and dysgeusia (11.8% each). No death due to drug-related toxicity occurred during the study. Overall, 6 (35.3%) subjects experienced at least one serious TEAE and serious TEAEs occurred in one subject each.

In the 14 subjects with low/intermediate-grade lung NET, a best response of SD was observed in 10 (71.4%) subjects, including 7 (50.0%) subjects with SD ≥ 4 months. The 2 subjects with prostate NEC and the MZL subject progressed.

1.2.1.4. Summary of Clinical PK and PD Data

Pharmacokinetic data from Part A of Study CC-90011-ST-001 are available for 50 subjects who received escalating oral doses of CC-90011 QW at 9 dose levels from 1.25 mg to 120 mg/dose (see IB version V6.0, dated 15 Feb 2021). Following oral administration of CC-90011, geometric mean exposure to CC-90011, based on C_{max} and AUC, generally increased with dose on Day 1 (single dose) and Day 22 (repeated weekly administration), in a manner approximately proportional with dose. Maximum observed plasma concentrations were observed a few hours after dosing, with median time to peak plasma concentration (t_{max}) ranging from 2.0 to 4.6 hours postdose across all dose levels and both dosing occasions. Half-life was generally similar across the dose levels (2.5 to 80 mg) and on both occasions, ranging from approximately 50 to 78 hours. Apparent clearance and volume of distribution ranged from 57.5 to 95.7 L/h and 5506 to 8077 L, respectively, across the 5 to 120 mg dose range. Results suggest an overall negligible accumulation after weekly dosing of CC-90011 between 2.5 mg to 80 mg, with accumulation ratios for C_{max} and AUC from 0 to the last quantifiable concentration (AUC_{LST}) ranging from 0.66 to 1.57. The interindividual variability (geometric coefficient of variation %) values ranged from 19.3% to 136.7% on Day 1 and 8.6% to 92.4% on Day 22 across C_{max} and AUC parameters.

Preliminary PK data from Part B of Study CC-90011-ST-001 and Study CC-90011-SCLC-001 suggest an overall similarity of PK parameters to the respective doses from Part A of Study CC-90011-ST-001. These preliminary data suggest that PK profile of CC-90011 is similar between subgroups of solid tumor subjects including lung NET, prostate NEC, and SCLC. Additionally, coadministration of cisplatin, or carboplatin, and etoposide does not appear to impact the PK profile of CC-90011 in SCLC subjects.

Preliminary PD analyses from Part A of Study CC-90011-ST-001 revealed a decrease in chromogranin A (CgA) neuroendocrine marker levels in response to CC-90011 at doses as low as 2.5 mg QW in subjects with NENs. Additionally, CC-90011 decreased expression of monocyte to macrophage differentiation-associated (MMD) ribonucleic acid (RNA) by ≥ 50% in subject blood samples at doses ≥ 60 mg QW. In Part B of the study, MMD suppression was consistent with the dose effects observed in Part A of Study CC-90011-ST-001. These preliminary findings indicate that downregulation of MMD is a potential marker for PD by CC-90011 in the clinical setting. In Study CC-90011-SCLC-001, preliminary PD analysis showed a ≥ 50% decrease of MMD expression in available samples from patients receiving CC-90011 (20 mg, 40 mg) plus Etoposide/Cisplatin and CC-90011 (20 mg) plus Etoposide/Carboplatin in 1L Extensive Stage (ES) SCLC patients.

Although the biomarker analyses in the current trial are exploratory in nature, they could reveal associations between biomarkers and responses that could provide a basis for future diagnostically-driven studies. Refer to Section 0 for additional information.

1.2.2. Safety Monitoring Plan

Thrombocytopenia is an on-target effect of LSD1 inhibition. Knockdown of LSD1 causes a block in the terminal platelet maturation step leading to thrombocytopenia with accumulation of megakaryocytes in the bone marrow (Sprussel, 2012).

Information from a First-In-Human study of the LSD-1 inhibitor ORY-1001 in refractory or relapsed Acute Leukemia resulted in predicted toxicities that included thrombocytopenia and anemia (Somervaille, 2016; Maes, 2018).

As of the 11 Sep 2020 data cutoff date, current experience with CC-90011 in humans is based on 3 ongoing clinical Phase 1 studies, CC-90011-ST-001 (monotherapy) CC-90011-SCLC-001 (combination therapy) and CC-90011-ST-002 (combination therapy) (see IB version V6.0, dated 15 Feb 2021).

Study CC-90011-ST-001

As of 11 Sep 2020, 50 subjects were enrolled in Part A of the study and received escalating oral doses of CC-90011 QW at 9 dose levels from 1.25 mg to 120 mg/dose and 17 subjects (14 subjects with low/intermediate-grade lung NETs [typical and atypical carcinoid], 2 subjects with prostate NEC and 1 subject with MZL) were enrolled in Part B of the study and received oral CC-90011 QW at 60 mg. The Part A of the study has been completed and the primary objectives were met. The nontolerated dose (NTD) was determined to be 120 mg, the MTD was 80 mg, and the RP2D was 60 mg, QW of 28-day cycles. Thrombocytopenia, an on-target effect, was the only dose-limiting toxicity (DLT); these events occurred mainly at the highest dose levels and were successfully managed with dose interruption for a week and/or dose reduction.

CC-90011 has been generally well tolerated with the majority of TEAEs being reversible and manageable by dose adjustments and/or supportive treatments.

In Part A of the study (N = 50), the most frequently reported TEAEs (in at least 10% of subjects) were thrombocytopenia (46.0%), anemia and vomiting (28.0% each), fatigue (26.0%), nausea, constipation and asthenia (22.0% each), diarrhea, pyrexia, and decreased appetite (20.0% each), musculoskeletal pain (16.0%), back pain (14.0%), neutropenia, abdominal pain, increased alanine aminotransferase (ALT), increased aspartate aminotransferase (AST), and cough (12.0% each), and tumor pain, headache, and dyspnea (10.0% each). Overall, 24 (48.0%) subjects experienced at least one Grade 3 or 4 TEAE and the most frequently reported Grade 3 or 4 TEAEs (in at least 2 subjects) were thrombocytopenia (24.0%), neutropenia (8.0%), anemia (6.0%), and general physical health deterioration, increased ALT, increased blood bilirubin, increased lipase, and hypophosphatemia (4.0% each). Grade 3 or 4 thrombocytopenia occurred from the dose level of 40 mg and Grade 3 or 4 neutropenia occurred from the dose level of 80 mg and only after clinically significant thrombocytopenia. Overall, 34 (68.0%) subjects experienced at least one TEAE assessed as related to the study treatment by the investigator and the most frequently reported treatment-related TEAEs (in at least 5% of subjects) were thrombocytopenia (40.0%), neutropenia (12.0%), fatigue (10.0%), and vomiting and asthenia (6.0% each). No death due to drug-related toxicity occurred during the study.
Overall, 23 (46.0%) subjects experienced at least one serious TEAE, and the most frequently reported serious TEAEs (in at least 2 subjects) were thrombocytopenia (8.0%) and general physical health deterioration (4.0%).

CC-90011 demonstrated preliminary evidence of antitumor activity in this difficult-to-treat patient population with very few treatment options. Among 27 NEN subjects, 7 subjects have demonstrated prolonged stabilization of disease (stable disease [SD] > 4 months). Notably, 3 subjects with bronchial NEN had prolonged SD of > 6 months and 2 subjects with prostate NEN remained on study treatment for over 6 months due to clinical benefit. The R/R NHL subject (transformed MZL) experienced a complete metabolic response.

In Part B of the study (N = 17), the most frequently reported TEAEs (in at least 10% of subjects) were thrombocytopenia (70.6%), asthenia (41.2%), anemia (35.3%), constipation, diarrhea, and nausea (29.4% each), neutropenia and dysgeusia (23.5% each), decrease appetite, arthralgia, musculoskeletal pain, cough and epistaxis (17.6% each), and leucopenia, stomatitis, vomiting, fatigue, hepatic pain, bronchitis, lipase increased, hypokalemia, bone pain, neck pain, dizziness, peripheral sensory neuropathy, sciatica, confusional state, dyspnea and pruritus (11.8% each). Overall, 13 (76.5%) subjects experienced at least one Grade 3 or 4 TEAE and the most frequently reported Grade 3 or 4 TEAEs (in at least 2 subjects) were thrombocytopenia (37.5%), and neutropenia (17.6%) and asthenia (11.8%). Overall, 16 (94.1%) subjects experienced at least one TEAE assessed as related to the study treatment by the investigator, and the most frequently reported treatment-related TEAEs (in at least 2 subjects) were thrombocytopenia (70.6%), asthenia (29.4%), anemia and neutropenia (23.5% each), diarrhea and nausea (17.6% each), and leucopenia and dysgeusia (11.8% each). No death due to drug-related toxicity occurred during the study. Overall, 6 (37.5%) subjects experienced at least one serious TEAE and serious TEAEs occurred in one subject each.

In the 14 subjects with low/intermediate-grade lung NET, a best response of SD was observed in 10 (71.4%) subjects, including 7 (50.0%) subjects with SD ≥ 4 months. The 2 subjects with prostate NEC and the MZL subject progressed.

Study CC-90011-SCLC-001

Study CC-90011-SCLC-001 is an open-label, Phase 1b, multicenter, dose-finding study to assess the safety, tolerability, PK, PD, and preliminary efficacy of CC-90011 given in combination with cisplatin or carboplatin and etoposide, defined as Chemotherapy, followed by CC-90011 single agent in maintenance, and CC-90011 given in combination with Chemotherapy plus nivolumab followed by CC-90011 plus nivolumab in maintenance, to adult subjects with first line, extensive stage (ES) SCLC. As of 11 Sep 2020, safety and efficacy data are available for 19 enrolled subjects with first line ES SCLC, who received escalating doses of oral CC-90011 at 20 mg (Cohort 1; N = 8), 40 mg (Cohort 2; N = 7) and 60 mg (Cohort 3; N = 4) in combination with etoposide plus cisplatin and 5 enrolled subjects with first line ES SCLC, who received escalating doses of oral CC-90011 at 20 mg (Cohort 1; N = 3) and 40 mg (Cohort 2; N = 2), in combination with etoposide plus carboplatin. Twelve subjects from the CC-90011 plus Cisplatin/Etoposide treatment arm and 3 subjects from the CC-90011 plus Carboplatin/Etoposide treatment arm received CC-90011 at 60 mg in the Maintenance Treatment Period.

CC-90011 plus Etoposide/Cisplatin Treatment Arm (N = 19)

One subject, who received CC-90011 20 mg and 2 subjects, who received CC-90011 60 mg plus Cisplatin/Etoposide, experienced a DLT during the Chemotherapy Treatment Period. No DLT was observed in the 6 evaluable subjects treated at the dose of 40 mg CC-90011 plus Cisplatin/Etoposide. CC-90011 at 60mg plus Cisplatin/Etoposide was determined as the NTD and CC-90011 at 40 mg on Days 1 and 8 of each 21-day chemotherapy cycle plus Cisplatin/Etoposide was determined as the RP2D of the combination.

During the dose escalation Chemotherapy Treatment Period (N = 19), the most frequently reported TEAEs (in at least 20% of subjects) were anemia (78.9%), thrombocytopenia and neutropenia (68.4% each), asthenia (52.6%), nausea (42.1%), constipation (31.6%), increased blood alkaline phosphatase (ALP) (26.3%), and mucosal inflammation, pyrexia, diarrhea, decreased appetite, hyponatremia, dyspnea and alopecia (21.1% each). Overall, 16 (84.2%) subjects experienced at least one Grade 3 or 4 TEAE and the most frequently reported Grade 3 or 4 TEAEs (in at least 2 subjects) were neutropenia (63.2%), thrombocytopenia (42.1%), febrile neutropenia (15.8%) and anemia (10.5%). Seventeen (89.5%) subjects experienced at least one TEAE assessed as related to CC-90011 treatment by the investigator, and the most frequently reported treatment-related TEAEs (in at least 2 subjects) were anemia and neutropenia (57.9% each), thrombocytopenia (52.6%), and febrile neutropenia, asthenia, and decreased appetite (10.5% each). No death due to drug-related toxicity occurred during the study. Overall, 4 (21.1%) subjects experienced at least one serious TEAE, each serious TEAE occurring in one subject each. The CC-90011 RP2D of 40 mg was well tolerated; the most frequent TEAEs assessed as related to CC-90011 treatment (in at least 2 subjects) were neutropenia (42.9%), and thrombocytopenia and anemia (28.6% each), with only 2 (28.6%) subjects, who experienced Grade 3 or 4 TEAEs related to CC-90011 treatment (neutropenia only). One subject experienced a serious TEAE, assessed as not related to CC-90011 treatment.

During the Maintenance Treatment Period (N = 12), the most frequently reported TEAEs (in at least 2 subjects) were thrombocytopenia (91.7%), anemia (50.0%), neutropenia and nausea (33.3%), dysgeusia (25.0%), asthenia, noncardiac chest pain, vomiting, gastro-esophageal reflux disease, back pain, headache, dizziness, peripheral sensory neuropathy, pruritus, and hypertension (16.7% each). Six (50.0%) subjects experienced at least one Grade 3 or 4 TEAE and the most frequently reported Grade 3 or 4 TEAEs (in at least 2 subjects) were thrombocytopenia (41.7%) and hypertension (16.7%). Seven (58.3%) subjects experienced at least one TEAE assessed as related to CC-90011 treatment by the investigator and the most frequently reported treatment-related TEAEs (in at least 2 subjects) were thrombocytopenia (41.7%), anemia (25.0%), and neutropenia (16.7%). Two (16.7%) subjects experienced at least one serious TEAE during the Maintenance Treatment Period, each serious TEAE occurring in one subject each.

As of 11 Sep 2020, a best objective response was partial response (PR) for 16 out of 19 treated subjects (3 non evaluable subjects).

CC-90011 plus Carboplatin/Etoposide Treatment Arm (N = 5)

One subject, who received CC-90011 40 mg plus Carboplatin/Etoposide experienced a DLT during the Chemotherapy Treatment Period.

During the Chemotherapy Treatment Period (N = 5), the most frequently reported TEAEs (in at least 2 subjects) were thrombocytopenia (80.0%), and anemia and neutropenia (60.0% each). Overall, 4 (80.0%) subjects experienced at least one Grade 3 or 4 TEAE and the most frequently reported Grade 3 or 4 TEAEs (in at least 2 subjects) were thrombocytopenia (80.0%) and neutropenia (40.0%). All subjects experienced at least one TEAE assessed as related to CC-90011 treatment by the investigator, and the most frequently reported treatment-related TEAEs (in at least 2 subjects) were thrombocytopenia (80.0%), and anemia and neutropenia (60.0% each). No death due to drug-related toxicity occurred during the study. One (20.0%) subject treated at 40 mg experienced 2 serious TEAEs (Grade 4 hyponatremia and Grade 3 ischemic stroke, assessed as not related to CC-90011 treatment).

During the Maintenance Treatment Period (N = 3), the most frequently reported TEAEs (in at least 2 subjects) were thrombocytopenia, anemia, and constipation (66.7% each). Two (66.7%) subjects experienced at least one Grade 3 or 4 TEAE with thrombocytopenia, aphasia, and inadequate analgesia in one subject each. One (33.3%) subject experienced Grade 2 asthenia assessed as related to CC-90011 treatment. Two (66.7%) subjects experienced at least one serious TEAE (Grade 3 and Grade 5 aphasia, secondary to progression of brain metastases, and Grade 3 inadequate analgesia) assessed as not related to study treatment.

As of 11 Sep 2020, the best objective response was PR for 4 out of the 5 treated subjects (1 non evaluable subject).

Study CC-90011-ST-002

CC-90011-ST-002 study is a Phase 2, multicenter, open-label, multi-cohort study to assess safety and efficacy of CC-90011 in combination with nivolumab in adult subjects with SCLC and squamous non-small cell lung cancer (sqNSCLC) who have progressed after 1 or 2 lines of therapy. As of 11 Sep 2020, 5 subjects with SCLC (4 subjects in Cohort A and 1 subject in Cohort B) were treated in the study. Three serious TEAEs (2 Grade 4 thrombocytopenia,

assessed as related to study treatments by the investigator and 1 Grade 3 muscular weakness, assessed as not related to study treatments) were reported in the first 2 subjects treated with CC-90011 at the dose of 60 mg QW (plus nivolumab at 480 mg Q4W). The initial dose of CC-90011 was further amended and reduced to 40 mg due to the occurrence of Grade 4 thrombocytopenia in 2 of the subjects.

Monitor for discomfort in left upper quadrant and bone pain. Analgesics such as paracetamol should be administered as necessary, but NSAIDS and aspirin should be avoided, if possible in view of the potential thrombocytopenia. If discomfort in the upper left quadrant is reported, subjects will be examined for any evidence of splenomegaly and monitored closely.

Frequent early monitoring of subjects' weight, hydration status, serum electrolytes, the incidence and severity of diarrhea and emesis, as well as episodes of abdominal pain (gastric, intestinal) are critical components of the safety monitoring plan and implementation of aggressive supportive care measures for the early onset (ie, Grade 1) of nausea, vomiting or diarrhea are highly recommended. Based on the morphologic changes, mucosal ulcerations, and acute inflammation observed in the GI tract of dogs, subjects with active ulcer/gastritis, malabsorption syndromes, or recurring episodes of GI bleeding will be excluded from enrollment. Mucosa coating agents for protection of esophageal/gastric mucosa will be recommended as well as monitoring subjects for GI bleeding. Subjects will be encouraged to report episodes of GI discomfort or pain, appetite loss, frequency of diarrhea or blood in stool.

Bone marrow hypocellularity findings in GLP toxicity studies emphasize the importance of frequent blood count monitoring, including platelet counts and white blood cell (WBC) differential. Similarly, the presence of increased size of megakaryocytes and/or megakaryocyte numbers emphasizes the importance of closely monitoring the platelet counts. Subjects will be monitored for possible toxicity through standard and specialized laboratory tests including complete blood counts, prothrombin time (PT)/activated partial thromboplastin time (APTT)/international normalized ratio (INR), and serum chemistries.

Serum chemistry findings such as decreased total protein, albumin, albumin:globulin (A:G) ratio, and increased cholesterol and alkaline phosphatase (ALP) will necessitate a more conservative eligibility criteria for total albumin and initial weekly monitoring of the serum chemistry in subjects.

Decrease in the weight of the seminal vesicles, testes, and uterus was seen in studies in mice. All changes observed during and/or at the end of treatment were partially or completely recovered by 4 weeks after treatment. No such changes were seen in dogs.

Fertility counseling for men: Subjects will be informed that the effects of CC-90011 on spermatogenesis are unknown and they will be encouraged to collect and bank sperm if appropriate, prior to taking CC-90011.

These findings warrant prohibition of semen donation and fathering children for male subjects and conceiving for female subjects for the duration of the clinical study as well as for at least 105 days after the last study dose. There were no histologic lesions in reproductive organs of female and male animals in the nonclinical studies. The significance of this pre-clinical finding and the potential and relative clinical risk is unknown at this time. Developmental and reproductive toxicology studies have not been conducted with CC-90011. Subjects will be required to follow the pregnancy prevention guidelines as described in Section 6.2.9.

As this is an FIH study, subjects with a history of heart failure, ischemic heart disease, uncontrolled hypertension, serious cardiac arrhythmias, or long QT interval on ECG will be excluded from enrollment. All study subjects will require documentation of adequate left ventricular ejection fraction (> 45%) at baseline.

Comprehensive studies to evaluate the phototoxicity potential of CC-90011 have not been conducted. As a precautionary measure, it is recommended that subjects avoid prolonged exposure to ultraviolet (UV) light, wear protective clothing and sunglasses, and use UV-blocking topical preparations while taking CC-90011.

The global coronavirus disease 2019 (COVID-19) pandemic has been identified as a potential risk to clinical trial subjects in general. Whether CC-90011, rifampicin or itraconazole administration increases the risk for contracting SARS-CoV-2 infection or increases the severity or duration of symptoms is currently unknown. This unknown risk must be considered when enrolling a subject.

No additional safety monitoring or routine screening tests will be required due to the SARS-CoV-2 pandemic. Subjects with recent or acute infections will be excluded or delay start of treatment as defined in Section 4.3. If a subject has a confirmed SARS-CoV-2 infection while on study treatment, dose delay or interruption of study treatment is required as described in Section 7.2. An exploratory analysis of the impact of SARS-CoV-2 serologic status on subjects receiving CC-90011 may be performed.

The study has been designed with study visits that allow for close monitoring of subjects' safety throughout the clinical trial (Section 6), and subjects are encouraged to contact the investigator if an intercurrent illness develops between study visits. Testing for COVID-19 to inform decisions about clinical care during the study should follow local standard practice.

Non-live COVID-19 vaccination is considered a simple concomitant medication within the study. However, the efficacy and safety of non-live vaccines (including non-live COVID-19 vaccines) in subjects receiving CC-90011, rifampicin or itraconazole is unknown.

1.2.3. Rifampicin and Itraconazole

Drug metabolizing enzymes and transporters affected by rifampicin include CYP 1A2, 2B6, 2C8, 2C9,2C19, and 3A/5, UDP-glucuronyltransferases (UGT), sulfotransferases, carboxylesterases, and transporters including P-gp and multidrug resistance-associated protein 2 (MRP2). Most drugs are substrates for one or more of these enzyme or transporter pathways, and these pathways may be induced concurrently by rifampicin capsules. Therefore, rifampicin capsules may accelerate the metabolism and reduce the activity of certain co-administered drugs, and has the potential to perpetuate clinically important drug-drug interactions against many drugs and across many drug classes. Rifampicin should be withdrawn if clinically significant changes in hepatic function occur. Some severe cutaneous adverse reactions have been reported with a not known frequency in association with rifampicin. Early manifestations of hypersensitivity, such as fever, lymphadenopathy or biological abnormalities may be present even though rash is not evident. If such signs or symptoms are present, the subject should be advised to consult immediately their physician. Importantly, rifampicin treatment reduces the systemic exposure of oral contraceptives. Diabetes may become more difficult to control. Rifampicin may accelerate

the metabolism and reduce the activity of certain co-administered drugs. To maintain optimum therapeutic blood levels, dosages of drugs may require adjustment.

Itraconazole is a potent CYP3A4 inhibitor and a P-gp inhibitor. The most serious adverse drug reaction (ADRs) with itraconazole are serious allergic reactions, cardiac failure/congestive heart failure/pulmonary oedema, pancreatitis, serious hepatotoxicity (including some cases of fatal acute liver failure), and serious skin reactions. Caution should be exercised when itraconazole is administered in subjects with hepatic impairment. Itraconazole should not be used in patients with congestive heart failure or with a history of congestive heart failure. When using concomitant medication together with itraconazole, it is recommended that the corresponding label be consulted for information on the route of metabolism and the possible need to adjust dosages.

Please refer to the Summary of Product Characteristics (SmPC) for more details on formulations, storage conditions (eg, refrigeration), known precautions, warnings, interactions, and adverse reactions for these drugs (Rifampicin SmPC) (Itraconazole SmPC).

1.3. Rationale

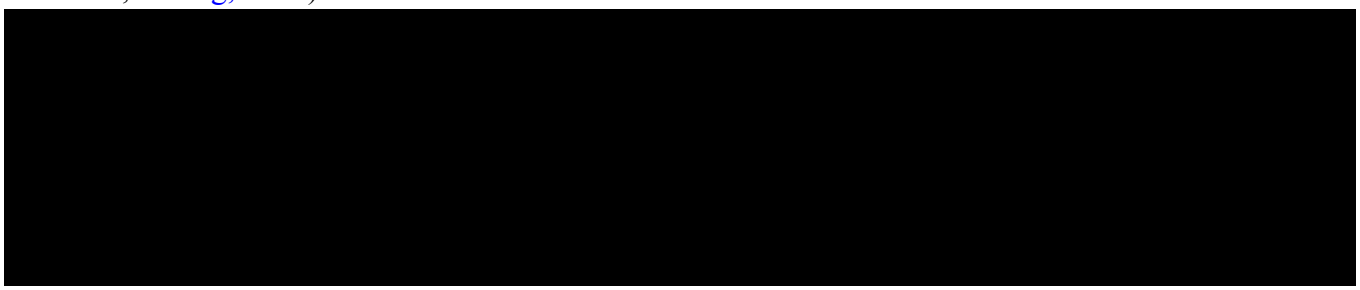
1.3.1. Study Rationale and Purpose

LSD1 is an eraser of the epigenetic code thereby regulating the expression of many genes important in cancer progression and cell proliferation (Scoumane, 2007; Hoffmann, 2012; Lynch, 2012). LSD1 over-expression promotes proliferation, migration, and tumor invasion (Lv, 2012) and has been documented in many human solid tumors including bladder, breast, colorectal, prostate and SCLC (Kahl, 2006; Kauffman, 2011; Hayami, 2010; Serce, 2012). Moreover, LSD1 over-expression has been correlated with poor prognosis in hepatocellular carcinoma, neuroblastoma, prostate cancer, non-small cell lung cancer, and ER negative breast cancer (Kahl, 2006; Schulte, 2009; Lv, 2012; Lim, 2010; Zhao, 2012; Chen, 2015).

LSD1 is required for normal differentiation in adult as well as embryonic cells (Wang, 2007). It controls the balance between H3K4 and H3K27 methylation, thereby regulating differentiation-associated genes (Adamo, 2011). It is required for normal hematopoiesis through interaction and modulation of GFI1b transcriptional programs and loss of LSD1 impairs hematopoiesis, through a block in differentiation (Saleque, 2007; Sprussel, 2012). Indeed, LSD1 expression is high in acute myeloid leukemia and correlates inversely with differentiation (Lynch, 2012). Furthermore, its expression increases as chronic phase myeloid leukemia progresses to blast phase. Additionally, LSD1 is over-expressed more commonly in high-grade ductal carcinoma of the breast than low grade ductal carcinoma in situ (Serce, 2012) and in subjects with a higher Gleason score in prostate cancer (Kahl, 2006). LSD1's importance in normal differentiation suggests that aberrant gene expression resulting from dysregulation of LSD1 may result in alterations in pathways associated with a stem-cell like phenotype.

Moreover, LSD1 plays a part in stem cell maintenance, regulation of epithelial-to-mesenchymal transition (Adamo, 2011; McDonald, 2011), and has been shown to be an essential regulator of leukemia stem cell potential (Harris, 2012). shRNA knockdown experiments in human ES cell lines show that decreased LSD1 activity lessens the proliferation and self-renewal ability of ES cells while promoting differentiation (DC QC6688, 2015). Hence inhibition of LSD1 might be a useful therapeutic approach for tumors with cancer stem cell involvement such as SCLC.

SCLC is one of the most genetically complex cancers. Additionally, epigenetic changes such as histone modification occur, including methylation regulation of key SCLC genes, such as over-expression of B-cell lymphoma 2 (BCL2) and silencing of the retinoblastoma (RB1) gene (Peifer, 2012; Poirier, 2015; Stewart, 2015). SCLC is a poorly differentiated tumor (Rechtman, 2010), believed to be derived from self-renewing pulmonary neuroendocrine progenitors (Park, 2011; Sutherland, 2011). The SCLC cell line (NCI-H446) has been shown to share the phenotypic characteristics of both neuroectoderm and mesoderm lineages with the cells possessing high stemness, tumorigenicity, and plasticity (Zhang, 2013). Indeed, SCLC retains stem cell markers such as CD133, Oct4, Sal4, PODXL-1, and Bmi-1 (Sarvi, 2014; Koch L-K, 2008; Zhang, 2013).



LSD1 over-expression has also been reported in other neuroendocrine tumours, including gastrointestinal neuroendocrine carcinomas (NECs) (Magerl, 2009). Furthermore, the stem cell marker, SOX2, is over-expressed in large cell neuroendocrine carcinoma (LCNEC), neuroendocrine prostate cancer (NEPC), and Merkel cell carcinoma (Laga, 2010; Sholl, 2010; Yu, 2014). Strong SOX2 expression was found in only 23% of low grade pulmonary neuroendocrine tumors such as carcinoid but in 72% of NEC. Hence, G2 NENs/NETs, SCLC, and other NECs with their documented cancer stem cell involvement seem appropriate tumors in which to investigate CC-90011.

Similarly, LSD1 expression has been reported in non-Hodgkin's lymphoma (Niebel, 2014) and appears to play a part in B cell differentiation (Hatzi, 2013; Haines, 2018; Haines, 2019). Hence, NHL subjects will also be enrolled.

CC-90011 is a new investigational product (IP) that has a strong biological rationale for the treatment of subjects with relapsed and/or refractory advanced unresectable solid tumors (including G2 NENs/NETs, SCLC, and other NECs) and R/R NHL (MZL, including EMZL, SMZL, NMZL and histologic transformation of MZL) (refer to Section 1.3). The safety and tolerability of CC-90011 in humans, as well as the biologic and clinical activity, will be evaluated in this study. The study will be conducted in 4 parts: dose escalation (Part A), dose expansion (Part B) and DDI evaluation (Parts C and D).

1.3.2. Rationale for Tumor Type Selection in Parts A and B

After the second Grade ≥ 2 study drug-related toxicity, which fall under the adverse event terms of thrombocytopenia/platelet count decrease, anaemia/red blood cell count decrease, neutropenia/white blood cell count decrease, and/ or gastrointestinal tract toxicities in Cycle 1 occurs, enrollment will be restricted to subjects with G2 NENs/NETs, SCLC, and other NECs which may secrete neuroendocrine markers such as Pro-GRP, CgA or calcitonin which expression is regulated by LSD1 (Takagi, 2017; Jotatsu, 2016; Mohammad, 2015). LSD1 binding has been demonstrated at possible regulatory sites for the gastrin releasing peptide

(GRP) locus and is consistent with GRP expression being directly regulated by LSD1(CC-90011 Pharmacology Report). Additionally, [redacted] in mouse xenograft SCLC models. Hence GRP seems to be a relevant PD marker for LDS1 inhibition. Pro-GRP is more stable than GRP and therefore is a more robust biomarker and will be used rather than GRP. Also, chromatin immunoprecipitation (ChIP) studies demonstrated binding of LSD1 to enhancer elements near the Chromogranin A (CgA) gene locus in SCLC cell lines. [redacted]. Medullary thyroid carcinoma (MTC) is a NEC associated with raised calcitonin levels. RREB1 (RAS responsive element binding protein) is a component of the multiprotein corepressor complex containing the c terminal binding protein and LSD1, which interacts with a Ras-responsive element in the calcitonin gene promoter (Ray, 2014).

Enrolling such subjects at a biologically active dose will also provide preliminary data in tumors of highest interest, to guide selection of Part B expansion cohorts.

In part B, the enrollment will be restricted to subjects with advanced low/intermediate-grade lung NETs, NEPCs and R/R NHL (MZL, including EMZL, SMZL, NMZL and histologic transformation of MZL) based on results from Part A of the study, pre-clinical efficacy data (for data in PDX models of SCLC tumors, see Section 1.2.2 and Section 1.2.1) and supportive literature.

1.3.2.1. Rationale for Selection of NHL Tumors

LSD1 expression is observed in approximately 25.5% of mature B-cell non-Hodgkin's lymphoma (B-NHL). Low-grade B-NHLs expressed LSD1 less often (12.9%) than did high-grade B-NHLs (39.7%) (Neibel, 2014).

LSD1 is highly expressed in germinal centers, indeed both transcripts and protein levels are induced during the transition from naïve to germinal center B cell state (Hatzi, 2013). Moreover, LSD1 has been shown to be necessary for proliferation and differentiation of naïve B cells and to regulate marginal zone B cell (MZB) development (Haines, 2018; Haines, 2019), however, the role of LSD1 in germinal center formation and BCL6-driven lymphomagenesis has only recently been elucidated. BCL6, a key regulator of germinal center function that is frequently translocated and constitutively expressed in B-cell lymphoma (Basso, 2010), was shown to physically interact with and recruit LSD1 to its target genes, indicating that LSD1 acts in concert with BCL6 to facilitate proliferation. Blocking LSD1 enzymatic activity was insufficient to suppress BCL6-driven lymphoma cell proliferation; the LSD1 domain required for protein–protein interaction was required for lymphoma cell proliferation (Hatzi, 2019). In vitro experiments have shown an extensive overlap of BCL6 and LSD1 binding sites and that genes bound or associated with BCL6-LSD1 complexes were significantly enriched in pathways such as B cell activation and cell cycle control among others (Hatzi, 2013). Taken together these results, suggest that LSD1 might act as a BCL6 co-repressor in germinal center being an essential transcriptional regulator for B cell differentiation. Due to the high LSD1 expression in lymphoma cells, targeting LSD1 might potentially be a good therapy for lymphoma. Notably, there is yet no predictive biomarker to differentiate BCL6-dependent and BCL6-independent lymphomas (Cardenas, 2016). BCL6 expression does not correlate with response to genetic or pharmacologic BCL6 inhibition. Further, tumors not typically classified as germinal center

derived, such as ABC subtype DLBCL, appear BCL6-dependent and exquisitely responsive to investigational BCL6 inhibitors.

Clinical experience with LSD1-targeted agents in lymphoma is thus far limited. The single subject [redacted] with tMZL enrolled in Part A of the current study experienced a durable CR to single-agent CC-90011 treatment. The subject, [redacted] with tMZL, received 6 lines of therapy prior to study enrollment, including involved field radiotherapy, 4 lines of combination chemotherapy, and an investigational agent. Disease regression (↓38%) was observed after 2 cycles of treatment with 80 mg QW of CC-90011, and a complete metabolic response was reported after cycle 5. Subject is currently ongoing in C49 with very good tolerability, without dose reductions, or evidence for disease progression. Like most cases of tMZL (Flossbach, 2011), this subject's disease was found to overexpress BCL6 by immunohistochemistry, but a corresponding chromosomal translocation was not identified. A chromosomal abnormality in BCL2 was also identified; LSD1 expression has not been assessed.

Dysregulation of c-MYC is essential in the pathogenesis of a number of B-cell NHLs, generally due to an overexpression of c-MYC by loss of the tight control of its expression rather than oncogenic mutations or fusion proteins seen in many other oncogenes (Nguyen, 2017). LSD1 inhibition significantly reduce transcription of MYC target genes (Amente, 2010; Ambrosio, 2017; Li, 2016) and, conversely, LSD1 expression is induced by c-MYC generating a positive feedback mechanism (Nagasaka, 2019).

The observed durable CR and the potential role for LSD1 in lymphomagenesis provide rationale for further exploration of CC-90011 in B-NHL within the ongoing study.

1.3.2.2. Rationale for Selection of Neuroendocrine Tumors

Neuroendocrine tumors (NET) arise from cells of the endocrine (hormonal) and nervous systems. The most common NETs are originating from lungs and gastrointestinal tract. Lung NETs can be classified into four subtypes: well differentiated, low-grade typical carcinoids (TCs) (2% of primary lung neoplasms); well-differentiated, intermediate-grade atypical carcinoids (ACs) (<1%); poorly differentiated, high-grade large cell neuroendocrine carcinomas (LCNECs) (3%); and poorly differentiated, high-grade SCLCs (20%) (Rechtman, 2010; Travis, 2015). Well-differentiated lung NETs comprise approximately 27% of all NETs (Yao, 2008; Modlin, 2003) and 1% to 2% of all primary lung cancers (Rechtman, 2010) with estimated age-adjusted incidence rates of 0.2 to two cases per 100,000 in the United States and Europe (Caplin, 2015). Although rare, the prevalence of well differentiated lung NET has increased by approximately 6% per year over the last 30 years in both men and women (Modlin, 2008; Gustafsson, 2008). Most well differentiated lung NETs are located centrally in the main (10%) or lobar bronchi (75%), with the remainder located in the peripheral lung (Yao, 2008; Oberg, 2012). As a result, symptoms usually reflect tumor location, with centrally located tumors (primarily TCs) often presenting with obstructive respiratory symptoms related to tumor mass, including cough, hemoptysis, dyspnea, chest pain, wheezing, and pneumonitis (Oberg, 2012; Caplin, 2015; Gustafsson, 2008; Fisseler-Eckhoff, 2012).

The availability of effective treatment options for patients with advanced/metastatic low/intermediate-grade lung NETs (typical carcinoid and atypical carcinoid) are limited. Platinum based doublets, mostly combinations with etoposide, are commonly used despite poor response rates and treatment outcomes since typical and atypical carcinoids tend to be less

chemo-sensitive than SCLC. While clinical data for these tumor types are limited because they have not been studied independently of other neuroendocrine neoplasms, temozolomide has shown activity. Results from a published phase II 36-patient neuroendocrine study with oral temozolomide given for 5 consecutive days every 28 days yielded 4 partial responses (31%) and 4 stable diseases (31%) among typical and atypical carcinoids (Ekeblad, 2007). Until recently, there has been no clinical data for targeted therapy in patients with lung NENs. RADIANT-4, the first phase III trial which randomized 302 patients with advanced lung carcinoids and gastrointestinal neuroendocrine tumors, recently reported a PFS benefit with everolimus (PFS was significantly prolonged by 7.1 months and the risk of progression of the disease was reduced by 52% in everolimus-treated patients), resulting in its approval by the FDA as the first treatment for adult patients with advanced, well-differentiated, nonfunctional lung NETs (Yao, 2016). After progression to first-line therapy, there is no standard treatment and patients may be offered a variety of treatments as palliative care.

NETs are a heterogenous group of tumors, which until recently have remained largely intractable to genetic characterization, with many research studies being performed with a small number of samples leading to the identification of low-frequency mutations, which do not appear to have significant prognostic or therapeutic impact, suggesting the presence of alternative pathogenic drivers (Yoshimoto, 1992; Yashiro, 1993; Chung, 1997).

There is a significant positive correlation between LSD1 and the expression of neuroendocrine differentiation genes in human cancer cell lines (Jotatsu, 2016). In addition, an alternative splice variant of LSD1, LSD1+8a, has been reported to be restricted expressed in neural tissues. Suppression of LSD1 led to inhibition of cell proliferation in SCLC in vitro and in vivo (Jotatsu, 2016; Mohammad, 2015). Moreover, a DNA hypomethylation signature was able to identify SCLC PDXs sensitive to LSD1 inhibition (Mohammad, 2015).

Deregulated Notch signaling has been shown in many solid tumors. In some tumors, Notch signaling prevents differentiation, while in others, the oncogenic role of Notch is likely due to inhibition of apoptosis. LSD1 act as a corepressor of the Notch signaling which is involved in the acquisition or maintenance a partially differentiated neuroendocrine phenotype while retaining the ability to proliferate (Crabtree, 2016).

CC-90011 has demonstrated preliminary evidence of antitumor activity in neuroendocrine tumors. Among 27 NEN subjects in Part A, 7 subjects have demonstrated prolonged stabilization of disease (stable disease [SD] > 4 months). Notably, 3 subjects with bronchial NEN had prolonged SD of > 6 months and 2 subjects with prostate NEN remained on study treatment for over 6 months due to clinical benefit. In Part B, the 14 subjects with low/intermediate-grade lung NET, a best response of SD was observed in 10 (71.4%) subjects, including 7 (50.0%) subjects with SD ≥ 4 months. The 2 subjects with prostate NEC and the MZL subject progressed (see IB version V6.0, dated 15 Feb 2021).

The unmet medical need for advanced NETs, and the observed preliminary antitumoral activity in neuroendocrine subjects in Part A of the study, provide rationale for further exploration of CC-90011 in NENs/NECs within the ongoing study.

1.3.3. Rationale for Tumor Type Selection in Parts C and D

As of 11 Sep 2020, in CC-90011-ST-001 study, 67 subjects have been treated with a number of malignancies at different dose levels. 40 subjects received doses from 20 mg CC-90011 weekly or higher. Two durable responses were observed (a CR and a PR in a R/R NHL and a low- grade rare type of sarcoma/solitary fibrous tumour, respectively). In addition, 10 more subjects experienced SD > 6 months under CC-90011 monotherapy. All these subjects had low-grade NETs (G1/G2 of various anatomical origin as bronchial, renal, paraganglioma and pheochromocytoma) and were clearly progressing at study entry. Our targeted population is based on our observation that CC-90011 confers a benefit in suppressing tumor growth in slow growing tumor types. We will prioritize unresectable solid tumors with no available established therapeutic alternatives which have a slow growth pattern.

1.3.4. Rationale for the Study Design

In Part A, this study will utilize a BLRM which is a well-established method to estimate the MTD and/or RP2D in cancer subjects. The adaptive BLRM will be guided by the EWOC principle to control the risk of DLT in future subjects on study. This method is more likely to assign fewer subjects to either sub-therapeutic or severely toxic dose levels and estimate the MTD with smaller average bias and error than the up-and-down methods such as 3+3. The use of Bayesian response adaptive models for small datasets has been accepted by EMA ("Guideline on clinical trials in small populations" February 1, 2007) and endorsed by numerous publications (Babb, 1998; Neuenschwander, 2008; Neuenschwander, 2010), and its development and appropriate use is one aspect of the FDA's Critical Path Initiative.

In Part A, during the initial dose levels, subjects with relapsed and/or refractory advanced unresectable solid tumors and R/R NHL will be enrolled until the 2nd occurrence of a Grade ≥ 2, study drug-related toxicity, which fall under the adverse event terms of thrombocytopenia/ platelet count decrease, anaemia/red blood cell count decrease, neutropenia/white blood cell count decrease, and/ or gastrointestinal tract toxicities in Cycle 1. At this point, the enrollment will be restricted to subjects with G2 NENs/NETs, SCLC, and other NECs likely to secrete, Pro-GRP, CgA or calcitonin, because these subjects may be more likely to gain clinical benefit and may provide evidence of a pharmacodynamic effect through changes in the baseline and on treatment levels of secreted neuropeptides.

In Part B, 3 cohorts, of approximately 10-20 evaluable subjects each, with advanced low/intermediate-grade lung NETs, NEPCs and R/R NHL (MZL, including EMZL, SMZL, NMZL and histologic transformation of MZL) will receive the RP2D to further evaluate safety, PK, PD and preliminary efficacy.

1.3.5. Rationale for Dose, Schedule and Regimen Selection (Part A and Part B)

The CC-90011 GLP 4-week toxicity studies were conducted in mice dosed on schedules that included QDx5/week, and in Beagle dogs dosed on schedules that included QW. Based on the doses and exposures at which the principal treatment-related effects occurred in the GLP-compliant 4-week mouse and dog studies, the dog is considered of greater sensitivity to the toxicities associated with CC-90011 administration. The proposed human starting dose was 1.25 mg CC-90011 based on a QW schedule. Alternative dosing schedules (eg, once every other week) may be evaluated based on the review of available safety, PK, PD, and efficacy data by

the SRC. This CC-90011 dose was calculated using the approach described in the ICH S9 Guideline entitled "Nonclinical Evaluation for Anticancer Pharmaceuticals (ICH, 2009) and is summarized in Table 2.

The proposed starting dose in humans was lower than 1/10th the STD10 in mice, less than 1/6th the HNSTD in dogs, and was considered likely to be safe based on multiples of exposure (as measured by AUC) in mice and dogs relative to the predicted human exposure at a dose of 1.25 mg CC-90011 base on a QW schedule. As noted in Table 2, the human exposure (AUC) at a 1.25 mg base QW dose was predicted to be 29 ng•hr/mL; this value is approximately 4785-fold lower than the mean exposure corresponding to the predicted weekly mouse STD10 exposure (138750 ng•hr/mL) and approximately 10-fold lower than the mean exposure corresponding to the dog QW HNSTD (287 ng•hr/mL). Based on these toxicokinetic data, the proposed human starting dose of 1.25 mg CC-90011 base was expected to be safe.

Table 2: Proposed Clinical Starting Dose and Schedule of CC-90011 Based on the Severely Toxic Dose in 10% of the Mice and the Highest Non-severely Toxic Dose in Dogs from Pivotal 4-Week Toxicity Studies

Species	Mouse STD10 or Dog HNSTD (mg base/kg/dose)	HED (mg base/kg/dose)	HED (mg base/dose)	Safety Factor	HED/Safety Factor (mg base/dose)[a]	Proposed Clinical Starting Dose and Schedule[b]
Mouse	45	3.66	219.6	10	22	1.25 mg base/dose, QW
Dog	0.250	0.139	8.34	6	1.4	

HED = human equivalent dose; HNSTD = highest non-severely toxic dose; STD10 = severely toxic dose in 10% of the animals.

[a] Based on HED conversion factor for a 60-kg person from the FDA Guidance for Industry entitled "Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers" (FDA, 2005) and the ICH S9 Guideline entitled "Nonclinical Evaluation for Anticancer Pharmaceuticals" (ICH, 2009).

[b] Using allometry derived plasma clearance (9.4 mL/min/kg) and volume of distribution (17.6 L/kg) estimates and assuming 80% oral bioavailability, the predicted C_{max} and AUC_{24h} at the intended human starting dose of 1.25 mg are approximately 0.8 ng/mL and 29 ng•h/mL, respectively.

Refer to the Investigator's Brochure for detailed information.

For the summary of clinical data, see Section 1.2.1.3 of the protocol and current IB (version 6.0, dated 15 Feb 2021).

Part B (expansion) of the study enrolled the first subject on 23 Oct 2018 within the advanced low/intermediate-grade lung NET cohort with CC-90011 at the RP2D of 60mg QW. No safety concerns were observed in the 17 treated subjects (14 Bronchial, 2 Prostate and 1 MZL) receiving 60 mg CC-90011 QW.

1.3.6. Rationale for Drug-Drug Interaction Evaluation (Part C and Part D)

The available preclinical data suggest that CC-90011 may be substantially eliminated via CYP3A4/5-mediated metabolism in humans. Studies using recombinant human CYP enzymes, human liver microsomes (HLMs), and CYP-selective monoclonal antibodies have shown that CYP3A4/5 appears to be predominantly responsible for the oxidative metabolism of CC-90011

(Report QC6688-ADME-2006, Report CC-90011-DMPK-2332). In bile duct cannulated (BDC) rats, following IV dosing of nonradiolabeled CC-90011, an average of 26.3% of the dose (8.5% of dose in urine and 17.8% of dose in bile) was excreted intact in the 24-hour period postdose (Report QC6688-ADME-2008). Furthermore, following oral administration of [^{14}C]CC-90011 to BDC dogs, less than half of the absorbed dose was recovered as unchanged parent drug (22.8% of the administered radioactivity was recovered in urine and bile as parent drug vs. 54% recovered as total radioactivity), while in BDC rats, approximately 68% of the absorbed dose was recovered as unchanged parent drug (19.6% of the administered radioactivity was recovered in urine and bile as parent drug vs. 29% as total radioactivity). Taken together, these data suggest that metabolism likely plays a significant role in the elimination of CC-90011 (Report QC6688-ADME-2008; Report CC-90011-DMPK-3315; Report CC-90011-DMPK-3369).

In addition, CC-90011 is a P-gp substrate as suggested by the in vitro cell-based permeability assay findings (Report QC6688-ADME-2003; Report CC-90011-DMPK-2450). Therefore, Parts C and D are designed to evaluate the effect of a strong CYP3A and P-gp inhibitor or inducer on the PK of CC-90011.

1.3.6.1. Rationale for DDI evaluation design

The overall study design of Parts C and D allows for the evaluation of the effect of a strong CYP3A and P-gp inhibitor or inducer on the PK of CC-90011, consistent with the EMA Guideline on the investigation of drug interactions (EMA, 2012References) and FDA Guidance for industry: clinical drug interaction studies (FDA, 2020). CC-90011. Rifampicin and Itraconazole will be administered in a fasted state as the potential effect of food on the PK of CC-90011 has not been evaluated, and this may represent an additional variable in this PK evaluation.

- **Part C** is designed to evaluate the potential for PK DDI between CC-90011 and rifampicin, a potent CYP3A inducer (EMA, 2012 and FDA, 2020) and based on published literature reports as a P-gp inducer (Elmeliegy, 2020).
- **Part D** is designed to evaluate the potential for PK DDI between CC-90011 and itraconazole, a potent CYP3A and P-gp inhibitor (EMA, 2012 and FDA,2020).

The key endpoints of the DDI cohorts are plasma PK parameters of CC-90011 with and without coadministration of rifampicin (Part C) or itraconazole (Part D). The fixed-sequence, crossover design used in Parts C and D is typical for DDI studies. A relatively small number of subjects are required, as this design minimizes inter-subject variability in the treatment comparison. The number of participating subjects is considered sufficient to achieve the objectives of the evaluation and is based on statistical calculations on precision and intrasubject standard deviation.

1.3.6.2. Rationale for Doses, Schedules and Regimen Selection in DDI cohorts

Thrombocytopenia, an on-target effect, was the only DLT reported in Part A of the CC-90011-ST-001 study. LSD1-inhibition affects the budding of platelets from the megakaryocytes (Rinske van Oorschot, 2019). This effect is completely reversable with one week interruption of treatment (see IB version V6.0, dated 15 Feb 2021). These events occurred mainly at the highest dose levels (80 mg QW and 120 mg QW) and were successfully managed with dose interruption

for a week (majority cases) and/or dose reduction (rare cases). CC-90011 has been generally well tolerated with the majority of treatment-emergent adverse events (TEAEs) reversible and manageable by dose adjustments and/or supportive treatments (see IB version V6.0, dated 15 Feb 2021). The RP2D of CC-90011 monotherapy was established at 60 mg QW administered on Days 1, 8, 15, and 22 of 28-day cycles. At this dose level (60 mg QW), thrombocytopenia is the only clinically significant (CS) toxicity observed. Around 40% of patients experience CS, mainly asymptomatic Grade 2/Grade 3 thrombocytopenia. Only 10% of patients experience Grade 4 thrombocytopenia. The thrombocytopenia follows a cyclical pattern within the 28 days cycle with a nadir on day 14 of each cycle and self-recovery by day 21. Drug management guidelines include dose reduction to 40 mg QW in cases of Grade 4 thrombocytopenia and interruption of dosing for a week in cases of Grade 2/Grade 3 thrombocytopenia. No treatment related deaths nor hospitalizations due to toxicity have occurred during the expansion Part B at 60 mg QW of CC-90011 in around 60 patients treated on different cohorts/studies (G2 NET, Prostate NEC, R/R Marginal Zone NHL, SCLC maintenance). Single agent CC-90011 decreased expression of target gene *MMD* by ≥ 50% in patient blood samples at doses ≥ 60 mg QW MMD suppression in part B is consistent with same dose effects in Part A.

The 60 mg CC-90011 dose level was selected for evaluation of CC-90011 DDI in combination with rifampicin, a potent CYP3A inducer, whereas the 20 mg CC-90011 dose level was selected for DDI evaluation in combination with itraconazole, a potent CYP3A and P-gp inhibitor. A 60 mg dose of CC-90011 administered twice within the 40 days of the DDI evaluation in combination with rifampicin is expected to result in a lower risk of thrombocytopenia. If thrombocytopenia occurs, it is expected to appear around 14/21 days after the first dose of the combination which would require observation/drug interruption if platelets fall below G2 levels. Platelet levels are expected to self-recover in around one week´s time from nadir. Platelet levels and a coagulation panel will be closely monitored during the study as described in Table 6.

A physiology based pharmacokinetic (PBPK) model projected that the maximum impact (worst case scenario) from coadministration of a strong index CYP3A inducer is ~ 80% decrease in CC-90011 AUC (internal data). Assuming 4- to 5-fold reduction in exposure, the resulting CC-90011 plasma concentrations are still expected to be quantifiable and expected to correspond to approximately 12 mg monotherapy dose of CC-90011. During the dose escalation (Part A) of the current study, exposures to CC-90011were well characterized following doses lower than 12 mg of CC-90011.

In Part D (CC-90011 coadministration with itraconazole) of this study, coadministration of a strong CYP3A and P-gp inhibitor is expected to result in increased exposure to CC-90011. The PBPK model projected that the maximum impact (worst case scenario) from coadministration of a strong index CYP3A4 inhibitor is ~ 4.7-fold increase in CC-90011 AUC. The exposure to CC-90011 resulting from this increase would be the equivalent of the exposure to CC-90011 achieved with an ~80-90 mg monotherapy dose, and is well below the exposure to the non-tolerated dose of 120 mg QW.

Based on the known human PK of CC-90011, and the fact that rifampicin could enhance CC-90011 clearance by inducing CYP3A4 expression and itraconazole could diminish CC-90011 clearance by inhibiting CYP3A4 expression, the sample collection timing and duration of Parts C and D of this study are considered adequate to achieve the objectives of Part C and D respectively.

Selection of rifampicin and itraconazole dosing regimen is based on a large body of published literature (Srinivas, 2016) (Liu, 2016) as well as DDI study designs utilized in the Sponsor's protocols.

Rationale for Washout Interval in Parts C and D

Based on the half-lives of CC-90011 and the study-specified perpetrator drugs, the inter-dose washout intervals are considered sufficient to prevent carryover. For example, the geometric mean half-life of CC-90011 following single 20- or 60-mg dose administration is approximately 65 hours. Thus, an inter-dose washout interval of 14 days (5 half-lives of CC-90011) between the Day 1 dose of CC-90011 in Period 1 and the first dose of study drug in Period 2 is expected to be sufficient.

In Part C, Period 2, a washout interval of 5 days between the last dose of rifampicin on Day 35 and start of CC-90011 treatment period on Day 40, is greater than 5 times rifampicin half-life of 3.35 ± 0.66 hours (reference: SmPC). It is understood that restoration of baseline level of enzyme activity after rifampicin treatment may take longer than the washout period. However, initiation of CC-90011 treatment period on Day 40 is planned in the best interest of the subjects and is not considered to be a safety concern.

In Part D, Period 2, a 9-day washout interval between the last dose of itraconazole on Day 31 and start of CC-90011 treatment period on Day 40, is greater than 5 times itraconazole half-life of 16 ± 5 hours (reference: SmPC). Additionally, the PBPK model predicted mean and upper 95th percentile plasma CC-90011 concentrations on Day 40 were 0.52 ng/mL and 2.68 ng/mL, respectively, which represent the normal range of trough concentrations following 20 mg QW dosing of CC-90011. Additionally, the predicted mean residual CC-90011 concentration on Day 40 (0.52 ng/mL) was approx. 5% of the predicted mean CC-90011 Cmax in Period 2 (10.9 ng/mL), indicating that the washout interval of 9 days between Period 2 and CC-90011 treatment period was adequate.

1.3.7. Rationale for Pharmacodynamics and Biomarkers

A key exploratory objective of this study is to identify a dose and schedule of CC-90011 that is not only safe but that exhibits pharmacologic activity. [redacted]

2. STUDY OBJECTIVES AND ENDPOINTS

Table 3: Study Objectives

Primary Objective
The primary objectives of the study are: Parts A and B • To determine the safety and tolerability of CC-90011 • To define the maximum tolerated dose (MTD) and/or the recommended Phase 2 dose (RP2D) of CC-90011 Parts C and D • To evaluate the effect of rifampicin, a strong cytochrome P450 (CYP) 3A and P-glycoprotein (P-gp) inducer, on the PK of CC-90011 (Part C) • To evaluate the effect of itraconazole, a strong CYP3A and P-gp inhibitor on the PK of CC-90011 (Part D)
Secondary Objective(s)
The secondary objectives are: Parts A and B • To provide information on the preliminary efficacy of CC-90011 • To characterize the pharmacokinetics (PK) of CC-90011 Parts C and D • To characterize the PK parameters of a single dose of CC-90011 alone and in combination with rifampicin (Part C) or itraconazole (Part D) • To assess the safety and tolerability of a single dose of CC-90011 alone and in combination with rifampicin (Part C) or itraconazole (Part D)
Exploratory Objective(s)
The exploratory objectives are: • To evaluate the PD effects of CC-90011 on gene expression in peripheral blood and if available, in tumor samples (in Parts A and B) • To evaluate the PD effects of CC-90011 on secreted neuropeptide (such as Pro-GRP, CgA and calcitonin only in Part A) levels in blood from G2 NENs/NETs, SCLC, and other NEC subjects (in Parts A and B) • To explore the relationship among CC-90011 dose, plasma exposure (in all Parts), and selected clinical endpoints (in Parts A and B) (eg, measures of toxicities, preliminary activity, and/or biomarkers) • To explore the relationship between baseline, on-treatment, and/or changes in gene expression in tumor samples (if available) and clinical response (in Parts A and B) • To characterize the metabolites of CC-90011 in plasma.

Table 3: Study Objectives (Continued)

Exploratory Objective(s)
• To assess the urinary excretion of CC-90011 and its M1 metabolite (CC7108272) following single oral dose of CC-90011 to cancer patients (Parts C and D). • Data from exploratory objectives may be included in the Clinical Study Report per SAP (Statistical analyses plan) To assess the impact of SARS-CoV-2 serologic status on subjects with R/R NHL (MZL, including EMZL, SMZL, NMZL and histologic transformation of MZL) and on subjects with advanced unresectable solid tumors enrolled in Parts C and D, receiving CC-90011

Table 4: Study Endpoints

Endpoint	Name	Description	Timeframe
Primary	Safety endpoints	DLTs and MTD evaluated using the NCI CTCAE criteria, Version 4.03	Dose escalation
	Effect of Rifampicin on CC-90011 PK (Part C)	C_{max}, $AUC_{0-\infty}$, AUC_{0-t}, AUC_{0-168}, for CC-90011 with and without coadministration with Rifampicin Ratio (CC-90011 + Rifampicin/ CC-90011 alone) of C_{max}, AUC_{∞}, AUC_{0-t}, AUC_{0-168}; as well as the difference (CC-90011 + Rifampicin – CC-90011 alone) in T_{max}.	At prespecified time points (Part C)
	Effect of Itraconazole on CC-90011 PK (Part D)	C_{max}, $AUC_{0-\infty}$, AUC_{0-t}, AUC_{0-168}, for CC-90011 with and without coadministration with Itraconazole Ratio (CC-90011 + Itraconazole/ CC-90011 alone) of C_{max}, AUC_{∞}, AUC_{0-t}, AUC_{0-168}; as well as the difference (CC-90011 + Itraconazole – CC-90011 alone) in T_{max}.	At prespecified time points (Part D)
Secondary	Preliminary efficacy	Clinical benefit rate (CBR) determined by response and stable disease rates by disease-appropriate response criteria, ORR, DOR, and PFS	Dose escalation and expansion
	Overall survival	From the first dose to death due to any cause	Dose escalation and expansion
	PK endpoints	Maximum observed plasma concentration (C_{max}), area under the plasma concentration time-curve (AUC), time to maximum plasma concentration (T_{max}), terminal half-life ($t_{1/2}$), apparent clearance (CL/F), and apparent volume of distribution (Vz/F) of CC-90011	Dose escalation

Table 4: Study Endpoints (Continued)

Endpoint	Name	Description	Timeframe
	Effect of Rifampicin on CC-90011 PK (Part C)	t½, CL/F, Vz/F for CC-90011	At prespecified time points (Part C)
	Effect of Itraconazole on CC-90011 PK (Part D)	t½, CL/F, Vz/F for CC-90011	At prespecified time points (Part D)
Exploratory	PD endpoints	• Gene expression in peripheral blood cell components • Gene expression in tumor tissue, if available • Secreted neuropeptides (such as Pro-GRP, CgA and calcitonin only in part A) levels in blood from low/intermediate-grade lung NET and NEPCs subjects in expansion Part B.	Dose escalation and expansion
	PK endpoints	• Clinically relevant covariates of PK parameters • Identification of principal CC-90011 metabolite(s) in plasma • Exposure-response relationships	
	Effect of Rifampicin on CC-90011 PK (Part C)	• Exploratory metabolite profiles in plasma and urine without coadministration of Rifampicin. • Measurement of pharmacokinetic (PK) parameters in urine for the parent drug, metabolite CC7108272 (M1), and other metabolites as needed, without coadministration of Rifampicin. • Measurement of PK parameters in plasma for CC7108272 and other metabolites as needed, with and without coadministration of Rifampicin.	At prespecified time points (Part C)
	Effect of Itraconazole on CC-90011 PK (Part D)	• Exploratory metabolite profiles in plasma and urine without coadministration of Itraconazole.	At prespecified time points (Part D)

Table 4: Study Endpoints (Continued)

Endpoint	Name	Description	Timeframe
		• Measurement of PK parameters in urine for the parent drug, CC7108272, and other metabolites as needed, without coadministration of Itraconazole. • Measurement of PK parameters in plasma for M1 and other metabolites as needed, without coadministration of Itraconazole.	
	SARS-CoV-2 serologic status	• Exploratory measurements of SARS-CoV-2 serology (anti-SARS-CoV-2 total or IgG).	At prespecified time points.

3. OVERALL STUDY DESIGN

3.1. Study Design

Study CC-90011-ST-001 is an open-label, Phase 1a, dose escalation and expansion, FIH clinical study of CC-90011 in subjects with relapsed and/or refractory advanced unresectable solid tumors (including G2 NENs/NETs, SCLC, and other NECs) and R/R NHL. The dose escalation part (Part A) of the study explored escalating oral doses of CC-90011 to estimate the RP2D/MTD of CC-90011. A Bayesian logistic regression model (BLRM) utilizing escalation with overdose control (EWOC) (Babb, 1998; Neuenschwander, 2008) helped guide CC-90011 dose escalation decisions with the final decisions being made by an SRC. The expansion part (Part B) will further evaluate the safety and efficacy of CC-90011 administered at 60 mg QW in the selected expansion cohorts of R/R NHL (MZL, including EMZL, SMZL, NMZL and histologic transformation of MZL), advanced unresectable low/intermediate-grade lung NETs and NEPCs, which may secrete neuroendocrine markers such as Pro-GRP, CgA, or calcitonin, of approximately 10-20 evaluable subjects each in order to further define the RP2D. One or more dosing regimens may be selected for cohort expansion (Part B). Parts A and B will consist of 3 periods: Screening, Treatment, and Follow-up periods (refer to Figure 2). The DDI cohorts will evaluate the effect of multiple doses of rifampicin (Part C) and itraconazole (Part D) on CC-90011 by comparison of the PK parameters of a single dose of CC-90011 alone and in combination with rifampicin or itraconazole. Part C and D will consist of 4 periods: Screening, DDI Evaluation, Treatment and Follow-up periods (refer to Figure 3).

The study will be conducted in compliance with the International Council for Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use/Good Clinical Practice (GCP) and applicable regulatory requirements.

Figure 2: Overall Study Design (Part A and Part B)

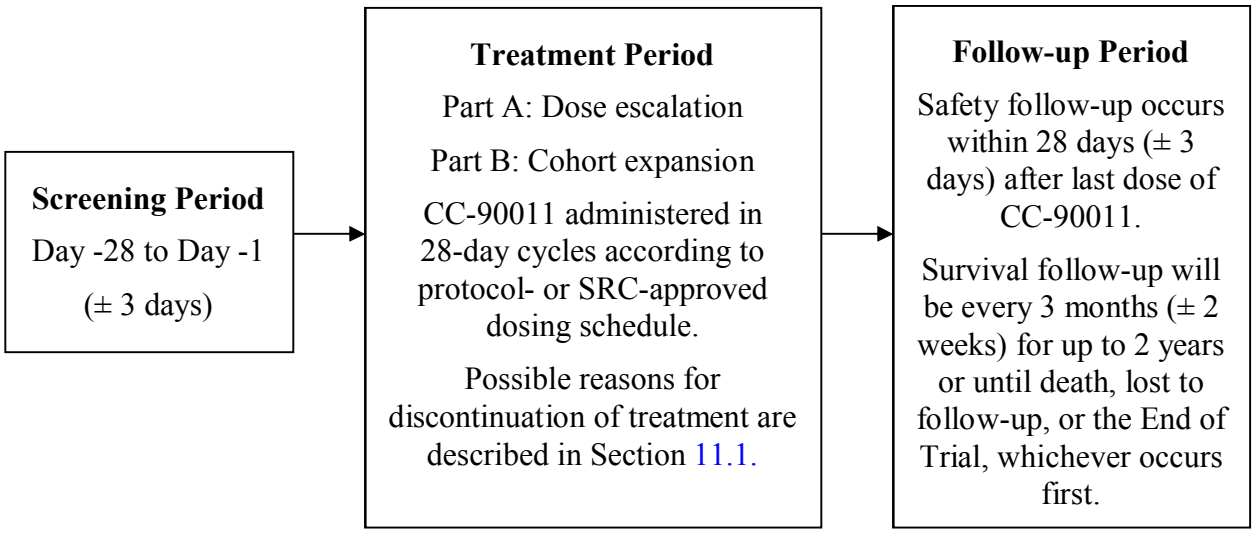


Figure 2: Overall Study Design (Continued)

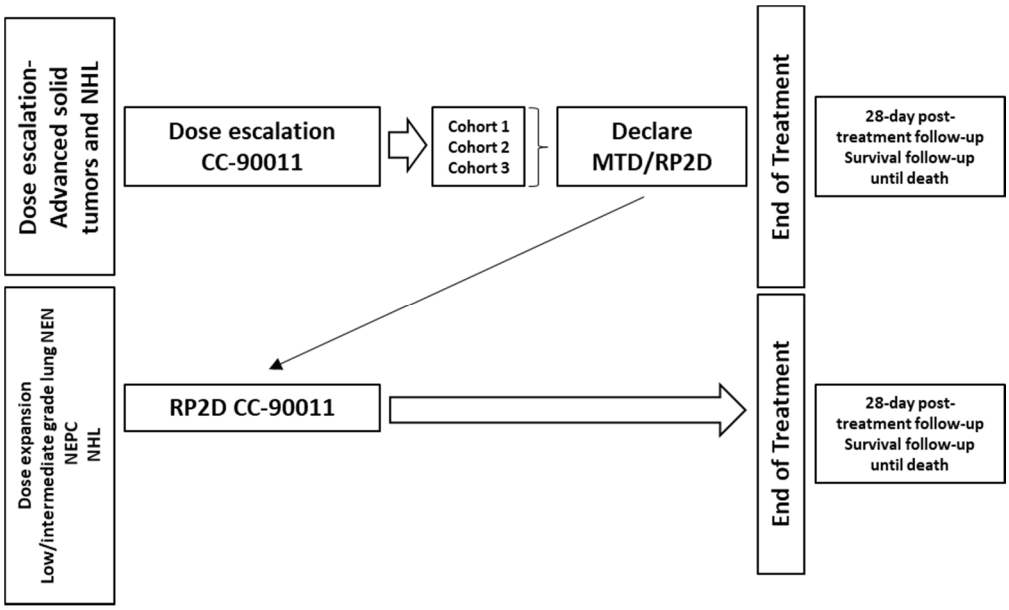
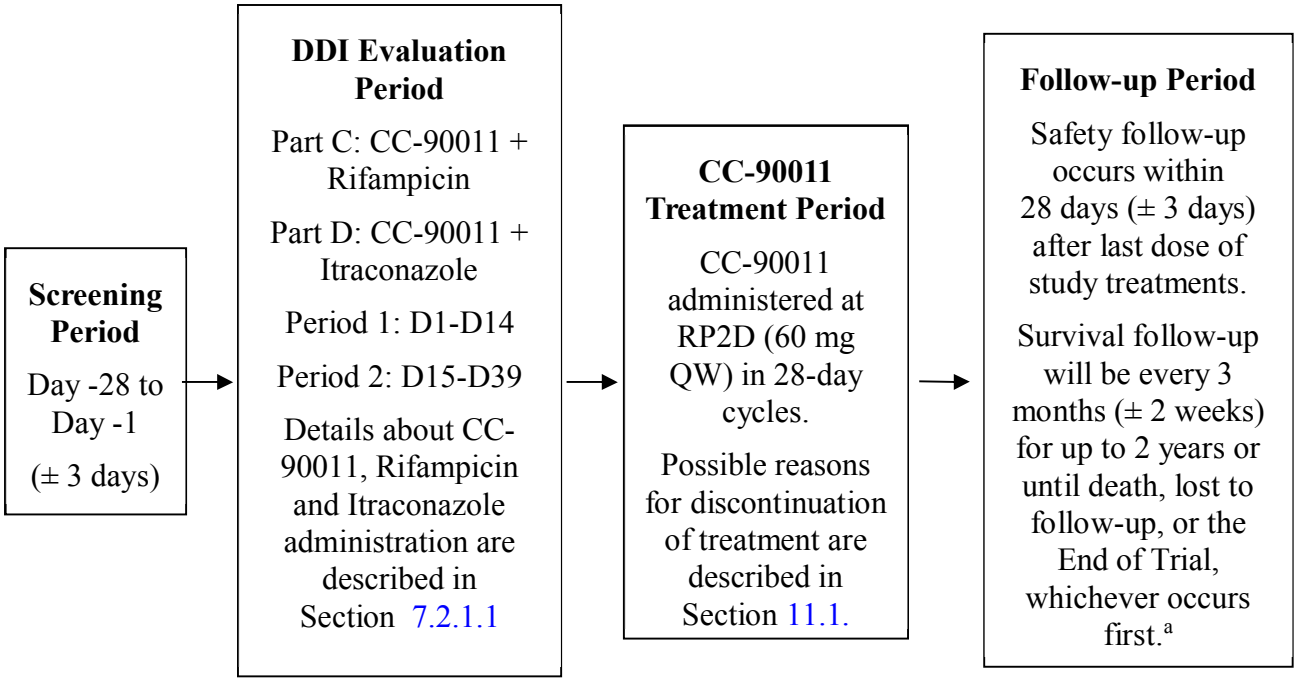


Figure 3: Study Design Part C and Part D



[a] Not applicable for subjects who discontinues during DDI evaluation period.

Screening Period

The Screening Period starts 28 days (± 3 days) prior to first dose of CC-90011. The informed consent form (ICF) must be signed and dated by the subject and the administering staff prior to the start of any other study procedures. All screening tests and procedures must be completed within the 28 days (±3 days) prior to the first dose of CC-90011.

Treatment Period

During the Treatment Period, CC-90011 will initially be administered orally once weekly in each 4-week (28 day) Cycle in Part A. Alternative dosing schedules (eg, once every other week or twice weekly) may be evaluated based on the review of available safety, PK, PD, and efficacy data by the SRC. In Part A, the window for evaluation of dose-limiting toxicity (DLT) will be 28 days (4 weeks) during Cycle 1. Once the MTD has been established for a once weekly schedule, and if the pharmacokinetics and clinical safety data in man suggest more frequent dosing might be appropriate, and if the SRC is supportive, alternative more frequent dosing schedules may be explored.

The DDI cohorts will evaluate the effect of multiple doses of rifampicin (Part C) and itraconazole (Part D) on CC-90011 by comparison of the PK parameters of a single dose of CC-90011 alone and in combination with rifampicin or itraconazole. The DDI evaluation period for each part will be conducted across 2 study periods (Period 1 and Period 2). Following completion of the DDI evaluation period, including a washout period of 5 days after the last dose of rifampicin (Part C) or 9 days after the last dose of itraconazole (Part D), subjects will start CC-90011 at the RP2D of 60 mg QW of 28-day cycles.

Follow-up Period

In the Follow-up Period, subjects will be followed for 28 days (± 3 days) after the last dose of CC-90011 (in Parts A and B) and after the last dose of any study treatment, whichever is the latest (in Parts C and D) for safety.

Subjects who discontinue treatment for reasons other than disease progression, start of a new anticancer therapy, or withdrawal of consent from the entire study will have disease assessments performed according to the specified tumor assessment schedule until progression and/or initiation of new systemic anticancer therapies. This does not apply to subjects who discontinue during the DDI evaluation period in Parts C and D.

After the Safety Follow-up visit, all subjects will be followed every subsequent 3 months (± 2 weeks) for survival follow-up for up until 2 years or until death, lost to follow-up, or the End of Trial, whichever occurs first. This does not apply to subjects who discontinue during the DDI evaluation period in Parts C and D.

Subjects who discontinue treatment during the DDI evaluation may be replaced if not DDI evaluable.

3.1.1. Part A-Dose Escalation

A minimum of 3 subjects will be enrolled at each dose level. The initial CC-90011 dose was 1.25 mg once per week. The BLRM with EWOC will incorporate available prior safety information and update the model parameters after each new cohort of subjects completes Cycle 1. The decision for the next dose will be made by the SRC based on a calculation of risk assessment

using the BLRM, and available safety (ie, DLT and non-DLT safety data), PK, PD, and preliminary efficacy information. In addition, relevant non-clinical data (eg, GLP toxicity studies, in vivo pharmacology from xenograft models, etc) may be utilized in the assessment. Details of the statistical methodology are provided in Appendix E.

At all decision time points, the BLRM permits alterations in the dose increments based on the observed DLTs; however, the dose for the next cohort will not exceed a 100% increase from the prior dose. The MTD is the highest dose for which less than 33% of the population (not sample from the population) treated with CC-90011 suffer a DLT in the first cycle and at least 6 evaluable subjects have been treated at this dose. The SRC will make the final decision regarding the CC-90011 dose for each cohort.

During dose escalation, a CC-90011 dose can be declared the MTD after meeting the following conditions:

- at least 6 evaluable subjects have been treated at the dose,
- the posterior probability that the DLT rate lying in the target interval (16-33%) at the dose exceeds 60% or a sufficient number of subjects have been entered into the study to ensure the precision of the MTD estimate, as the posterior probability approaches but fails to exceed 60%, and
- the dose is recommended according to the BLRM and the SRC approves it.

Dose escalation may be terminated by SRC at any time based on emerging safety concerns without establishing the MTD. The SRC will include Investigators (and/or designated representatives), the Sponsor's study physician, safety physician, study statistician, and the study manager. Ad hoc attendees may include the study pharmacokineticist, the study biomarker- and study clinical scientists. Other internal and external experts may be consulted by the SRC, as necessary.

All decisions made at the SRC meetings will be formally documented (via SRC meeting minutes) and circulated to all sites in writing. No dose escalation, de-escalation, change to dosing schedule, or expansion of existing dose cohorts will commence prior to a written notification being sent to all participating sites of the respective SRC decision.

The decision to evaluate additional subjects within a dose cohort, a higher dose cohort, intermediate dose cohorts, smaller dose increments, alternative dosing schedules (eg, once every other week or twice weekly), or declare a MTD will also be determined by the SRC, based on the BLRM assessment and their review of available safety (ie, DLT and non-DLT data), PK, PD, and preliminary efficacy information. The final decision will be made by the SRC.

After the first dose is administered in any cohort during dose escalation, subjects in each cohort are observed for 28 days (Cycle 1, DLT window, as defined in Section 7.2.6) before the next dose cohort can begin. A subject evaluable for DLT is defined as one that:

- Has received ≥ 75% of the total planned dose amount of CC-90011 during Cycle 1 without experiencing a DLT,

or

- Experienced a DLT after receiving at least one dose of CC-90011.

Subjects not evaluable for DLT will be replaced.

During the initial dose levels, subjects with advanced unresectable solid tumors and R/R NHL will be enrolled until the 2nd occurrence of a Grade ≥ 2, study drug-related toxicity, which fall under the adverse event terms of thrombocytopenia/platelet count decrease, anaemia/red blood cell count decrease, neutropenia/white blood cell count decrease, and/ or gastrointestinal tract toxicities in Cycle 1. At this point, the enrollment will be restricted to subjects with G2 NENs/NETs, SCLC, or other NECs who may secrete Pro-GRP, CgA and calcitonin.

Intra-subject dose escalation will not be allowed during the DLT assessment period, however, in Cycles ≥ 3, subjects without evidence of disease progression who are tolerating their assigned dose of CC-90011 may (at the Investigator's discretion and in consultation and agreement with the Sponsor's study physician) escalate to the highest dose level shown to be adequately tolerated by at least one cohort of subjects in this study (ie, overdose risk is less than 25% based on the BLRM assessment).

3.1.2. Part B-Cohort Expansion

Following completion of dose escalation (Part A), in Part B, 3 cohorts, of approximately 10-20 evaluable subjects each, with advanced low/intermediate-grade lung NETs, NEPCs and R/R NHL (MZL, including EMZL, SMZL, NMZL and histologic transformation of MZL) will receive the RP2D to further evaluate safety, PK, PD and preliminary efficacy. Expansion will occur at the RP2D and schedule established in the dose escalation phase (60 mg QW), and/or at an alternative tolerable dose and schedule, based on review of available safety, PK, PD and efficacy data from Part A. The SRC will select the doses and schedules of interest for cohort expansion. One or more dosing regimens may be selected for cohort expansion. The SRC will continue to review safety data regularly throughout the study and make recommendations about study continuation and dose modification, as appropriate.

In Part B of the study, SRC meetings will be held after at least 6 subjects have been recruited with at least 2 months of follow up; or after the number of subjects specified in the futility analyses has been reached; and/or ad-hoc as advised by emerging safety/efficacy data.

3.1.3. Part C and Part D- DDI Cohorts

The DDI cohorts will consist of a nonrandomized, fixed-sequence, crossover, two-period design that will evaluate the effect of multiple doses of rifampicin (Part C) and itraconazole (Part D) on CC-90011 PK parameters in approximately 16 DDI evaluable subjects with advanced unresectable solid tumors. The DDI evaluation period for each part will be conducted across 2 study periods (Period 1 and Period 2) followed by a CC-90011 treatment period in which subjects will receive CC-90011 at the RP2D of 60 mg QW in 28-day cycles. Both Part C and Part D will have a 14-day washout interval between Day 2 and Day 14 (inclusive of Days 2 and 14) and another washout interval after last dose of rifampicin on Day 35 (Part C) or Itraconazole on Day 31(Part D), before starting the CC-90011 treatment period. The total duration of DDI treatment period (Period 1 + Period 2) will be 40 days.

Blood samples and urine will be collected at prespecified times for PK analyses. Subject safety will be monitored throughout the study. Overnight stay for subjects can be arranged or subjects can be hospitalized at any time point due to study procedures, without this constituting a serious

adverse event (SAE), if the treating physician considers this appropriate for an individual subject.

Following confirmation of eligibility during screening, subjects will be alternatively enrolled in Part C and Part D, respectively. In each part, approximately 8 DDI evaluable subjects will be enrolled, leading to a total of up to 16 DDI evaluable subjects for Parts C and D.

Part C and D are as described below:

Part C (CC-90011 and Rifampicin)

During Period 1, subjects will:

- On Day 1: Receive a single oral dose of CC-90011 60 mg under fasting condition as described in Section 7.2.
- On Days 2 to 14 inclusive: Observe a washout period

Blood samples and urine for measurement of CC-90011 and metabolites in plasma and urine will be collected at predose and postdose until 336 hours (D15), following 60 mg dose of CC-90011 on Day 1.

During Period 2, subjects will:

- On Days 15 to 21: Receive rifampicin oral dose of 600 mg once daily fasting under condition
- On Day 22: Receive a single oral dose of CC-90011 60 mg coadministered with a single oral dose of rifampicin 600 mg under fasting condition
- On Days 23 to 35: Receive rifampicin 600 mg once daily under fasting condition
- On Days 36 to 39 inclusive: Observe a washout period

Blood samples, for measurement of plasma CC-90011 and metabolites, will be collected at predose and postdose until 432 hours, following 60 mg dose of CC-90011 on Day 22.

After Period 2 completion, on Day 40, subjects will start the CC-90011 Treatment Period, receiving CC-90011 at the RP2D of 60 mg QW in each 28-day cycle (Figure 4).

Figure 4: Overall Study Design for Part C

Screening	DDI evaluation period					CC-90011 treatment period
Day -28 to -1 (± 3 days)	Period 1 (D1 – CD14)		Period 2 (D15 – D39)			
	D1	D2 - D14	D15 - D21	D22 – D35	D36-D39	D40 (+3 days) →
Screening procedures	CC-90011 60 mg single dose (Gen 2 Capsule)	Washout	Rifampicin 600 mg tablet QD 7-day run-in	CC-90011 60 mg single dose (D22) + Rifampicin 600 mg QD (D22 – D35)	Washout	Participants start their therapeutic dosing regimen (CC-90011 60 mg QW)

Part D (CC-90011 and Itraconazole)

During Period 1, subjects will:

- On Day 1: Receive a single oral dose of CC-90011 20 mg under fasting conditions as described in Section 7.2
- On Days 2 to 14 inclusive: Observe a washout period

Blood samples and urine for measurement of CC-90011 and metabolites in plasma and urine will be collected at predose and postdose to 336 hours (D15), following 20 mg dose of CC-90011 on Day 1.

During Period 2, subjects will:

- On Days 15 to 17: Receive itraconazole 200 mg once daily under fasting conditions
- On Day 18: Receive a single oral dose of CC-90011 20 mg coadministered with a single oral dose of Itraconazole 200 mg under fasting conditions
- On Days 19 to 31: Receive itraconazole 200 mg once daily under fasting conditions
- On Days 32 to 39 (inclusive): Observe a washout period

Blood samples for measurement of plasma CC-90011 will be collected at predose and postdose to 528 hours, following 20 mg dose of CC-90011 on Day 18.

After Period 2 completion, on Day 40, subjects will start CC-90011 Treatment Period receiving CC-90011 at the RP2D of 60 mg QW in each 28-day cycle (Figure 5).

Figure 5: Overall Study Design for Part D

Screening	DDI evaluation period					CC-90011 treatment period
Day -28 to -1 (± 3 days)	Period 1 (D1 – D14)		Period 2 (D15 – D39)			
	D1	D2– D14	D15 – D17	D18 – D31	D32-D39	D40 (+3 days) →
Screening procedures	CC-90011 20 mg single dose (Gen 2 Capsule)	Washout	Itraconazole 200 mg QD 3-day run-in	CC-90011 20 mg single dose (D18) + Itraconazole 200 mg QD (D18 – D31)	Washout	Participants start their therapeutic dosing regimen (CC-90011 60 mg QW)

3.1.4. Overview of Assessments

The schedule of assessments is shown in Table 5 (for Parts A and B) and Table 6 (for Parts C and D)and assessments are described in Section 6 and Section 7. The safety variables for this study include adverse events, safety clinical laboratory variables, 12-lead electrocardiograms, Eastern Cooperative Oncology Group Performance Status, left ventricular ejection fraction assessments, physical examinations, vital signs, exposure to study treatment, assessment of concomitant medications, and pregnancy testing for females of child bearing potential.

Subjects will be evaluated for efficacy after every 2 cycles through Cycle 6, and then every 3 cycles thereafter. Subjects with NENs/NETs, SCLC, and other NECs will have neuroendocrine

markers taken at the start of each cycle. Tumor markers such as prostate-specific antigen (PSA) for prostate cancer (PC) and NEPC and alfa-fetoprotein (AFP) for hepatocellular carcinoma (HCC) and neuroendocrine hepatocellular carcinoma (NEHCC) will be taken on D1 of each cycle. All subjects who discontinue treatment for reasons other than disease progression, start of a new anticancer therapy, or withdrawal of consent from the entire study will be followed until progression and/or initiation of new systemic anticancer therapies.

Blood samples will be collected at specified time-points for determining the PK profiles of CC-90011 and for exploratory PD assessments. Paired tumor biopsies for analysis of biomarkers of treatment activity will be collected whenever safe and feasible in the dose escalation phase and during the dose expansion phase (Part B), unless exemption granted by Sponsor's study physician in exceptional circumstances. For Part C and D, blood samples and urine will be collected at specified time-points for determining PK profiles of CC-90011 and metabolite CC7108272 and possibly other metabolites.

The study will be conducted in compliance with the ICH of Technical Requirements for Registration of Pharmaceuticals for Human Use/GCP and applicable regulatory requirements.

3.2. Study Duration for Subjects

Enrollment is expected to take approximately 67 months to complete (24 months for dose escalation, and 24 to 43 months for expansion). Completion of active treatment and post-treatment follow-up is expected to take an additional 4 to 28 months. Enrollment and DDI evaluation are expected to take 12 to 15 months. Completion of treatment and post-treatment follow-up is expected to take an additional 6 to 24 months. The entire study is expected to last approximately 9-10 years.

3.3. End of Trial

The End of Trial is defined as either the date of the last visit of the last subject to complete the post-treatment follow-up, 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 pre-specified in the protocol, whichever is the later date.

4. STUDY POPULATION

4.1. Number of Subjects

This is a multicenter, open-label study in which approximately 50 evaluable subjects will be enrolled during Part A (dose escalation). During the Part B (dose expansion), approximately 20 evaluable subjects may be enrolled in each of the selected dose expansion cohorts. Enrollment will occur at approximately 4 to 8 sites in Europe for Part A. Enrollment in Part B may include additional sites in Europe with approximately 12 sites for this part.

In Parts C and D, approximately 8 DDI evaluable subjects with advanced unresectable solid tumors will be enrolled in each part, leading to a total of up to 16 DDI evaluable subjects. Enrollment will occur at approximately 3 sites in Spain.

4.2. Inclusion Criteria

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

1. Subject is a man or woman ≥ 18 years of age, at the time of signing the informed consent form (ICF).
2. Subject must understand and voluntarily sign an ICF prior to any study-related assessments or procedures being undertaken.
3. Subject is willing and able to adhere to the study visit schedule and other protocol requirements.

Entry Criteria Specific for Dose-Escalation Phase (Part A)

4. Subjects with histological or cytological confirmation of advanced unresectable solid tumors (including G2 NENs/NETs, SCLC, and other NECs) or R/R NHL (DLBCL and FL or MZL). Sporadic and familial NECs can be enrolled, as can endocrine-producing tumors or non-functioning NECs.

   NECs and G2 NENs/NETs must have:

   - Appropriate pathological features according to WHO classification (Rindi, 2010; Travis, 2015)
   - Expression of neuroendocrine markers (eg, synaptophysin or chromogranin-A) by immunohistochemistry
   - Mitotic count ≥ 2 per 10 HPF or ≥ 2 per 2mm^2 and/or ≥ 3% Ki67 index (if reliably available)

   - Specific additional criteria for certain NEC tumor types are as follows:
   - **Small Cell Lung Cancer (SCLC);**
     - Histologic or cytologic confirmation of SCLC according to 2015 WHO classification (Travis, 2015)

     or

  - Immunohistochemistry suggestive of SCLC such as AE1/AE3 positive cytoplasmic staining, NCAM (CD56) positivity, chromogranin positivity, synaptophysin positivity, TTF1 positivity and high proliferation activity as demonstrated by Ki-67 in uncertain cases. Combined SCLC is permitted.

- **Large Cell Neuroendocrine Carcinoma (LCNEC);**
  - Histologic confirmation of LCNEC according to 2015 WHO classification (Brambilla, 2015)
  - Immunohistochemistry > 10% of tumor cells positive for CD56, chromogranin or synaptophysin. Combined LCNEC is permitted.
- **Neuroendocrine variant of EGFR mutant Lung Cancer;**
  - Known EGFR mutation
  - Progression on/following prior EGFR inhibitor
  - Histologic or cytologic confirmation of SCLC according to 2015 WHO classification (Brambilla, 2015)
  - Immunohistochemistry suggestive of SCLC such as AE1/AE3 positive cytoplasmic staining, NCAM (CD56) positivity, chromogranin positivity, synaptophysin positivity, TTF1 positivity and high proliferation activity as demonstrated by Ki-67 in uncertain cases.
  - Subjects with mixed adenoneuroendocrine carcinoma (MANEC), which has at least 30% adenocarcinoma and 30% NEC, are eligible.
- **Medullary Thyroid Carcinoma (MTC);**
  - Previously confirmed cytologic or histologic diagnosis of unresectable, locally advanced or metastatic hereditary or sporadic MTC
  - Immunochemistry suggestive of MTC including positive staining for calcitonin (Perros, 2014)
  - Documented disease progression following prior therapy with vandetanib and/or cabozantinib
  - Calcified lesions at baseline should not be used as a target lesion at baseline unless no other lesions are available.
  - Calcitonin levels above the normal range
- **Neuroendocrine Prostate Cancer (NEPC);**
  - Metastatic prostate cancer and at least one of
    i. Histologic diagnosis of small cell or neuroendocrine prostate cancer, supported by immunochemistry
    ii. Histologic diagnosis of prostate adenocarcinoma plus > 50% IHC staining for neuroendocrine markers (chromogranin, synaptophysin, CD56, or neuron-specific enolase (NSE))

iii. Development of liver metastases in the absence of PSA progression as defined by PCWG3 (Scher, 2016)

- Subjects with histologic evidence of pure neuroendocrine or small cell carcinoma do not need to have received prior androgen deprivation therapy or castrate levels of testosterone, but their testosterone state should be maintained for the duration of the study. Other subjects must have undergone surgical or ongoing medical castration and have baseline serum testosterone levels <50 ng/dL or <1.73 nmol/L.

- **Neuroendocrine Pancreatic Carcinoma;**
  - Pathologic diagnosis of neuroendocrine pancreatic carcinoma (Klimstra WHO Classification 2010), with supportive immunochemistry
  - Evidence of radiologic disease progression ≤ 12 months prior to Cycle 1, Day 1
  - No receptor-targeted radiolabeled therapy ≤ 3 months prior to Cycle 1, Day 1
  - No liver-directed therapy ≤ 4 weeks prior to Cycle 1, Day 1
  - Subjects with mixed adenocarcinoma are eligible
- **Neuroendocrine Hepatocellular Carcinoma (NEHCC);**
  - Histologically or cytologically-confirmed NEHCC, with supportive immunochemistry
  - Platelet count ≥ 75 x 10^9/L (≥ 75,000/mm^3) if subject has portal hypertension, otherwise ≥ 100 x 10^9/L (≥ 100,000/mm^3)
  - Child-Pugh score < 7 (ie, class A liver function) (Appendix H)
  - BCLC C Advanced stage disease (Llovet, 1999)
  - At least 4 weeks from last dose of α-interferon and/or ribavirin
  - At least 4 weeks from prior percutaneous ethanol injection, radiofrequency ablation, transarterial embolization, or cryotherapy with documentation of progressive or recurrent disease
  - Measurable disease per RECIST 1.1 outside the liver or measurable disease per RECIST 1.1 on triple phase contrast enhanced hepatic CT or MRI that is suitable for repeat measurement and shows intratumoral arterial enhancement. Poorly demarcated or lesions showing atypical enhancement in the liver should be recorded as non-target lesions
  - No prior liver transplant
  - No gastrointestinal or variceal bleed in the previous 3 months requiring transfusion or endoscopic or operative intervention
  - No history of, or current, encephalopathy
  - No current clinically significant ascites (ie, not easily controlled with diuretics)

Other NECs such as Merkel cell carcinoma, neuroendocrine colorectal cancer, and neuroendocrine melanoma may be enrolled. Additionally, NEN/NET G2 (mitotic count 2 - 20 per 10 HPF or 2 - 20 per 2mm^2 and/or 3- 20% Ki67 index) may be enrolled if they have documented progression on or following prior standard anticancer therapy as per institutional practice. However, pathology and immunochemistry must confirm the neuroendocrine element and pathologic diagnosis.

Entry Criteria Specific for Dose-Expansion Phase (Part B).

1. **Neuroendocrine tumors**

   Subjects with histological or cytological confirmation of advanced unresectable solid tumors (including low/intermediate-grade lung NETs and NEPCs) which fall under one of the following categories:

   - **Lung NETs;**
     - The following 2 histologies Subjects with demonstrated tumor progression in the last 12 months on last prior therapy assessed by CT/MRI scan.
       i. Typical carcinoid (TC)
       ii. Atypical carcinoid (AT)
   - **Prostate NECs (NEPCs);**
     - Appropriate pathological features according to WHO classification (Rindi, 2010, Travis, 2015)
     - Expression of neuroendocrine markers (eg, synaptophysin or chromogranin-A)
     - Mitotic count ≥ 2 -10 per 10 HPF or ≥ 2-10 per 2mm2 and/or ≥ 3% Ki67 index (if reliably available)

2. **R/R NHL;**

   - Subjects with MZL (including EMZL, SMZL, NMZL and histologic transformation of MZL), relapsed/refractory after ≥2 prior therapies and ineligible for potentially curative therapy with the adequate immunohistochemistry markers.

     Local therapy such as surgery, radiotherapy accounts for a first line treatment. Regarding gastric EMZL, antibiotics only does not count for one line of treatment. Prior therapies must contain at least one prior line with anti-CD20 antibody.

     Subjects must have progressed on (or not been able to tolerate due to medical comorbidities or unacceptable toxicity), or following standard anticancer therapy or for whom no other approved conventional therapy exists or is acceptable.

Entry Criteria Specific for DDI evaluation (Part C and Part D):

1. Advanced unresectable solid tumors including those who have progressed on (or not been able to tolerate due to medical comorbidities or unacceptable toxicity) standard anticancer therapy or for whom no other approved conventional therapy exists.

2. Subject with solid tumor that has at least one site of measurable disease per RECIST 1.1, subjects with R/R NHL has at least one site of measurable disease per the Lugano Classification (Cheson, 2014)
3. Tumor biopsies, wherever safe and feasible, will be collected in Part A and during cohort expansion (Part B), unless an exemption is granted by the Sponsor's study physician in exceptional circumstances. Fresh biopsies will not be collected in Parts C and D.
4. Subject has ECOG Performance Status of 0 to 1.
5. Subjects must have the following laboratory values:
   - Absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/L without growth factor support for 7 days (14 days if subject received pegfilgastrim) (except Part B, NHL cohort)
     - ANC $\geq 1.0 \times 10^9$/L (Part B, NHL cohort)
   - Hemoglobin (Hgb) $\geq$ 10 g/dL ($\geq$ 100 g/L or > 6.2 mmol/L)
   - Platelet Count
     - Platelet count (plt) $\geq 100 \times 10^9$/L ($\geq$ 50 x 109/L for NHL subjects) or $\geq$ 75 x 109/L for HCC or NEHCC subjects with portal hypertension without transfusion for 7 days (Part A).
     - Platelet count (plt) $\geq 150 \times 10^9$/L (Part B, solid tumor cohort in particular NET and CRPC, Part C and Part D).
     - Platelet count (plt) $\geq 50 \times 10^9$/L (Part B, NHL cohort)
   - Serum potassium concentration within normal range, or correctable with supplements (Part A only)
   - Serum AST/SGOT and ALT/SGPT $\leq$ 3.0 x Upper Limit of Normal (ULN) or $\leq$ 5.0 x ULN if liver metastases are present
   - Serum total bilirubin $\leq$ 1.5 x ULN
   - Subjects must have serum albumin $\geq$3.0 g/dL
     - **Adequate hepatic function for subjects with HCC or NEHCC includes (Part A only):**
       - Serum AST and ALT $\leq$ 5 x ULN
       - Serum total bilirubin $\leq$ 3 mg/dL ($\leq$ 51µmol/L)
       - Serum albumin $\geq$ 3.0 g/dL
   - Serum creatinine $\leq$ 1.5 x ULN, or measured glomerular filtration rate (GFR) $\geq$ 50 mL/min/1.73m^2 using an exogenous filtration marker such as iohexol, inulin, ^{51}Cr EDTA or ^{125}I iothalamate. In cases where the serum Creatinine is < 1,5xULN, there is no need to calculate GFR.
   - PT (or INR) and activated partial thromboplastin time (APTT)
     - within normal range (Part A)

- ≤1.5 ULN (Parts B, C and D)

6. Females of childbearing potential (FCBP)[1] must:
   - Either commit to true abstinence[2] from heterosexual contact (which must be reviewed on a monthly basis and source documented) or agree to use, and be able to comply with, at least two effective contraceptive methods (oral, injectable, or implantable hormonal contraceptive; tubal ligation; intra-uterine device; barrier contraceptive with spermicide; or vasectomized partner), one of which must be barrier, from signing the ICF, throughout the study, and for up to 45 days following the last dose of CC-90011 (and for 1 week after last dose of rifampicin and 2 months after last dose of itraconazole in Parts C and D; and
   - Have two negative pregnancy tests as verified by the Investigator prior to starting CC-90011:
     - a negative serum pregnancy test (sensitivity of at least 25 mIU/mL) at Screening
     - a negative serum or urine pregnancy test within 72 hours prior to Cycle 1 Day 1 of study treatment
   - Avoid conceiving for 45 days after the last dose of CC-90011 (and for one week after last dose of rifampicin and 2 months after last dose of itraconazole in Parts C and D).
   - Agree to ongoing pregnancy testing during the course of the study, and after the end of study treatment. This applies even if the subject practices true abstinence[2] from heterosexual contact
7. Males must practice true abstinence[2] (which must be reviewed on a monthly basis) or agree to use a condom (a latex condom is recommended) during sexual contact with a pregnant female or a FCBP and will avoid conceiving from signing the ICF, while participating in the study, during dose interruptions, and for at least 105 days following CC-90011 discontinuation, even if he has undergone a successful vasectomy

4.3. Exclusion Criteria

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

1. G1 neuroendocrine tumors (< 2 per HPF or < 2 per mm^2 and/or ≤ 2% Ki67 index) such as carcinoid are excluded (Part A).
2. Subject has received anti-cancer therapy (either approved or investigational) ≤ 4 weeks or 5 half-lives, whichever is shorter, prior to Cycle 1 Day 1.
   - < 42 days for prior nitrosureas or mitomycin C

[1] A female of childbearing potential is a sexually mature woman who 1) has not undergone a hysterectomy (the surgical removal of the uterus) or bilateral oophorectomy (the surgical removal of both ovaries) or 2) has not been naturally postmenopausal for at least 24 consecutive months (ie, has had menses at any time during the preceding 24 consecutive months).

[2] True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. [Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception].

3. Toxicities resulting from prior systemic cancer therapies must have resolved to ≤ NCI CTCAE Grade 1 prior to starting CC-90011 treatment (with exception of grade 2 peripheral neuropathy and alopecia).
4. Prior autologous stem cell transplant ≤ 3 months before first dose or those who have not recovered.
5. Prior allogeneic stem cell transplant with either standard or reduced intensity conditioning.
6. Subject has undergone major surgery ≤ 4 weeks or minor surgery ≤ 2 weeks prior to Cycle 1 Day 1 or who have not recovered from surgery.
7. Subject has completed any radiation treatment < 4 weeks prior to Cycle 1 Day 1 or < 2 weeks for palliative bone radiotherapy (single fraction). Subjects with > 25% of myelopoetic BM radiation are not allowed to be enrolled on this study.
8. Subject has persistent diarrhea due to a malabsorptive syndrome (such as celiac sprue or inflammatory bowel disease) ≥ NCI CTCAE Grade 2, despite medical management), or any other significant GI disorder that could affect the absorption of CC-90011.
9. Subject with symptomatic or uncontrolled ulcers (gastric or duodenal), particularly those with a history of and/or risk of perforation and GI tract hemorrhages.
10. Subject with any hemorrhage/bleeding event > CTCAE Grade 2 or haemoptysis > 1 teaspoon within 4 weeks prior to the first dose
11. Symptomatic and untreated or unstable central nervous system (CNS) metastases.
    - Subject recently treated with whole brain radiation or stereotactic radiosurgery for CNS metastases must have completed therapy at least 4 weeks prior to Cycle 1, Day 1 and have a follow-up brain CT or MRI demonstrating either stable or improving metastases 4 or more weeks after completion of radiotherapy (the latter to be obtained as part of the Screening Assessments, refer to Section 6.1)
    - Subject must be asymptomatic and off steroids or on stable dose of steroids for at least 4 weeks (≤10 mg/day prednisone equivalent)
12. Subject with SCLC that has history of interstitial lung disease (ILD) OR a history of pneumonitis that has required oral or IV steroids
13. Subject has known symptomatic acute or chronic pancreatitis.
14. Subject has impaired cardiac function or clinically significant cardiac diseases, including any of the following:
    - LVEF < 45% as determined by multiple gated acquisition scan (MUGA) or echocardiogram (ECHO)
    - Complete left bundle branch or bifascicular block
    - Congenital long QT syndrome
    - Persistent or clinically meaningful ventricular arrhythmias or atrial fibrillation.
    - QTcF ≥ 480 msec on Screening ECG (mean of triplicate recordings)

- Unstable angina pectoris or myocardial infarction ≤ 6 months prior to starting CC-90011

15. Subject has other clinically significant heart disease such as congestive heart failure requiring treatment or uncontrolled hypertension (blood pressure ≥ 160/95 mm Hg).
16. Subject is a pregnant or nursing female.
17. Subject has known HIV infection.
18. Subject has known chronic active hepatitis B or C virus (HBV, HCV) infection.
    - Subjects who are seropositive due to HBV vaccination are eligible
    - Subjects who have no active viral infection and are under adequate prophylaxis against HBV re-activation are eligible
    - Subjects with HCC and NEHCC are exempt from the above criteria (applies to subjects in Part A only)
19. Subject with ongoing treatment with chronic, therapeutic dosing of anti-coagulants (eg, warfarin, low molecular weight heparin, Factor Xa inhibitors, thrombin antagonist). Low dose low molecular weight heparin for catheter maintenance and for short-term prophylaxis for subjects with prior PE and DVT are permitted under careful consideration by the Investigator.
20. Subject has a history of concurrent second cancers requiring active, ongoing systemic treatment.
21. Subject has any significant medical condition (eg, active or uncontrolled infection or renal disease), laboratory abnormality, or psychiatric illness that would prevent the subject from participating (or compromise compliance) in the study or would place the subject at unacceptable risk if he/she were to participate in the study.
22. Subjects with poor bone marrow reserve as assessed by Investigator such as in the following conditions of (Part B only):
    - Having received extensive bone radiotherapy
    - Having experienced several episodes of bone marrow aplasia in previous treatments
    - Confirmed histological bone marrow cancer infiltration
    - Requiring regular hematopoietic support (blood transfusion, erythropoietin, GCSF)
23. Subject has any condition that confounds the ability to interpret data from the study.
24. Previous SARS-CoV-2 infection within 10 days for mild or asymptomatic infections or 20 days for severe/critical illness prior to C1D1.

    Acute symptoms must have resolved and based on investigator assessment in consultation with the Sponsor's study physician, there are no sequelae that would place the subject at a higher risk of receiving study treatment.
25. Previous SARS-CoV-2 vaccine within 14 days of C1D1 (Parts A and B) or Day 1 (Parts C and D). For vaccines requiring more than one dose, the full series (e.g. both doses of a

two-dose series) should be completed prior to enrollment when feasible and when a delay in enrollment would not put the study subject at risk. The administration of live SARS-CoV-2 vaccine is prohibited up to 14 days prior to initiation of treatment.

26. Subject has a past history or current diagnosis of platelet disorder, bleeding disorder, or clotting disorder regardless of the clinical significance (Parts C and D only).
27. Subject has used any strong or moderate CYP3A enzyme or P-gp/BCRP transporter inhibitors or inducers within 15 days or 4-5 half-lives before the first dose of IP. The following link should be used to determine strong or moderate inhibitors and/or inducers of metabolic enzymes: http://medicine.iupui.edu/clinpharm/ddis/table/aspx. The following link should be used to determine inhibitors of P-gp/ BCRP: https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers#transporter
The Sponsor's study physician should be contacted for questions about potential DDIs and exclusions/prohibitions when necessary (Parts C and D only).
28. Subject is allergic to or hypersensitive to any of the drugs used in the DDI evaluation part of the study in which the subject will participate (Parts C and D only).
29. Subjects with known hypersensitivity or previous adverse events associated with azole antifungals (Parts C and D only)
30. Subject has used St. John's wort within 7 days; or grapefruit, grapefruit products, Seville oranges or starfruit within 3 days of the first dose of IP and during the conduct of DDI evaluation (Parts C and D only).

5. TABLE OF EVENTS (PART A AND PART B AND CC-90011 TREATMENT PERIOD FOR PART C AND PART D)

For a detailed description of the procedures listed, please refer to Section 6. For details regarding study drug administration, please refer to Section 7.

Table 5: Table of Events (Part A and Part B and CC-90011 Treatment Period for Part C and Part D)

		Treatment Period													Follow-up Period[a]	
		Cycle 1						Cycles 2-5				Cycles 6+				
	Screening	WK1			WK2	WK3	WK4	WK1	WK2	WK3	WK4	WK1	WK3	EOT	Safety	Long Term
Events[b]	D-28 to -1	D1	D2	D3	D8	D15	D22	D1	D8[j]	D15	D22[j]	D1	D15[c]	≤ 28 days	28 days (±3 days)	q3 mo (±2 wks)[r]
Study Entry (Section 6.1)																
Informed consent	X															
Contraceptive counseling for FCBP and males[l]	X	X						X				X		X		
Informed consent for optional exploratory analyses	X															
Inclusion/ exclusion criteria	X															
Medical/ oncologic history and therapies[q]	X															
Demographics	X															
IRT registration	X	X	Day 1 of every Cycle. Please refer to IRT instruction manual.											X		
Prior/concomitant medications & procedures	X	X	X[p]	X[p]	X	X	X	X	X	X	X	X	X	X	X	
Study Drug (Section 7)																
Administer oral CC-90011 per assigned dosing schedule (Section 7.2.1)		Weekly Note: Alternative dosing schedules may be implemented based on SRC decisions.														
Provide/review of diary card		X			X	X	X	X	X	X	X	X	X	X		

Table 5: Table of Events (Part A and Part B and CC-90011 Treatment Period for Part C and Part D) (Continued)

Events[b]	Screening	Treatment Period													Follow-up Period[a]	
		Cycle 1						Cycles 2-5				Cycles 6+				
		WK1			WK2	WK3	WK4	WK1	WK2	WK3	WK4	WK1	WK3	EOT	Safety	Long Term
	D-28 to -1	D1	D2	D3	D8	D15	D22	D1	D8[j]	D15	D22[j]	D1	D15[c]	≤ 28 days	28 days (±3 days)	q3 mo (±2 wks)
IP accountability		X						X				X		X		
Safety Assessments (Section 6)																
Adverse Event Evaluation (Section 6.2.2)	X	X	X[p]	X[p]	X	X	X	X	X	X	X	X	X	X	X	
Height	X															
Weight	X	X			X	X	X	X	X (C2 only)	X	X (C2 only)	X		X		
Vital Signs (Section 6.2.4)	X	X			X	X	X	X	X (C2 only)	X	X (C2 only)	X		X		
Physical Examination (Section 6.2.5)	X	X						X				X		X		
ECOG PS (Appendix D)	X	X						X				X		X		
B Symptoms Assessment (only NHL; Section 6.2.6)	X	As clinically indicated														
12-lead ECG (single or triplicate; Section 6.2.7)[d,s]	X (≥72 hours prior to D1)	X			X	X	X	X				X		X		
LVEF (ECHO/MUGA; Section 6.2.8)	X	As clinically indicated														
Pregnancy Testing (FCBP only; Section 6.2.9)[n]	X	X						X				X		X		
Hematology laboratory (Section 6.2.10)	X (D-14 to -1)	X		X[p]	X	X	X	X	X (C2 only)	X	X (C2 only)	X		X		

Table 5: Table of Events (Part A and Part B and CC-90011 Treatment Period for Part C and Part D) (Continued)

		Treatment Period													Follow-up Period[a]	
		Cycle 1						Cycles 2-5				Cycles 6+				
	Screening	WK1			WK2	WK3	WK4	WK1	WK2	WK3	WK4	WK1	WK3	EOT	Safety	Long Term
Events[b]	D-28 to -1	D1	D2	D3	D8	D15	D22	D1	D8[j]	D15	D22[j]	D1	D15[c]	≤ 28 days	28 days (±3 days)	q3 mo (±2 wks)
Chemistry laboratory with LDH & uric acid tests (Section 6.2.10)	X (D-14 to -1)	X			X	X	X	X	X (C2 only)	X	X (C2 only)	X		X		
HbA1C (Section 6.2.10)		X (pre-dose)						X (odd cycles only from Cycle 3)				X (odd cycles only from Cycle 7)		X[k]		
Cholesterol and HDL	X	X						X				X		X		
PT (or INR), APTT	X (D-14 to -1)	As clinically indicated												X		
Amylase, lipase, T-cell subsets (CD4+ and CD8+), TSH	X							X (odd cycles only from Cycle 3)				X (odd cycles only from Cycle 7)		X		
Urinalysis (Section 6.2.10)	X (D-14 to -1)	X						X				X		X		
(Part A only) Hepatitis viral assessment for subjects with HCC and NEHCC (HBV only)	X							X (odd cycles only from cycle 3)				X (odd cycles only from cycle 7)		X[k]		

Table 5: Table of Events (Part A and Part B and CC-90011 Treatment Period for Part C and Part D) (Continued)

Events[b]	Screening	Treatment Period: Cycle 1 WK1			Cycle 1 WK2	Cycle 1 WK3	Cycle 1 WK4	Cycles 2-5 WK1	Cycles 2-5 WK2	Cycles 2-5 WK3	Cycles 2-5 WK4	Cycles 6+ WK1	Cycles 6+ WK3	EOT	Follow-up Period[a]: Safety	Follow-up Period[a]: Long Term
	D-28 to -1	D1	D2	D3	D8	D15	D22	D1	D8[j]	D15	D22[j]	D1	D15[c]	≤ 28 days	28 days (±3 days)	q3 mo (±2 wks)
Tumor markers (for any subjects with PC and NEPC and HCC and NEHCC and other tumors, if relevant)	X	X						X				X		X[e]		
PK & PD Assessments (Section 6.5 & 0)																
Blood, PK (Parts A and B only)		Refer to Table 7 for a detailed collection schedule														
Blood (whole), PD (Parts A and B only)		Refer to Section 0 for a detailed collection schedule														
NEPD markers Blood PD (G2NEN/NET, SCLC, and other NEC)		X		X	X			X				X		X[e]		
Tumor Biopsy[f] (Parts A and B only)	X (D-28 to D1 predose)					X (D16 or D17)[f]								X[f]		
Archival Tumor Tissue (FFPE)	X[g]															
SARS-CoV-2 serology[o]	X	Serum collected every 6 months during study treatment (eg, C6D1, C12D1, etc.) and approximately 4 weeks after a documented or suspected SARS-CoV-2 infection												X		
Efficacy (Section 6.4)																
Solid tumor/NHL assessments: CT/MRI imaging[h]	X										X (D28 ±7d; C2 & C4)	X (D28 ± 7d in C6, then q3 cycles, ie, end of C9, C12, etc)		X[e]		

Table 5: Table of Events (Part A and Part B and CC-90011 Treatment Period for Part C and Part D) (Continued)

		Treatment Period													Follow-up Period[a]	
		Cycle 1						Cycles 2-5				Cycles 6+				
	Screening	WK1			WK2	WK3	WK4	WK1	WK2	WK3	WK4	WK1	WK3	EOT	Safety	Long Term
Events[b]	D-28 to -1	D1	D2	D3	D8	D15	D22	D1	D8[j]	D15	D22[j]	D1	D15[c]	≤ 28 days	28 days (±3 days)	q3 mo (±2 wks)
Additionally, Subjects with known or suspected cerebral involvement and all neurologically symptomatic NEPC subjects, brain scan (CT or MRI)	X															
NHL-specific: bone marrow evaluation if known or suspected bone marrow involvement	X[i]											X, only when confirming CR		X, only when confirming CR		
NHL-specific: FDG PET or PET/CT scan (not required if tumor is FDG-negative)	X											X, when confirming CR		X, only when confirming CR		
(Part A only) MTC subjects, isotope bone scan	X[m]										X (D28 ±7d; C2 & C4)[m]	X (D28 ± 7d in C6, then q3 cycles, ie, end of C9, C12, etc[m]		X [e,m]		
(Part A only) For MTC subjects, liver MRI or triple phase CT, also MRI or CT scan of the neck (only if known lesions) should be done	X										X (D28 ±7d; C2 & C4)	X (D28 ± 7d in C6, then q3 cycles, ie, end of C9, C12, etc		X[e]		

Table 5: Table of Events (Part A and Part B and CC-90011 Treatment Period for Part C and Part D) (Continued)

		Treatment Period													Follow-up Period[a]	
		Cycle 1						Cycles 2-5				Cycles 6+				
	Screening	WK1			WK2	WK3	WK4	WK1	WK2	WK3	WK4	WK1	WK3	EOT	Safety	Long Term
Events[b]	D-28 to -1	D1	D2	D3	D8	D15	D22	D1	D8[j]	D15	D22[j]	D1	D15[c]	≤ 28 days	28 days (±3 days)	q3 mo (±2 wks)
For PC (Part A only) and NEPC, 99mTc-methylene diphosphonate radionuclide bone scan	X										X (D28 ±7d; C2 & C4)	X (D28 ± 7d in C6, then q3 cycles, ie, end of C9, C12, etc		X[e]		
(Part A only) For HCC and NEHCC subjects a contrast enhanced triple phase CT/MRI scans of the abdomen	X										X (D28 ±7d; C2 & C4)	X (D28 ± 7d in C6, then q3 cycles, ie, end of C9, C12, etc		X[e]		
Additional Follow-up (Section 6.3)																
Follow-up anticancer therapies															X	X
AE/SAE follow-up															X	
Survival follow-up																X

Abbreviations: AFP = alpha fetoprotein; anti-HBc = Hepatitis B core antibody; anti-HCV = Hepatitis C surface antibody; anti-HBS = Hepatitis B surface antibody; APTT = activated partial thromboplastin time; β - hCG = beta human chorionic gonadotropin; C = cycle; CBC = complete blood count; CR = complete response; CT = computed tomography; D = day(s); ECHO = echocardiogram; ECOG Eastern Cooperative Oncology Group; FCBP = females of child bearing potential; FDG PET = 18-Fluoro-deoxyglucose positron emission tomography; FFPE = formalin-fixed, paraffin embedded; HBsAg; Hepatitis B Surface Antigen; HCC = hepatocellular carcinoma; HDL = High density lipoprotein; INR = international normalized ratio; IRT = interactive response technology; LVEF = left ventricular ejection fraction; mo = months; MUGA = multi-gated acquisition scan; NHL = Non-Hodgkin's lymphoma; PD = pharmacodynamics; PK = pharmacokinetics; PS = performance status; PT = prothrombin time; q = every; SAE = serious adverse event; SARs-CoV-2 = severe acute respiratory syndrome coronavirus 2; TSH = thyroid-stimulating hormone; WK(s) = week.

[a] This Safety follow-up assessment may be by telephone (refer to Section 6.3.1). Long Term survival follow-up for up to 2 years or until death, lost to follow-up, or End of Trial, whichever occurs first. May be conducted by record review.

[b] From Cycle 2 onwards all study visits/procedures will have a ± 3 days window and all laboratory blood samples should be drawn predose, unless otherwise specified in this table or Section 6. If the visit is delayed the dose is also delayed. NE markers must be collected predose at D1 of subsequent cycles, so if visit is delayed the intake is delayed too.

[c] At Cycle 6 on and onwards only Day 1 required.

[d] Triplicate ECGs must be performed prior to dosing on Day 1. Site will also take the standard 12 lead ECG as per Table of Events. The ECG at screening will be assessed by PI and shared with Sponsor's study physician for eligibility.
[e] Unless PD has been previously documented.
[f] Paired tumor biopsies will be collected for Part A and Part B unless an exemption is granted by the Sponsor's study physician in exceptional circumstances. The Screening biopsy (D-28 to D1 predose) should be obtained after all inclusion/exclusion criteria have been fulfilled. The Cycle 1 biopsy may be obtained on Day 16 or 17 (+ 7-day window) provided that 2 consecutive CC-90011 doses have been administered. The EOT biopsy is optional. No fresh biopsies will be collected in Parts C and D.
[g] Mandatory only if fresh biopsy is not collected during Screening unless an exemption is granted by the Sponsor's study physician in exceptional circumstances. In Parts C and D, archival tumor tissue will be collected whenever feasible.
[h] All subjects who discontinue treatment for reasons other than disease progression, start of a new anticancer therapy, or withdrawal of consent from the entire study will be followed according to the specified tumor assessment schedule until progression and/or initiation of new systemic anticancer therapies.
[l] May be omitted if results were normal on the subject's most recent historical bone marrow biopsy. Additionally, this analysis may be omitted if a prior analysis was performed within 90 days before Cycle 1 Day 1. Historical results will be recorded in the eCRF.
[j] Day 8 and 22 visits may be omitted from Cycle 3 onwards
[k] May be omitted if it was performed in the previous 28 days
[l] Fertility counseling including sperm banking for males, if appropriate.
[m] If screening baseline isotope scan suggestive of bone metastases an X ray, CT or MRI of the bone lesion should be performed at BL and the same technique repeated at each scheduled efficacy assessment.
[n] Contraception counselling must be recorded over 45 days in females and 105 days in males post last dose.
[o] Serum collected at Screening or predose on Cycle 1 Day 1. Serum collected approximately every 6 months during study treatment to be used for potential future measurements of anti-SARS-CoV-2 serology (anti-SARS-CoV-2 total or IgG). Serum should also be collected approximately 4 weeks after a documented or suspected SARS-CoV-2 infection. At EOT, serum will be collected to be used for potential future measurements of anti-SARS-CoV-2 serology (anti-SARS-CoV-2 total or IgG). See Section 6.6.2
[p] Not applicable for Parts C and D
[q] Medical history will also include COVID-19 vaccines, toxicities of prior treatments, and known allergies.
[r] Not applicable to those subjects who discontinue during DDI evaluation
[s] In Parts C and D, ECGs will be performed only at screening and if clinically indicated.

Table 6: Table of Events for DDI Evaluation Period (Part C and Part D)

	DDI Evaluation Period							
	Period 1		Period 2					
Events	**D1**	**D8**	**D15**	**D18**	**D21**	**D22**	**D29**	**D36**
Study Drugs (Section 7)								
Administer CC-90011	X			X[b]		X[a]		
Administer Rifampicin (Part C only)			From D15 to D35					
Administer Itraconazole (Part D only)			From D15 to D31					
Diary card	X							X[c]
Safety Assessments (Section 6)								
Adverse Event Evaluation	X	X	X		X[b]	X[a]	X	X
Prior/Concomitant medications and procedures	X	X	X		X[b]	X[a]	X	X
Weight	X	X	X		X[b]	X[a]	X	X
Vital Signs	X	X	X		X[b]	X[a]	X	X
Physical Examination	X	X	X		X[b]	X[a]	X	X
ECOG Performance Status	X	X	X		X[b]	X[a]	X	X
12-lead ECG	If clinically indicated							
LVEF (ECHO/MUGA)	If clinically indicated							
Pregnancy Testing	X							
Hematology laboratory	X	X	X		X[b]	X[a]	X	X
Chemistry laboratory with LDH & uric acid tests	X	X	X		X[b]	X[a]	X	X
HbA1C	X				X[b]	X[a]		

Table 6: Table of Events for DDI Evaluation Period (Part C and Part D) (Continued)

	DDI Evaluation Period							
	Period 1		Period 2					
Events	**D1**	**D8**	**D15**	**D18**	**D21**	**D22**	**D29**	**D36**
Cholesterol and HDL	X				X[b]	X[a]		
PT (or INR), APTT	As clinically indicated							
Amylase, lipase, T-cell subsets (CD4+ and CD8+), TSH	X				X[b]	X[a]		
Urinalysis	X				X[b]	X[a]		
Efficaly Assessment (Section 6.4)								
Solid tumor assessments: CT/MRI imaging								X[d]
PK Assessments (Section 6.5)								
Blood, PK, metabolites	Refer to Table 8 (Part C) and Table 9 (Part D) for a detailed collection schedule							
Urine, PK, metabolites	Refer to **Error! Reference source not found.** for a detailed collection schedule							

[a] Only Part C.
[b] Only Part D
[c] Patient diary must be returned at the end of the DDI Evaluation Period.
[d] CT Scan/MRI must be done at the end of the DDI Evaluation Period, before starting CC-90011 treatment.

6. PROCEDURES

Any questions regarding the protocol should be directed to the Sponsor's study physician or designee. The procedures conducted for each subject enrolled in Parts A and B of the study are outlined in Table 5. For subjects enrolled in Part C and Part D, procedures to be conducted during the DDI evaluation period are outlined in Table 6, except screening procedures that will follow Table 5. After completion of the DDI evaluation period, once subjects start the CC-90011 Treatment period, will follow procedures shown in Table 5.

All study visits will have a ± 3 days window unless otherwise specified below or in the Table of Events (refer to Table 5). Please note that this applies only after Cycle 2. During Cycle 1, this window is not allowed as PK/PD must be collected. During DDI evaluation period in Part C and Part D, this window is not allowed either. In Parts C and D, the start of the CC-90011 treatment period might be delayed until 3 days (40 + 3).

All laboratory blood samples should be drawn predose unless otherwise specified (eg, PK samples).

The study procedures should be recorded in the source document and the electronic case report forms (eCRF). In the event subjects fail Screening, minimal information will be documented on the eCRFs, per database instructions.

6.1. Screening Period

The Screening window starts 28 days (± 3 days) prior to the first dose of CC-90011. Refer to Table 5, this section, and Section 6.2 for detailed information on procedures performed and the schedule for all study parts.

Waivers to the protocol will not be granted during the conduct of this trial, under any circumstances.

Safety laboratory analyses will be performed locally. Screening laboratory values must demonstrate subject eligibility, but may be repeated within the screening window, if necessary.

The ICF will be administered at the Screening visit to all subjects by qualified study staff. It must be signed and dated by the subject and the administering staff prior to the start of any other study procedures and its completion documented in source documents and in the eCRF. All screening tests and procedures must be completed within 28 days (± 3 days) prior to the first dose of CC-90011 according to the schedule shown in Table 5.

The following will be performed at Screening, after informed consent has been obtained:

- Inclusion and exclusion criteria will be assessed at Screening and recorded in the source documents and the eCRF.
- Contraceptive counseling: qualified healthcare professionals will be trained by Celgene, or designee, in the requirements specific to contraceptive counseling of subjects. Once trained the healthcare staff will counsel subjects prior to the administration of CC-90011 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-90011.

- Fertility counseling for men: Subjects will be informed that the effects of CC-90011 on spermatogenesis are unknown and they will be encouraged to collect and bank sperm if appropriate, prior to taking CC-90011.
- Medical, oncologic, and surgical history, and demographic data (including each subject's date of birth, sex, race, and ethnicity) will be collected during Screening as consistent with local regulations. Oncologic history will include a detailed history of the primary diagnosis and date, therapies, and responses. Medical history will also include Covid-19 vaccines, toxicities of prior treatments, and known allergies.
- Information on prior and concomitant medications and procedures will be collected (refer to Section 6.2.1).
- Registration in the interactive response technology system (IRT)
- Adverse event monitoring (refer to Section 10)
- Height and weight measured
- Vital signs assessed (refer to Section 6.2.4)
- Physical examination (source documented only) and ECOG performance status (refer to Section 6.2.5 and Appendix D)
  - For subjects with NHL, measurements of lymph nodes and documentation of any enlargement of the spleen and/or liver will be documented radiographically and recorded in the source document and in the eCRF (Part A and B only)
- The B symptom assessment: B symptoms are fever (> 100.5ºF or 38°C) for 2 or more weeks without other evidence of infection, night sweats for more than 1 month without evidence of infection, and weight loss greater than 10% within the prior 6 months (Part A and B only)
- A 12-lead ECG in triplicate (refer to Section 6.2.7) will be performed prior to the first dose of CC-90011 Site will also take the standard 12 lead ECG as per Table of Events which will be assessed by PI and shared with the Sponsor Study Physician for eligibility.
- Left Ventricular Ejection Fraction (LVEF) assessment (refer to Section 6.2.8)
- Pregnancy testing (refer to Section 6.2.9) for all females of childbearing potential (FCBP). Appropriate methods of contraception and potential risks of fetal exposure will be discussed with FCBP and male subjects during Screening. Double contraceptive methods (one of which must be a barrier method) for females of childbearing potential (eg, oral, injectable, or implantable hormonal contraceptive; intra-uterine device; barrier contraceptive with spermicide; or vasectomized partner) and a single contraceptive method for males (a condom) must be used from the time the ICF is signed, throughout the study (including dose interruptions), and for 45 days in females and 105 days in males after the last dose of CC-90011 (and for 1 week after the last dose of rifampicin and for 2 months after last dose of itraconazole in Parts C and D). This will be documented in source documents.

- Clinical laboratory tests (refer to Section 6.2.10) are to be completed within 14 days prior to the first dose of CC-90011
- Efficacy/tumor assessments (refer to Section 6.4)
  - Tumor markers such as PSA for PC (Part A only) and NEPC, Alpha fetoprotein (AFP) for HCC (Part A only) and NEHCC (Part A only), CEA for MTC, or CA125 for ovarian/NE ovarian cancer (Part A only) will be measured at baseline.
- Fresh tumor biopsy (Part A and B only)
  - Archival tumor tissue (FFPE) collection is mandatory only if a fresh biopsy is not collected during Screening but can be omitted under exceptional circumstances after agreement with the Sponsor's study physician. In Parts C and D, archival tumor tissue will be collected whenever feasible.
- For HCC and NEHCC subjects only (applies only to Part A):
  - AFP.
  - HBsAg, anti-HBS, anti-HBc, and anti-HCV (screening only).
  - Measurement of hepatitis B viral load (HBV DNA quantitative by PCR) if HBsAg, HBcAb total, and/or HBcAb IgM is/are positive.
  - Measurement of Hepatitis C viral load (HCV RNA quantitative by PCR) if HCV antibody is positive (only applies to HCC).
  - Confirmation of antiviral therapy with an appropriate antiviral agent for HBV is required in subjects with positive hepatitis B surface antigen, HBcAb IgM, and/or viral load - appropriate first line agents include entecavir, tenofovir, and lamivudine (note that lamivudine has higher resistance rates).
  - Confirmation of antiviral therapy with an appropriate antiviral agent for HCV is required in subjects with positive hepatitis C viral load.
  - Subjects with a positive HBV viral load, HBcAb IgM, and/or HBs Ag or positive HCV viral load should be referred to a hepatologist if not already under the care of a hepatologist.
- SARS-CoV-2 serology (Screening or Predose on Cycle 1 Day 1 [Parts A and B] or Predose Day 1 [Parts C and D])
- Testing for asymptomatic SARS-CoV-2 infection by RT-PCR or viral antigen is not required. However, some subjects may develop suspected or confirmed symptomatic SARS-CoV-2 infection, or be discovered to have asymptomatic SARS-CoV-2 infection during the screening period. In such cases, subjects may be considered eligible for the study after meeting all inclusion/exclusion criteria related to active infection, and after meeting the following criteria:
  - At least 10 days (20 days for severe/critical illness) have passed since symptoms first appeared or positive RT-PCR or viral antigen test result, and

  - At least 24 hours have passed since last fever without the use of fever-reducing medications, and
  - Acute symptoms (e.g. cough, shortness of breath) have resolved and
  - In the opinion of the investigator, there are no COVID-19 sequelae that may place the participant at a higher risk of receiving investigational treatment
- In the instance of a SARS-CoV-2 infection during screening, the screening period may be extended beyond the protocol-specified timeframe with Sponsor's study physician approval.
- Any screening tests already performed which could potentially be affected by the SARS-CoV-2 infection or its complications on an individual basis and agreed upon with the Sponsor's study physician (e.g. safety labs, SpO2, chest CT scan) should be repeated within 7 days prior to cycle 1 Day 1.

6.2. Treatment Period

Visits and assessments are shown in Table 5 and in Table 6 for DDI evaluation period in Part C and Part D. Subjects completing 6 cycles of treatment and continuing on study drug are only required to have clinic visits/assessments performed on Day 1 (± 3 days) of each subsequent cycle (Cycles 6 and higher) unless more frequent visits are clinically indicated. This is applicable beyond Cycle 2. If the visit is delayed the dose is also delayed. NE markers must be collected predose at D1 of subsequent cycles, so if visit is delayed the intake is delayed too.

6.2.1. Concomitant Medication and Procedures

All concomitant medications and procedures taken or conducted beginning when the subject signs the ICF throughout the study, and until 28 days after the last dose of CC-90011 will be recorded in the source documents and eCRF.

6.2.2. Adverse Event Monitoring

Adverse events and serious adverse events (SAEs) will be recorded from the time since the subject signs the ICF until 28 days after the last dose of CC-90011.

Subjects experiencing AEs will be monitored with relevant clinical assessments and laboratory tests, as determined by the Investigator. Every attempt will be made to document resolution dates for ongoing AEs. The AEs will be recorded on the AE page of the eCRF and in the subject's source documents. Photographs of skin rashes should be obtained whenever possible, anonymized, and stored appropriately for future retrieval.

6.2.3. Weight

The subject's weight will be recorded in the source document and eCRF at the visits listed in Table 5.

6.2.4. Vital Signs

Vital signs include body temperature, blood pressure and pulse rate will be recorded during the study at various time points for safety monitoring as described in Table 5 and in Table 6 for DDI evaluation period in Part C and Part D.

Recorded measurements will be captured in the source document and eCRF.

6.2.5. Physical Examination and ECOG Performance Status

Complete physical examination and Eastern Cooperative Oncology Group Performance Status (ECOG PS; refer to Appendix D) will be performed at the visits listed in Table 5 and in Table 6 for DDI evaluation period in Part C and Part D. Results for both will be recorded in the source document. Results for the ECOG PS will also be collected on the eCRF.

Physical examination findings will be classified as either normal or abnormal. If abnormal, a description of the abnormality and clinical importance will be provided in the source documents. Clinically significant changes from baseline will be recorded in the AE section of the eCRF.

6.2.6. B Symptom Assessment (NHL Subjects only)

For subjects with NHL, B symptom assessments will be performed at the visits listed in Table 5 and results recorded in the source documents and on the eCRF.

B symptoms are fever (> 100.5ºF or 38°C) for 2 or more weeks without other evidence of infection, night sweats for more than 1 month without evidence of infection, and weight loss greater than 10% within the prior 6 months.

6.2.7. 12-Lead-Electrocardiograms

Triplicate or single standard 12-lead electrocardiograms (ECGs) will be recorded at the visits listed in Table 5. In Part C and Part D, ECGs will be performed only at screening and subsequently only if clinically indicated as described in Table 6 for the DDI evaluation period and in Table 5 for the CC-90011 treatment period. The 12-lead ECG should be collected prior to any blood draws if both are scheduled for the same nominal time. The 12-lead ECGs (12-lead at 25 mm/sec reporting rhythm, ventricular rate, PR interval, QRS complex, QT interval, and QTcF interval) will be performed after the subject has been in the supine position for at least 5 minutes.

Triplicate ECGs (3 recordings within 2 ± 1 minute intervals) will be performed at:

- Screening
- Cycle 1
  - Day 1: predose (within 30 minutes prior to dosing) and 2, 4, 8, 24 hours (± 10 minutes) postdose. In Part B: predose (within 30 minutes prior to dosing) and 2 hours postdose.
  - Days 8, 15 and 22: predose (within 30 minutes prior to dosing) and 4 hours (± 10 minutes) postdose. In Part B: predose (within 30 minutes prior to dosing) and 2 hours postdose.
- Cycles 2 and higher

– Day 1: predose (within 30 minutes prior to dosing).

A single ECG will be performed at the EOT visit (only Parts A and B).

For alternative dosing schedules, the Cycle 1 Day 15 ECGs will be performed on the last day of CC-90011 dosing in Cycle 1.

Investigators will make immediate clinical decisions based on their interpretation of the ECG results and provide their overall assessment of the ECG in the eCRF. Clinically significant changes from baseline will be recorded in the AE section of the eCRF.

The ECG outputs will also be uploaded to the central ECG laboratory for definitive analysis and interpretation.

6.2.8. Left Ventricular Ejection Fraction

Left ventricular ejection fraction (LVEF), (multiple gated acquisition scan [MUGA], or echocardiogram [ECHO]) will be conducted at Screening in all subjects. Follow-up assessments should be performed as clinically indicated. Follow up assessments should use the same procedure used at the screening assessment. A clinically significant reduction is defined as either a ≥ 20% absolute reduction in LVEF or drop to below 45%.

6.2.9. Pregnancy Test

A female of childbearing potential (FCBP) is defined as a sexually mature woman who has:

- Not undergone a hysterectomy or bilateral oophorectomy, and
- Not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (eg, has had menses at any time in the preceding 24 consecutive months).

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

For a FCBP, pregnancy testing will be conducted at the visits listed in Table 5 and in Table 6 for DDI evaluation period in Part C and Part D.

- A serum pregnancy test with sensitivity of at least 25 mIU/mL is to be obtained at Screening and serum or urine pregnancy test within 72 hours prior to Cycle 1 Day 1 of study treatment. The subject may not receive CC-90011 until the Investigator has verified the two screening pregnancy tests to be negative.
- A serum or urine pregnancy test (based on Investigator's discretion and minimum test sensitivity [25 mIU/mL]) should be done within 72 hours prior to Day 1 of every cycle and at the end of treatment (EOT) visit. The subject may not receive CC-90011 until the Investigator has verified the pregnancy test to be negative.
- A FCBP or a male subject whose partner is a FCBP must avoid activities that could lead to conception while receiving CC-90011 and for 45 days after the last dose of CC-90011. Practice of true abstinence from sexual activity will be monitored monthly and source documented.

- Contraception counselling must be recorded over 45 days in females and 105 days in males post last dose.

Results for pregnancy tests will be recorded in the source document and eCRF.

6.2.10. Clinical Laboratory Tests

The following laboratory assessments will be performed during the study at the time points as described in Table 5 and in Table 6 for DDI evaluation period in Part C and Part D.

All samples should be drawn predose unless otherwise specified. Laboratory assessments will be recorded in the source document and eCRF and are the following:

- Hematology: Complete blood counts including hemoglobin, hematocrit, WBC count with absolute counts for WBC parameters and platelet count.
  - On Cycle 1, Day 1, the complete blood counts with absolute counts should be performed and results checked against entry criteria before drug administration.
- Serum chemistry: albumin, total protein, magnesium, phosphorus, calcium, creatinine, urea/BUN, glucose, potassium, sodium, chloride, total bilirubin (fractionate if outside normal range), alkaline phosphatase, AST or serum glutamic oxaloacetic transaminase (SGOT), ALT or serum glutamate pyruvic transaminase (SGPT), LDH, and uric acid.
- HbA1c at C1D1 pre-dose, each odd numbered cycle starting from C3D1 and EOT (unless performed in previous 28 days).
- High density lipoprotein (HDL) and cholesterol.
- Special chemistry: amylase, lipase, T-cell subsets (CD4+ and CD8+), thyroid-stimulating hormone (TSH; if abnormal reflex to free T4).
  - During screening, then pre-dose each odd numbered cycle starting from C3D1 and EOT.
- Coagulation: PT (or INR), and APTT (as clinically indicated for Parts C and D).
- Urinalysis: dipstick (protein and blood assessment at a minimum).
  - microscopy and urinary albumin to creatinine ratio in the event of first appearance of 2+ or greater protein.
- Measured glomerular filtration rate (GFR) determination using an exogenous filtration marker such as iohexol, inulin, ^{51}Cr EDTA or ^{125}I iothalamate required at Screening to fulfill inclusion criteria if serum creatinine > 1.5 x ULN (refer to Section 4.2).
- For HCC and NEHCC subjects Part A only:
  - AFP (if elevated at baseline).
  - Hepatitis B viral DNA quantitative in subjects with positive hepatitis B viral load at baseline and/or positive HBsAg, HBcAb total, and/or HBcAb IgM (odd cycles only starting with Cycle 3 or more frequently at investigator's discretion) and at

EOT (unless performed in previous 28 days). Hepatitis C viral RNA quantitative in subjects (applies to HCC only) with positive hepatitis C viral load at baseline (odd cycles only starting with Cycle 3 or more frequently at investigator's discretion) and at EOT (unless performed in previous 28 days).

- For all G2 NENs/NETs, SCLC, and NEC subjects Pro-GRP, Cg-A and calcitonin will be followed at: C1D1, predose, C1D3, C1D8 pre-dose and D1 of each cycle and EOT, unless disease progression documented previously.

- Tumor markers such as PSA for PC (Part A only) and NEPC, AFP for HCC (Part A only) and NEHCC **(Part A only)**, CEA for MTC **(Part A only)**, or CA125 for ovarian/NE ovarian cancer **(Part A only)** will be measured as appropriate at Day 1 of every cycle and EOT, unless disease progression documented previously.

6.2.11. End of Treatment (EOT)

An EOT evaluation (refer to Table 5 for procedures) should be performed for subjects who are withdrawn from treatment for any reason as soon as possible (≤ 28 days) after the decision to permanently discontinue treatment has been made.

6.3. Follow-up Period

6.3.1. Safety Follow-up

All subjects will be followed for 28 days after the last dose of CC-90011 in Parts A and B (or 28 days after last dose of CC-90011, rifampicin or itraconazole, whichever is the latest, in Part C and Part D), for AE reporting and concomitant medication information. The 28-day (±3 days) safety follow-up contact may be by telephone. In addition, any SAEs made known to the Investigator at any time thereafter that are suspected of being related to CC-90011 will be reported as described in Section 10.1.

6.3.2. Survival Follow-up

After the Safety Follow-up visit, all subjects will be followed every subsequent 3 months (± 2 weeks) for survival follow-up for up to 2 years or until death, lost to follow-up, or the End of Trial, whichever occurs first. New disease therapies should be collected at the same time schedule. This does not apply to subjects who discontinue during the DDI evaluation period in Part C and Part D.

Survival follow-up may be conducted by record review (including public records) and/or telephone contact with the subject, family, or the subject's treating physician.

6.4. Efficacy Assessment

Tumor assessments will be performed at Screening and will include CTs of the chest, abdomen and pelvis, and a brain scan (CT or MRI) for subjects with known or suspected cerebral involvement and all neurologically symptomatic subjects with NEPC (Part A only). After Screening, radiologic tumor assessments will be performed at the end (Day 28 ± 7 days) of Cycles 2, 4, and 6, and then every 3 cycles thereafter, using the same CT/MRI scanning

modalities used at Screening. An EOT scan does not need to be obtained if the prior scan was within 28 days.

- Additionally, for R/R NHL subjects, a Screening FDG PET or FDG PET/CT scan will be performed unless the tumors are known not to be FDG-avid. A subsequent scan will only be obtained to confirm a CR (Parts A and B only).
- For R/R NHL subjects with known or suspected bone marrow involvement, a bone marrow evaluation with flow immunophenotyping will be performed at Screening, and to confirm a complete response (CR). For NHL subjects, the size of the spleen and/or liver should be measured radiologically. For NHL subjects, to document a CR the normal radiologic size of the spleen and/or liver should be recorded in the source document and in the eCRF (unless splenic enlargement due to another documented reason) (Parts A and B only).
- For MTC subjects (Part A only) a screening isotope bone scan will be performed at baseline. If this is suggestive of bone metastases an X ray, CT or MRI of the bone lesion should be performed at BL and the same technique repeated at each scheduled efficacy assessment.
- For MTC subjects (Part A only) a liver MRI should be performed or if not available, a contrast enhanced triple phase CT scan. Also an MRI or CT scan of neck should be performed if neck lesions are known or suspected. These should be performed at baseline and as stipulated above.
- For PC (Part A only) and NEPC subjects, a 99mTc-methylene diphosphonate radionuclide bone scan should be performed at screening and subsequently only if progressive disease in the bone is suspected.
- For HCC and NEHCC subjects (Part A only), a contrast enhanced triple phase CT/MRI scan of the abdomen should be performed at screening and all subsequent efficacy assessments.

In Parts C and D, a CT/MRI will be performed at the end of the DDI evaluation period, before starting the CC-90011 treatment period, to be considered as the baseline.

All subjects who discontinue treatment for reasons other than disease progression, start of a new anticancer therapy, or withdrawal of consent from the entire study will be followed according to the specified tumor assessment schedule until progression and/or initiation of new systemic anticancer therapies. This does not apply to subjects who discontinue during the DDI evaluation period in Part C and Part D.

Tumor response at each post-screening assessment will be determined by the Investigator, based on Response Evaluation Criteria in Solid Tumors (RECIST) v 1.1 as described in Appendix B for solid tumors, the Lugano Classification in Appendix C for NHL, PCWG3 (Scher, 2016) for PC, and NEPC (Appendix J) and mRECIST for HCC and NEHCC (Appendix I).

Tumor markers ie, PSA for PC (Part A only) and NEPC and AFP for HCC and NEHCC (Part A only) at screening, Day 1 of every cycle and EOT unless disease progression documented previously.

6.4.1. Neuroendocrine Pharmacodynamic Markers

Neuroendocrine pharmacodynamic (NEPD) markers will be performed at the visits listed in Table 5. For all G2 NENs/NETs, SCLC (Part A only), and NEC subjects Pro-GRP, Cg-A and calcitonin (in Part A only) will be measured centrally at C1D1 (pre-dose) and followed at C1D3, C1D8 (pre-dose) and D1 of each cycle and EOT, unless disease progression documented previously.

The results from any neuroendocrine pharmacodynamic (NEPD) markers analysis performed at local laboratories at the visits listed above or at any unscheduled visit, should be recorded in the source documents and on the CRF.

6.5. Pharmacokinetics

The PK assessments for Part A and Part B are described below.

For evaluation of PK of CC-90011 in plasma, blood samples will be collected from all subjects at the time points listed in Table 7. The actual time of each sample collection will be recorded in the source documents and on the electronic case report forms (eCRFs). An exploratory analysis of CC-90011 metabolites in plasma may be performed utilizing the plasma samples collected for PK evaluation.

Table 7: Blood Pharmacokinetic sampling Schedule for Part A and Part B, Cycle 1

Time in Hours Relative to CC-90011 Dose	Collection Window	Day 1	Day 8	Day 15	Day 22
0 (predose)	Within 30 min prior	X	X	X	X
1	± 5 min	X			X
2	± 10 min	X			X
4	± 10 min	X			X
6	± 10 min	X			X
8	± 10 min	X			X
11	± 1 hour	X			X
24	± 1 hour	X			X
48	± 1 hour	X			X
72	± 2 hours	X			X
96	± 2 hours	X			X

The Sponsor may conduct additional analyses on the PK samples and collect extra PK samples in order to follow up the safety of the study treatment or to better understand the progression of the disease or the disease's response to the study treatment.

See the Laboratory Manual and Appendix G for sample collection, handling, and processing instructions.

In Part C and Part D, during the DDI evaluation period, blood samples will be collected for the evaluation of PK of CC-90011 in plasma, at the timepoints listed in Table 8 (for Part C) and Table 9 (for Part D). In addition, urine samples will be collected for exploratory measurements of parent drug and metabolites, according to **Error! Reference source not found.** for both Part C and Part D. During the first 24 hours, due to the frequency of PK sampling, overnight stay for subjects can be arranged or subjects can be hospitalized at any time point, without this constituting a serious adverse event (SAE), if the treating physician considers this appropriate for an individual subject. The actual time of each sample collection will be recorded in the source documents and on the electronic case report forms (eCRFs).

Importantly, for subjects enrolled in Part C or Part D, PK samples should only be collected during the DDI evaluation period, and not during the CC-90011 Treatment period.

Table 8: Blood Pharmacokinetic Sampling Schedule for CC-90011 and metabolites for Part C

Study Day		Time with respect to CC-90011 dose administration on D1 or D22	Allowed PK Window
Period 1	Period 2		
D1	D22	Predose, and 0.5, 1, 2, 3, 4, 6, 8, 12 hr post dose	Predose: Within 60 minutes prior to dosing 0.5 to 4 hours post dose: ± 5 minutes 6 to 12 hours post dose: ± 10 minutes
D2	D23	24 hr post dose	± 60 minutes
D3	D24	48 hr post dose	± 60 minutes
D4	D25	72 hr post dose	± 60 minutes
D6	D27	120 hr post dose	± 120 minutes
D8	D29	168 hr post dose	± 120 minutes
D10	D31	216 hr post dose	± 180 minutes
D12	D33	264 hr post dose	± 180 minutes
D15	D36	336 hr post dose	± 180 minutes
	D40	432 hr post dose	± 180 minutes

Table 9: Blood Pharmacokinetic Sampling Schedule for CC-90011 and metabolites for Part D

Study Day		Time with respect to CC-90011 dose administration on D1 or D18	Allowed PK Window
Period 1	Period 2		
D1	D18	Predose, and 0.5, 1, 2, 3, 4, 6, 8, 12 hr post dose	Predose: Within 60 minutes prior to dosing 0.5 to 4 hours post dose: ± 5 minutes 6 to 12 hours post dose: ± 10 minutes
D2	D19	24 hr post dose	± 60 minutes
D3	D20	48 hr post dose	± 60 minutes
D4	D21	72 hr post dose	± 60 minutes
D6	D23	120 hr post dose	± 120 minutes
D8	D25	168 hr post dose	± 120 minutes
D10	D27	216 hr post dose	± 180 minutes
D12	D29	264 hr post dose	± 180 minutes
D15	D32	336 hr post dose	± 180 minutes
	D36	432 hr post dose	± 180 minutes
	D40	528 hr post dose	± 180 minutes

Table 10: Urine Sampling Schedule for CC-90011 and metabolites for Parts C and D

Study Day	Urine Collection Interval	Collected by
Period 1		
D1	0 (predose)	Site
D1	0 to 6 hr	Site
D1	6 to 12 hr	Site
D2	12 to 24 hr	Site
D3	24 to 48 hr	Site
D4	48 to 72 hr	Site
D5	72 to 96 hr	Nursing Service
D6	96 to 120 hr	Site
D7	120 to 144 hr	Nursing Service
D8	144 to 168 hr	Site

Study Day	Urine Collection Interval	Collected by
Period 1		
D9	168 to 192 hr	Nursing Service
D10	192 to 216 hr	Site
D11	216 to 240 hr	Nursing Service
D12	240 to 264 hr	Site
D13	264 to 288 hr	Nursing Service
D14	288 to 312 hr	Nursing Service
D15	312 to 336 hr	Site

6.6. Biomarkers and Pharmacodynamics

6.6.1. Pharmacodynamic and Predictive Biomarkers (only Parts A and B)

The schedules for pharmacodynamic biomarkers are provided below:

- Whole blood for PD biomarker studies
  - Cycle 1 Day 1: predose (≤ 3 hours)
  - Cycle 1 Day 3
  - Cycle 1 Day 5
  - Cycle 1 Day 8: predose (≤ 3 hours)
  - Cycle 1 Day 24
- Tumor tissue for PD biomarker studies
  - Screening: Day -28 to Day 1 predose (after all inclusion and exclusion criteria are fulfilled)
  - Cycle 1 Day 16 or 17 (+ 7 days)
  - Optional, any other time until EOT visit.

The Sponsor may conduct additional analyses on the PD samples in order to follow up the safety of the study treatment or to better understand the progression of the disease or the disease's response to the study treatment.

6.6.2. Whole Blood samples for Anti-SARS-CoV-2 Serology

Serum and plasma samples may be assessed by enzyme-linked immunosorbent assay, seromics, ctDNA measurements, metabolomics, and/or other relevant multiplex-based protein assay methods for immune-related factors that may be associated with efficacy or AEs; such factors may include, but are not limited to, assessments of cytokines, chemokines, inflammatory factors, SARS-CoV-2 serologic status, and ctDNA.

Table 11: Biomarker Sampling schedule for Anti-SARS-CoV-2-Serology

Study Day of Sample Collection	Anti-SARS-CoV-2-Serology
Screening or Predose Cycle 1 Day 1 (Parts A and B) or Predose Day 1 (Parts C and D)	X
On-treatment Collection	
Approximately every 6 months (e.g. C6D1, C12D1 etc.)	X
Approximately 4 weeks after confirmed or suspected SARS-CoV-2 infection	X
End of Treatment visit	X

Abbreviations: C = cycle; D = day(s); SARs-CoV-2 = severe acute respiratory syndrome coronavirus 2

During Screening or pre-dose on Day 1, serum will be collected to be used for potential future measurements of anti-SARS-CoV-2 serology (anti-SARS-CoV-2 total or IgG). Serum will also be collected approximately every 6 months during study treatment to be used for potential future measurements of anti-SARS-CoV-2 serology (anti-SARS-CoV-2 total or IgG). Serum should also be collected approximately 4 weeks after a documented or suspected SARS-CoV-2 infection. At EOT, serum will be collected to be used for potential future measurements of anti-SARS-CoV-2 serology (anti-SARS-CoV-2 total or IgG).

6.6.3. Tumor Biopsies

Tumor biopsies will be collected whenever safe and feasible in Part A and during expansion (Part B), unless an exception is granted by the Sponsor's study physician in exceptional circumstances. No fresh tumor biopsies will be collected in Part C and Part D. The biopsy is collected by either surgical biopsy (preferred) or core needle (at least 3 passages, if possible) at Screening and in Cycle 1 on Day 16 or 17 (+ 7 days). If study drug treatment is interrupted or reduced before this time, the biopsy should be delayed until 1 to 2 days (+7 days) after the subject has received two consecutive planned doses of CC-90011. An archival tumor sample must be provided if a fresh biopsy is not collected during Screening. In Parts C and D, archival tumor sample will be collected whenever feasible. Fine needle aspiration is not sufficient as a source of tumor biopsy material. Samples should be processed as formalin-fixed paraffin-embedded (FFPE). Optimally, the tumor tissue samples (Screening and on-treatment) will be obtained from the same tumor site.

Additionally, an optional tumor biopsy may be obtained in both Part A and Part B, during later treatment cycles or following treatment discontinuation (any time during the 28-day follow-up period), to elucidate effects of long-term treatment or resistance mechanisms, respectively.

See the Laboratory Manual for sample collection, handling, and processing instruction.

7. DESCRIPTION OF STUDY TREATMENTS

7.1. Description of Investigational Product(s)

7.1.1. CC-90011

CC-90011 is a besylate salt with a molecular weight of 609.65. It is a white to pale yellow solid.

Part A and Part B

CC-90011 will be supplied to the clinic by Celgene Corporation (Celgene) as opaque Swedish orange/Grey capsules containing only the active pharmaceutical ingredient at dosage strengths of 0.50 mg, 0.75 mg, 2.00 mg, 5.00 mg, and 15 mg. The capsules will be supplied in HDPE bottles with child-resistant caps, labeled appropriately for investigational use as per the regulations of the relevant country health authorities.

Part C and Part D

Celgene Corporation (Celgene) will supply the IP, CC-90011 capsules [available as Blend in Capsule (BIC, Gen 2) with 20 mg, 40 mg and 60 mg strengths] for oral administration.

Mechanistic PBPK modeling conducted using validated with clinical data GastroPlus software (internal data) predicted that AIC and BIC (Gen2) formulations provide comparable exposures over 20 mg to 60 mg dose range. Given the exposure of CC-90011 is approximately dose-proportional over a wide range of 5 - 80 mg, the formulation is not expected to be a factor in the assessment of the extent of DDI on CC-90011 exposure.

Gen 2 formulation is a step closer to the proposed Phase 3 formulation (Gen 3 tablet) in terms of composition and therefore preferred over the AIC formulation for DDI evaluation. The outcome of the DDI evaluation will inform the future Phase 3 studies.

In addition, CC-90011 capsules (BIC, Gen 2) with 20 mg, 40 mg or 60 mg strengths for oral administration are more convenient to take for subjects as for Part C only 1 capsule of 60 mg CC-90011 will be required and for Part D only 1 capsule of 20 mg CC-90011 will be required. For the CC-90011 treatment period only 1 capsule of 60 mg CC-90011 will be given QW for the convenience of the subjects and to avoid potential dosing errors.

7.1.2. Rifampicin and Itraconazole

Subjects enrolled in countries where Rifampicin and Itraconazole is commercially available (Spain) may obtain commercial product through the local hospital pharmacy at the sites or licensed distributor.

The study drugs supplied by Celgene will be labeled appropriately for investigational use as per the regulations of the relevant health authorities.

Please refer to local prescribing information for more details on formulations, storage conditions (eg, refrigeration), known precautions, warnings, and adverse reactions for these drugs (see current version of SmPC).

The dosing schedules to be followed for this study are described in Section 7.2.

7.2. Treatment Administration and Schedule

7.2.1. CC-90011 Administration

Part A, Part B, and CC-90011 treatment period of Part C and Part D

Subjects will administer CC-90011 orally once weekly in each 4-week (28 day) Cycle. Alternative dosing schedules may be implemented based on the review of clinical safety and laboratory data by the SRC. CC-90011 will be administered with at least 240 mL of water. Subjects should fast for a minimum of 4 hours in both Parts A and B prior to CC-90011 administration and refrain from any food intake for up to 1 hour after dosing.

CC-90011 will be administered in the clinic after any predose assessments are completed (refer to Section 7.6).

Study treatment may be discontinued if there is evidence of clinically significant disease progression, unacceptable toxicity or subject/physician decision to withdraw (refer to Section 11).

If patient vomits after study drug intake and there is no certainty drug has been digested, study drug will not be made up to. No further study drug will be administered for that weekly visit. Only in cases when study drug is vomited completely and once the vomiting event has settled, patient may be challenged to take oral drug again. Otherwise, no further attempts will be made and study drug will be missed until next weekly administration.

7.2.1.1. CC-90011, Rifampicin and Itraconazole Administration during DDI evaluation period in Part C and Part D

CC-90011, rifampicin and itraconazole will be administered orally with at least 240 mL of water in fasting condition at least 4 hours prior to dosing. Subjects should fast for a minimum of 4 hours prior to CC-90011 administration and should abstain from food or other medication intake for ≥ 2 hour after CC-90011 dosing. Additional water may be given to facilitate the swallowing of the dose(s). Those days that subject will receive CC-90011 and rifampicin or itraconazole, both drugs should be taken as close to the intake of each one as possible. All subjects will receive the following oral doses of IPs:

Part C (CC-90011 and Rifampicin):

- Period 1 Day 1: 1 × 60-mg CC-90011 capsule
- Period 2 Days 15 to 35 (inclusive): 2 × 300-mg rifampicin tablets (equivalent to 600-mg rifampicin) once daily
- Period 2 Day 22: 1 × 60-mg CC-90011 capsule

Part D (CC-90011 and Itraconazole):

- Period 1 Day 1: 1 × 20-mg CC-90011 capsule.
- Period 2 Days 15 to 31 (inclusive): 2 × 100-mg itraconazole capsules (equivalent to 200-mg itraconazole) once daily
- Period 2 Day 18: 1 × 20-mg CC-90011 capsule

7.2.2. Dose Escalation Process (Part A)

For the purposes of dose escalation decisions, at least 3 subjects will be enrolled in successive cohorts. The first cohort will be treated with the starting dose of 1.25 mg once weekly. Subjects must complete a minimum of 1 cycle of treatment with the minimum safety evaluation and drug exposure or have had a DLT within the first cycle of treatment to be considered evaluable for dose escalation decisions. Dose escalation decisions will occur when the cohort of subjects has met these criteria. Dose escalation decisions will be made by the SRC. Decisions will be based on a synthesis of all relevant data available from all dose levels evaluated in the ongoing study including safety information, DLTs, all treatment related CTCAE grade ≥ 2 toxicity data during Cycle 1, and PK data from evaluable subjects. PK data from subjects will be made available on an on-going basis throughout the study and dosing will be adapted accordingly. The recommended dose for the next cohort of subjects will be guided by the BLRM with EWOC principle.

The adaptive Bayesian methodology provides an estimate of the dose levels of CC-90011 that do not exceed the MTD and incorporates all DLT information at all dose levels for this estimation. In general, the next recommended dose will have the highest chance that the DLT rate will fall in the target interval (the true DLT rate lying in 16-33%) and will always satisfy the EWOC principle. Per EWOC it should be unlikely (<25% posterior probability) that the DLT rate at the next dose will exceed 0.33. In all cases, the recommended dose for the next cohort will not exceed a 100% increase from the previous dose. Smaller increases in dose may be recommended by the SRC upon consideration of all of the available clinical data.

The procedure for subject accrual in each dose cohort and provisions for dose escalation/de-escalation decisions for the study is as follows:

1. This study will begin by evaluating CC-90011 in cohorts of at least 3 evaluable subjects at each dose level. Initially, the dosing increments between cohorts will be 100%. When a single subject experiences a DLT, or 2 subjects experience grade ≥ 2 treatment-related toxicity, which fall under the adverse event terms of thrombocytopenia/platelet count decrease, anaemia/red blood cell count decrease, neutropenia/white blood cell count decrease, and/or gastrointestinal tract toxicities, the cohort size may be increased to 6 evaluable subjects for the current and subsequent cohorts. The increase in CC-90011 dose will be ≤ 50% for each subsequent dose escalation cohort. Once 2 subjects experience grade ≥ 2 treatment-related toxicity, which fall under the adverse event terms of thrombocytopenia/platelet count decrease, anaemia/red blood cell count decrease, neutropenia/white blood cell count decrease and/or gastrointestinal tract toxicities, the enrollment will be restricted to subjects with G2 NENs/NETs, SCLC, and other NECs who may secrete Pro-GRP, CgA, or calcitonin.
2. Following completion of Cycle 1 for all evaluable subjects in a cohort, the two-parameter BLRM with EWOC principle will be used to make recommendations to the SRC for the next dose level with the following exceptions:
    - If the first 2 subjects in a cohort experience DLTs, no additional subjects will be enrolled into that cohort until the Bayesian model has been updated with this new information. Likewise, the model will be re-evaluated if 2 subjects in a cohort experience DLTs before the enrollment of any additional subject.

3. After each cohort, the SRC will meet and review data from the BLRM assessment and available safety (ie, DLT and non-DLT data), PK, PD, and preliminary efficacy information. The final dose escalation decisions will be made by the SRC.

After repeating the above steps, a CC-90011 dose can be declared the MTD after meeting the following conditions:

- at least 6 evaluable subjects have been treated at the dose,
- the posterior probability that the DLT rate lying in the target interval (16-33%) at the dose exceeds 60% or a sufficient number of subjects have been entered into the study to ensure the precision of the MTD estimate, as the posterior probability approaches but fails to exceed 60%, and
- the dose is recommended according to the BLRM and the SRC approves it.

Dose escalation may be terminated by SRC at any time based on emerging safety concerns without establishing the MTD. At the discretion of the SRC to better understand the safety, tolerability and PK of CC-90011, additional cohorts of subjects may be enrolled at prior dose levels or to intermediate dose levels before or while proceeding with further dose escalation.

7.2.3. Dose Escalation Decisions (Part A)

Provisional dose levels to be assigned to separate cohorts of subjects are described in Section 9.9.1. Dose decisions during escalation are however not limited to these doses. Based on the recommendation of the BLRM regarding the highest dose that may not be exceeded at any decision point during escalation and the maximum increase in dose allowed by the protocol, intermediate doses may be administered to subsequent new cohorts of subjects.

The decision to evaluate additional subjects within a dose cohort, a higher dose cohort, intermediate dose cohorts, smaller dose increments, alternative dosing schedules, or declare an MTD will also be determined by the SRC, based on their review of clinical and laboratory safety data.

7.2.4. Definition of a Subject Evaluable for DLT (Part A)

All subjects who receive at least one dose of CC-90011 will be evaluable for safety.

After the first dose is administered in any cohort during dose escalation, subjects in each cohort are observed for 28 days (Cycle 1, DLT window) before the next dose cohort can begin. A subject evaluable for DLT is defined as one that:

- Has received ≥ 75% of the total planned dose amount of CC-90011 during Cycle 1 without experiencing a DLT,

or

- Experienced a DLT after receiving at least one dose of CC-90011.

Subjects not evaluable for DLT will be replaced. Additional subjects within any dose cohort may be enrolled at the discretion of the SRC. Intra-subject dose escalation will not be allowed during the DLT assessment period.

7.2.5. Definition of Maximum Tolerated Dose (MTD) (Part A)

The MTD is the highest dose at which less than 33% of the population (not sample of the population) treated with CC-90011 suffer a DLT in the first cycle and at least 6 evaluable subjects have been treated at this dose. The estimation of MTD is described in Section 7.2.2.

A variable dose cohort (eg, less frequent dosing or more frequent dosing at a lower dose) may be evaluated to accurately determine the MTD at the discretion of the SRC.

7.2.6. Definition of Dose-Limiting Toxicity (DLT) (Part A)

During dose escalation, the DLT assessment period is Cycle 1 (28 days).

National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), Version 4.03 are used as a guide for the grading of severity of adverse events. A DLT is defined as any of the following toxicities occurring within the DLT assessment unless the event can clearly be determined to be unrelated to CC-90011. Dose-limiting toxicities are described below:

- Any Grade 4 non-hematologic toxicity of any duration
- Any non-hematologic toxicity Grade ≥ 3 EXCEPT for:
  - Grade 3 diarrhea, nausea, or vomiting of ≤ 3 days duration (with optimal medical management).
  - Grade 3 rash of the acneiform, pustular or maculopapular type which resolves to Grade ≤ 2 within 7 days of study drug interruption and does not recur at the same level with resumption of study drug at the same dose (with optimal medical management).
  - Grade 3 fatigue which resolves to Grade ≤ 2 within 7 days of study drug interruption and does not recur at the same level with resumption of study drug at the same dose (with optimal medical management).
- Hematological toxicities as follows:
  - Febrile neutropenia.
  - Grade 4 neutropenia lasting > 7 days.
  - Grade 4 thrombocytopenia lasting > 7 days, Grade ≥ 3 thrombocytopenia with clinically significant bleeding.
- Any AE, unless clearly determined to be unrelated to study drug, necessitating dose-level reduction during Cycle 1.
- Any other toxicity at any time during the trial that the safety committee deem dose limiting.

Isolated laboratory changes without associated clinical signs or symptoms (eg, hypomagnesemia, hypermagnesemia, hypoalbuminemia, hypophosphatemia, lymphocyte count increased or decreased) may not be included in this definition. These findings will be discussed and reviewed by the SRC.

7.2.7. Criteria for Dose Escalation in the Next Cohort of Subjects (Part A)

During Part A, the dose escalation criteria are described in Section 7.2.2 and Section 7.3.

7.2.8. Permitted Study Drug Adjustments

Dose reductions are permitted in any cycle, including Cycle 1. Dose reductions that occur in Cycle 1 during dose escalation will constitute DLT as outlined in Section 7.2.6, but subjects will be allowed to continue on CC-90011 at a reduced dose.

When a dose adjustment is indicated, the dose frequency will be adjusted first. Dose omission and reduction are allowed after consultation with the Sponsor's study physician. Once the dose has been reduced, it can be escalated when toxicity reaches Grade ≤ 1. If toxicity recurs at the higher dose, the dose will be reduced a second time, but no re-escalation is then permitted. If any subject continues to experience unacceptable toxicity after two dose reductions (one for the dose level), CC-90011 will be discontinued permanently.

Intra-subject dose escalation will not be allowed during the DLT assessment period. Refer to Section 7.2.10 for additional information on possible dose increases.

Dose modifications or interruptions are not allowed during the DDI evaluation period unless discussed and agreed upon by the Study Sponsor Physician and only for safety reasons.

During the CC-90011 Treatment period:

CC-90011 will be given orally at the RP2D of 60 mg QW in 28-day cycles. Dose modifications or interruptions are allowed, after discussion and agreement by the Study Sponsor Physician.

7.2.9. Criteria for Dose Reduction

Any AE meeting the definition of DLT will require dose frequency adjustment and subsequent dose interruption if no recovery. Subjects with Grade ≥ 2 thrombocytopenia should not be dosed until recovery of thrombocytopenia to Grade ≤ 1, with the exception of subjects with R/R NHL with G2 thrombocytopenia who may be dosed if no other safety concerns occur and with a weekly hematology follow up. Once the thrombocytopenia has resolved to Grade ≤ 1, treatment can be resumed (discussion with the Sponsor's study physician is highly recommended).

Treatment related Grade ≥ 3 toxicity or chronic Grade 2 toxicity may warrant dose reduction of CC-90011. Subjects with R/R NHL with G2 thrombocytopenia may be dosed at the same dose with weekly hematology follow up if no other safety concerns occur. Such cases should be discussed with the Sponsor's study physician before dosing changes are made.

In Part C and Part D (DDI cohorts), treatment related Grade ≥ 3 toxicity or chronic Grade 2 toxicity may warrant dose reduction of CC-90011. Investigators are encouraged to discuss such cases with the Sponsor's study physician.

Rifampicin and itraconazole dosing regimens are not intended to be altered. If the second CC-90011 dose in Period 2 cannot be administered as planned, then the Sponsor may decide to stop the concomitant doses of rifampicin or itraconazole, in which case the subject will be considered DDI non-evaluable.

7.2.10. Criteria for Dose Increase

Intra-subject dose escalation will not be allowed during the DLT assessment period, however, in Cycles ≥ 3, subjects without evidence of disease progression who are tolerating their assigned dose of CC-90011 may (at the Investigator's discretion and in consultation and agreement with the Sponsor's study physician) escalate to the highest dose level shown to be adequately tolerated by at least one cohort of subjects in this study (ie, ≤ 33% of evaluable subjects having experienced a DLT at that dose level).

In Part B (expansion phase), no dose escalation beyond the MTD is allowed.

In Part C and Part D (DDI cohorts), no dose escalation beyond the pre-specified doses for DDI evaluation and treatment periods is allowed.

7.2.11. Treatment Interruption for Adverse Events

Treatment may be interrupted up to 4 weeks until toxicity (excluding alopecia) reaches either Grade ≤ 1 or baseline levels. Treatment may restart either at the same, or a reduced dose, at the Investigator's discretion or as described in Section 7.2. Any such treatment interruptions must be discussed with the Sponsor´s study physician.

In the DLT assessment period of the dose escalation phase, a treatment interruption with > 1 missed dose of CC-90011 for reasons other than DLT will make a subject non-evaluable for DLT and necessitate replacement of that subject in the dosing cohort. Any such treatment interruptions must be discussed with the Sponsor´s study physician.

In Part C and Part D (DDI cohorts), treatment related toxicity may warrant dose interruptions of CC-90011. Such cases should be discussed with the Sponsor's study physician before dosing interval changes are made. In case of safety concerns, the physician may interrupt treatments to protect the safety of the subject. Such subjects will become non-evaluable for DDI assessment and will need to be replaced.

Subjects with confirmed SARS-CoV-2 infection following initiation study treatment with CC-90011 must have treatment interrupted. Subjects with confirmed SARS-CoV-2 infection may resume treatment after 1) at least 10 days (20 days for severe/critical illness) have passed since symptoms first appeared, positive RT-PCR test result, or positive viral antigen test result, 2) resolution of acute symptoms (including at least 24 hours has passed since last fever without fever reducing medications), 3) evaluation by the Investigator with confirmation that there are no sequelae that would place the subject at a higher risk of receiving investigational treatment, and 4) consultation by the Sponsor's study physician. For suspected cases, treatment may also resume if SARS-CoV-2 infection is ruled-out and other criteria to resume treatment are met.

Prior to re-initiating on-study treatment in a subject with a dosing delay lasting > 4 weeks due to SARS-CoV-2 infection, the Sponsor's study physician /designee must be consulted.

7.2.12. Management of Select Adverse Events

7.2.12.1. Neutropenia, Thrombocytopenia, and Anemia

Hematopoietic growth factors or other hematologic support, such as erythropoietin, darbepoetin, granulocyte-colony stimulating factor (G-CSF), granulocyte macrophage colony stimulating

factor (GM CSF), and RBC- or platelet- transfusions are allowed in the study with therapeutic intent. Therapeutic use of G-CSF is allowed at any time for subjects experiencing Grade 3/4 neutropenia or any grade febrile neutropenia. Prophylactic use of granulocyte (or granulocyte-macrophage) growth factors is not allowed during Cycle 1.

Subjects with Grade 3 or 4 neutropenia and/or Grade ≥ 2 thrombocytopenia should be monitored frequently with laboratory tests until resolution to Grade ≤ 1. Antimicrobial, antifungal, and antiviral prophylaxis should be considered, as appropriate.

As of 11 Sep 2020, 50 subjects were enrolled in Part A of the study and received escalating oral doses of CC-90011 QW at 9 dose levels from 1.25 mg to 120 mg/dose and 16 subjects (14 subjects with low/intermediate-grade lung NETs [typical and atypical carcinoid], 2 subjects with prostate NEC and 1 subject with MZL) were enrolled in Part B of the study and received oral CC-90011 QW at 60 mg. The Part A of the study has been completed and the primary objectives were met. The NTD was determined to be 120 mg, the MTD was 80 mg, and the RP2D was 60 mg, QW of 28-day cycles. Thrombocytopenia, an on-target effect, was the only dose-limiting toxicity (DLT); these events occurred mainly at the highest dose levels and were successfully managed with dose interruption for a week and/or dose reduction. CC-90011 has been generally well tolerated with the majority of treatment-emergent adverse events (TEAEs) being reversible and manageable by dose adjustments and/or supportive treatments.

Subjects with Grade ≥ 2 thrombocytopenia should not be dosed until recovery of thrombocytopenia to Grade ≤ 1, with the exception of subjects with R/R NHL with G2 thrombocytopenia who may be dosed if no other safety concerns occur and with a weekly hematology follow up. Once the thrombocytopenia has resolved to Grade ≤ 1, treatment can be resumed (discussion with the Sponsor's study physician is highly recommended).

7.2.12.2. Pain

Tumor pain or treatment-induced pain can be controlled with opioid and opioid-related analgesics, such as codeine, meperidine, propoxyphene or morphine, administered at the clinician's discretion, and as dictated by medical need. The risk of bleeding, especially in the setting of thrombocytopenia, should be considered prior to use of non-steroidal anti-inflammatory drugs (NSAIDs) and aspirin. NSAIDS and aspirins should be avoided if possible and paracetamol should be administered instead.

7.2.12.3. Gastrointestinal Effects

Mucosa coating agents for protection of esophageal/gastric mucosa are recommended at the discretion of the Investigator as well as monitoring subjects for GI bleeding. However, proton pump inhibitors may affect the neuroendocrine markers in NEN/NET/SCLC and other NEC subjects, so histamine (H2) receptor antagonists should be administered preferentially if appropriate in these subjects. Subjects will be encouraged to report all episodes of GI discomfort or pain, appetite loss, change of stool, or blood in stool.

It is recommended that subjects experiencing diarrhea be managed according to the guideline provided in Appendix F. Anti-diarrheal medication, such as loperamide, should be initiated at the earliest onset of Grade 1-2 diarrhea. Anti-diarrheal medication may be administered as prophylaxis and for treatment of diarrhea. Dehydration and electrolyte disturbances should be

rapidly corrected. General measures to improve diarrhea, such as a low-fiber diet and increased liquid consumption, should be considered and weight should be closely monitored.

7.2.13. Definition of Overdose

Overdose, as defined for this protocol, refers to CC-90011 dosing only. In Part C and Part D, overdose refers to CC-90011, rifampicin or itraconazole. On a per dose basis, an overdose is defined as the following amount over the protocol-specified dose of CC-90011, rifampicin or itraconazole 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. Refer to Section 10 for the reporting of adverse events associated with overdose.

7.3. Method of Treatment Assignment

Eligible subjects will be enrolled sequentially in Part A (dose escalation). Enrollment in Part B (dose expansion) will be stratified by disease cohort and dosing schedule, as applicable. In Part C and Part D, subjects will be alternatively enrolled: first subject will be assigned to Part C and the following subject to Part D, etcetera.

An Interactive Response Technology (IRT) system will be used to track subject assignments to the dose levels in Part A and tumor cohorts in Part B.

7.4. Packaging and Labeling

The label(s) for CC-90011 will include, but not limited to, sponsor name, address and telephone number, the protocol number, CC-90011, dosage form and strength (where applicable), amount of CC-90011 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.

The labels for rifampicin and itraconazole contain information found on the commercial label(s) for these products.

7.5. Investigational Product Accountability and Disposal

Celgene (or designee) will review with the Investigator and relevant site personnel the procedures for documenting receipt of investigational products, as well as the procedures for counting, reconciling investigational products, and documenting this process. Celgene (or designee) will also review with the Investigator and relevant site personnel the process for investigational products return, disposal, and/or destruction including responsibilities for the site vs. Celgene (or designee).

7.6. Investigational Product Compliance

Only the pharmacist or the Investigator's designee will dispense investigational products. A record of the number of dosing units of the investigational products dispensed to and taken by each subject must be maintained. The pharmacist or the Investigator's designee will document the doses dispensed/administered in the appropriate study records.

8. CONCOMITANT MEDICATIONS AND PROCEDURES

All medications (excluding prior cancer therapy for the tumor under evaluation) taken beginning when the subject signs the ICF and all concomitant therapy during the study until 28 days after treatment discontinuation, together with dose, dose frequency and reasons for therapy use will be documented in the source documents and on the concomitant medication eCRF.

All prior chemotherapy (biologic, immunologic, or radiation therapy) and anticancer surgery prior to the administration of study drug, will be recorded in the appropriate section of the eCRF.

The Investigator will instruct subjects to notify the study staff about any new medications taken after signing the ICF. All medications and significant non-drug therapies (herbal medicines, physical therapy, etc.) and any changes in dosing with existing medications will be documented on the eCRFs.

8.1. Permitted Concomitant Medications and Procedures

Subject to the precautions described in Section 8.2, the use of any concomitant medication/therapies deemed necessary for the care of the subject should be used. Repeat PK evaluations may be conducted if changes are made to concomitant medications suspected of affecting drug absorption or metabolism. The following are permitted concomitant medications and procedures:

- Subjects with ≥ Grade 1 diarrhea should promptly initiate treatment with diphenyoxylate/atropine (Lomotil), or loperamide (Imodium) or an alternative over-the-counter remedy for diarrhea. Premedication with antidiarrheal medication for subsequent doses of CC-90011 may be appropriate and should be discussed with Sponsor's study physician.
- Subjects may receive prophylactic anti-emetics at the discretion of the Investigator, including dexamethasone.
- Prophylactic mucosa protective agents may be appropriate at the discretion of the Investigator. However, proton pump inhibitors may affect the neuroendocrine markers in G2 NENs/NETs, SCLC, and other NEC subjects, so histamine (H2) receptor antagonists should be administered preferentially in such subjects if appropriate.
- Antiviral therapy with an appropriate antiviral agent for HBV is required in HCC and NEHCC subjects with positive hepatitis B surface antigen, HBcAb IgM, and/or viral load appropriate first line agents include entecavir, tenofovir, and lamivudine (note that lamivudine has higher resistance rates). Confirmation of antiviral therapy with an appropriate antiviral agent for HCV is required in subjects with positive hepatitis C viral load. Regimens appropriate for the treatment of HCV should not be interrupted when administering CC-90011.
- Therapeutic use of granulocyte growth factors is allowed at any time for subjects experiencing febrile neutropenia or Grade 3/4 neutropenia. Routine prophylaxis with granulocyte colony stimulating factor or granulocyte-macrophage colony stimulating factor is allowed at Investigator discretion starting with Cycle 2 and beyond.

- Subjects receiving stable doses of recombinant erythropoietin or darbepoetin alfa for at least 4 weeks prior to starting the CC-90011 may continue their pretreatment doses throughout the study. Subjects may initiate de novo treatment with erythropoietin stimulating agents (ESAs) beginning in Cycle 2 for hypoproliferative anemias secondary to prior chemotherapy exposure provided there is no clinical suspicion of a concurrent cause for the anemia (eg, CC-90011-induced).
- Parenteral flu vaccination is permitted.
- Routine infectious disease prophylaxis is not required. However, antibiotic, antiviral, anti-pneumocystis, antifungal, or other prophylaxis may be implemented during the study at the discretion of the Investigator.
- Treatment with bisphosphonates (eg, pamidronate, zolendronate) or other agents (eg, denosumab) is permitted to prevent or delay progression of bone metastases. Maintenance of a stable dosing regimen throughout the study is recommended.
- Focal palliative radiotherapy for treatment of cancer-related symptoms (eg, localized bone pain) is allowed during study treatment at the discretion of the investigator, provided this is not indicative of disease progression, in which case the subject should be discontinued.
- Subjects may receive physiologic replacement doses of glucocorticoids (up to the equivalent of 10 mg daily prednisone) as maintenance therapy.
- Maintenance hormonal therapies are allowed in subjects with a history of breast or prostate cancer.
- Somatostatin analogs (SSA) may be used for symptom control as appropriate.
- As a precautionary measure, it is recommended that subjects avoid prolonged exposure to ultraviolet (UV) light, wear protective clothing and sunglasses, and use UV-blocking topical preparations while taking CC-90011.
- Subjects may receive authorized or approved SARS-CoV-2 vaccines while continuing on study treatment at the discretion of the Investigator.
- Treatment of active SARS-CoV-2 infections or high risk exposures, including use of investigational therapies, is allowed and should be discussed with the Sponsor's study physician.

8.2. 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 while the subject is on the study. If such treatment is required the subject must be discontinued from the study. Treatment with immunosuppressive agents is not allowed while the subject is on the study. If such treatment is required the subject must be discontinued from the study.

Treatment with chronic, therapeutic dosing of anti-coagulants (eg, warfarin, low molecular weight heparin, Factor Xa inhibitors, thrombin antagonists) is not allowed. Short-term,

prophylactic dosing of anticoagulants may be considered in subjects if medically indicated (eg, hospitalized subjects, post-operatively) under careful consideration by the Investigator.

Since drug-drug interactions have not been investigated in clinical studies; and in vitro studies have shown that CC-90011 is primarily metabolized by CYP3A4/5, drugs that are known strong inducers or inhibitors of these enzymes should not be co-administered with CC-90011. If use of one of these drugs is necessary, the risks and benefits should be discussed with the Sponsor's study physician prior to its concomitant use with CC-90011. Grapefruit juice and St. John's Wort should also be avoided during study treatment.

Examples of these drugs are (not inclusive):

- CYP3A4/5 inhibitors: atazanavir, clarithromycin, indinavir, itraconazole (allowed during DDI evaluation period in Part D), ketoconazole, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telithromycin and voriconazole.
- CYP3A4/5 inducers: rifampicin (allowed during DDI evaluation period in Part C), apalutamide, carbamazepine, enzalutamide and phenytoin.

A more exhaustive list of CYP inhibitors and inducers of potential clinical relevance is provided at the following link:

https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers#transporter.

Administration of investigational SARS-CoV-2 vaccines is not allowed during the study. Live vaccines are prohibited during the study treatment. In addition, the administration of live SARS-CoV-2 vaccine is prohibited up to 14 days prior to initiation of treatment.

Treatment of active SARS-CoV-2 infections or high risk exposures, including use of investigational therapies, is allowed and should be discussed with the Sponsor's study physician.

8.2.1. Medications to be used with caution

Proton pump inhibitors should be avoided, if possible, in the G2 NENs/NETs, SCLC, and other NEC subjects due to a possible effect on the biomarkers. If clinically appropriate, subjects should be changed to a H2 antagonist at least 7 days prior to the first dose.

In view of the potential for thrombocytopenia, NSAIDS and aspirins should be avoided. Based on the experience from part A, there has not been any noticeable interference/safety concern with the concomitant use of Omeprazole, NSAID or aspirin when clinically indicated. If use of one of these drugs is necessary, the risks and benefits should be discussed with the Sponsor's study physician prior to its concomitant use with CC-90011. If possible and paracetamol should be administered instead of NSAIDS and aspirins.

9. STATISTICAL CONSIDERATIONS

9.1. Overview

Part A and Part B

The primary objectives of this study are to determine the safety, tolerability, and MTD of CC- 90011 when administered orally once a week for 4 weeks (28-day Cycle) to adult subjects with advanced unresectable R/R solid tumors (including G2 NENs/NETs, SCLC, and other NECs) and R/R NHL. The secondary objectives are to make a preliminary assessment of the antitumor activity of CC-90011, and to determine its PK characteristics.

Part C and Part D

The primary objectives of the DDI evaluation periods are:

- To evaluate the effect of rifampicin, a strong cytochrome P450 (CYP) 3A and P-glycoprotein (P-gp) inducer, on the PK of CC-90011 (Part C) and,
- To evaluate the effect of itraconazole, a strong CYP3A and P-gp inhibitor on the PK of CC-90011 (Part D).

The secondary objectives of the DDI evaluation periods are:

- To characterize the PK parameters of a single dose of CC-90011 alone and in combination with rifampicin (Part C) or itraconazole (Part D) and,
- To assess the safety and tolerability of a single dose of CC-90011 alone and in combination with rifampicin (Part C) or itraconazole (Part D)

Data summaries/statistical analyses will be performed by study part (Part A or B), dose schedule, dose level (Part A), tumor cohort (Part B), and study period (DDI period/CC-90011 treatment period) in Part C and Part D as applicable.

9.2. Study Population Definitions

The study population definitions are as follows:

- Enrolled Population – All subjects who meet inclusion/exclusion criteria.
- Treated Population – All subjects who enroll and receive at least one dose of CC-90011.
- Efficacy Evaluable (EE) Population – All subjects who enroll in the study, meet eligibility criteria, complete at least one cycle of CC-90011 (taking at least 75% of assigned doses), and have baseline and at least one valid post-baseline tumor assessment.
- Pharmacokinetic (PK) Evaluable Population – all subjects who enroll and receive at least one dose of CC-90011 and have at least one measurable concentration of CC-90011.

- DDI Evaluable Population (only Parts C and D) – all subjects who enroll and complete both periods in Parts C or D, and have adequate number of blood samples collected for assessment of primary PK endpoints.
- Biomarker Evaluable (BE) Population – all subjects who enroll, receive at least one dose of study drug, and have at least one biomarker assessment, excluding disqualified assessments.

9.3. Sample Size and Power Considerations

During Part A of the study an adaptive Bayesian logistic regression (BLR) model (with 2 parameters) guided by the escalation with overdose control (EWOC) principle will be for dose escalation as described in Section 7.2.2. No formal statistical power calculations to determine sample size were performed for this study. The actual number of subjects will depend on the number of dose levels/cohorts that are tested. However, the anticipated number of subjects will be approximately 55.

After the MTD/RP2D is determined from Part A, Part B will enroll 3 selected cohorts of advanced low/intermediate-grade lung NETs, NEPCs and R/R NHL (MZL, including EMZL, SMZL, NMZL and histologic transformation of MZL) with up to 10-20 evaluable subjects for each cohort.

For Part B, sample sizes are not determined based on power calculation but rather on clinical, empirical and practical considerations traditionally used for exploratory studies of this kind. During the Part B dose expansion, at least 10-14 efficacy evaluable subjects for each tumor cohort will initially be accrued. The tumor cohort will be expanded to approximately 10-20 subjects if a responder or SD of 4 months or longer is observed.

Parts C and D

The sample size estimation is based on the observed dose- response association of CC-90011 with thrombocytopenia, an on-target, completely reversible and clinically manageable DLT. In the CC-90011-SCLC-001 study in 1 L ES SCLC patients, a 40 mg QW dose of CC-90011 in combination with chemotherapy (Cisplatin/Etoposide) was identified as the RP2D based on the incidence of thrombocytopenia, thus providing a 2-fold no-effect boundary to the 20 mg dose of CC-90011 selected for Part D (itraconazole DDI).

In the preliminary population pharmacokinetic (PPK) analysis of study ST-001 Part A data, residual variability was estimated to be ~30%. Also, a preliminary PBPK model was developed for prediction of CC-90011 DDI with itraconazole, which predicted a geometric mean ratio (GMR) of 4.7 for $AUC_{0-\infty}$ parameter between treatments ("CC-90011+ itraconazole"/ "CC-90011"). Using a conservative intra-subject SD of 0.5 and model predicted GMR of 4.7 for $AUC_{0-\infty}$, a sample size of 6 and 8 DDI evaluable subjects in Part D would achieve 81% and 92% power, respectively, to reject null hypothesis that the geometric mean ratio is less than or equal to 2. The calculation used a 1-sided paired t-test at significance level of 0.05. Based on these calculations, sample size of 6 to 8 DDI evaluable subjects is considered adequate (>80% power) for Cohort D.

Six (6) to 8 DDI evaluable subjects enrolled in Part C (rifampicin DDI) are also expected to provide adequate precision in the comparison of PK parameters. The precision is calculated for

different estimates of intra-subject standard deviation (SD) on the natural log scale and sample size (Table 12). The precision represents the width of the 90% CI of the geometric mean ratios on the original scale.

The subjects for Parts C and D will be replaced if not DDI evaluable.

Table 12: Precision and Intrasubject Standard Deviation

Sample Size	Precision				
	Intra-SD = 0.2	**Intra-SD = 0.3**	**Intra-SD = 0.4**	**Intra-SD = 0.5**	**Intra-SD = 0.6**
n = 6	26.2%	41.8%	59.3%	78.9%	101.0%
n = 7	23.1%	36.6%	51.5%	68.1%	86.5%
n = 8	20.9 %	32.9 %	46.1 %	60.6 %	76.5 %
n = 10	17.8 %	27.9 %	38.8 %	50.7 %	63.5 %
n = 12	15.8 %	24.6 %	34.1 %	44.3 %	55.3 %
n = 14	14.3 %	22.2 %	30.7 %	39.7 %	49.4 %
n = 16	13.2 %	20.4 %	28.1 %	36.3 %	45.0%

Abbreviations: n = number of subjects; SD = standard deviation.

Although the target sample size of 8 DDI evaluable subjects is planned for each of the Cohorts C and D, the enrollment may be stopped when a sample size of 6 DDI evaluable subjects is reached for each cohort.

9.4. Background and Demographic Characteristics

The baseline characteristics of subjects will be summarized by study part (Part A or B), dose schedule, dose level (Part A), tumor cohort (Part B), and study period (DDI period/CC-90011 treatment period) in Part C and Part D as applicable. The age, weight, height and other continuous demographic and baseline variables will be summarized using descriptive statistics. Performance status, gender, race and other categorical variables will be summarized with frequency tabulations. Medical history data will be summarized using frequency tabulations by system organ class and preferred term.

9.5. Subject Disposition

Subject disposition (analysis population allocation, on-going, discontinued, along with primary reason) from treatment and study will be summarized using frequency and percent. A summary of subjects enrolled by site will be provided. Protocol violations will be summarized using frequency tabulations. Supportive corresponding subject listings will also be provided.

9.6. Efficacy Analysis

Efficacy analyses will be based on the treated population by dose cohort in Part A, tumor type in Part B, and CC-90011 treatment period in Parts C and D and include summaries of clinical benefit rate (CBR), objective response rate (ORR), duration of response or stable disease,

progression-free survival (PFS), and OS by dose cohort and dosing schedule (Part A) or tumor type and dosing schedule (Part B), and treatment period in Parts C and D. Tumor response (CR, PR, SD, PD, or inevaluable) will be assessed by investigators according to Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1, mRECIST for HCC and NEHCC, PCWG3 for PC and NEPC and the Lugano Classification criteria for NHL. The CBR is defined as tumor responses (as assessed by the Investigators) of CR, PR and durable SD (SD of ≥ 4 months duration). The ORR is defined as the percent of subjects whose best response is CR or PR. When SD is the best response, it must be documented radiographically at least once after study entry after a minimal interval of 8 weeks from first dose (ie, coincident with the first post baseline response assessment time point minus assessment window). If the minimal time for a best response of SD is not met, the subject's best response will depend on the outcome of subsequent assessments. For example, a subject who exhibits SD at first assessment (where the first assessment does not meet minimal duration criteria for SD) and PD at the second assessment, would be classified as having a best response of PD. A subject lost to follow-up after the first SD assessment would be considered non-evaluable, if the minimal duration criteria for SD were not met.

Two-sided 95% Clopper-Pearson exact confidence intervals will be provided for ORR and CBR estimates. Similar analyses will be performed to include those subjects with confirmed responses as well as for the Efficacy Evaluable population.

For subjects with best response of CR or PR, duration of response is measured from the time when criteria for CR/PR are first met (whichever is first recorded) until the first date at which progressive disease is objectively documented. For subjects with best response of SD, duration of SD is measured from the first dose date until the criteria for progression are met. If progression is not documented prior to CC-90011 discontinuation, duration of overall response, and duration of SD will be censored at the date of the last adequate tumor assessment.

Duration of response/SD based on investigators' assessments will be summarized by descriptive statistics (mean, standard deviation, median, minimum and maximum) for the treated population. Except for medians, which will be calculated based on both observed and censored values using the Kaplan-Meier method, all other statistics (mean, standard deviation, minimum and maximum) will be calculated based on observed values only.

Progression-Free Survival (PFS) is defined as the time from the first dose of CC-90011 to the first occurrence of disease progression or death from any cause. Subjects who neither progress nor die at a data cutoff date will be censored at the date of their last adequate tumor assessment. The PFS will be summarized using descriptive statistics (mean, standard deviation, median, minimum and maximum) for the treated population. Except for the median, which will be calculated based on both observed and censored values using the Kaplan-Meier method, all other statistics (mean, standard deviation, minimum and maximum) will be calculated based on observed values only.

Overall Survival (OS) is measured as the time from the first dose of CC-90011 to death due to any cause and will be analyzed in a manner similar to that described for PFS.

The assessments of serum neuroendocrine markers over time in neuroendocrine subjects will be summarized.

9.7. Safety Analysis

Adverse events, including treatment-emergent adverse events (TEAEs), laboratory assessments, vital signs, ECG results, ECOG performance status, LVEF assessments, physical examinations, vital signs, exposure to study treatment, assessment of concomitant medications, and pregnancy testing for females of childbearing potential will be summarized for the treated population by dose cohort in Part A, tumor type in Part B and study period (DDI period/CC-90011 treatment period) in Part C and Part D.

Adverse events observed will be classified using the Medical Dictionary for Regulatory Activities (MedDRA), Version 18.1 or higher, system organ class (SOC) and preferred term (PT). In the by-subject analysis, a subject having the same AE more than once will be counted only once. All adverse events will also be summarized by SOC, PT, and NCI CTCAE grade (Version 4.03). Adverse events leading to discontinuation of study treatment, those classified as Grade 3 or 4, study drug-related AEs, and SAEs (including deaths) will be tabulated separately. By-subject listings of all AEs, TEAEs, SAEs (including deaths), and their attribution will be provided.

Clinical laboratory results will be summarized descriptively by dose cohort (Part A) or tumor type (Part B), study period (Part C and Part D) and visit, which will also include a display of change from baseline. Shift tables demonstrating the changes (low/normal/high) from baseline to worst post-baseline laboratory value will be displayed in cross-tabulations by dose cohort (Part A). tumor type (Part B) or study period (Part C and Part D). Similar shift tables demonstrating the change of NCI CTCAE grades from baseline to the worst post-baseline severity grade during the treatment period will also be presented by dose cohort (Part A), tumor type (Part B) or study period (Part C and Part D) for applicable analytes. Listings of abnormal clinical laboratory data according to NCI CTCAE severity grades (if applicable), abnormal flags (low or high) and clinical significance of the latter will be provided.

Graphical displays (eg, “spaghetti” plots or box plots) will be provided for key laboratory analytes.

Descriptive statistics for vital signs, both observed values and changes from baseline, will be summarized by dose cohort (Part A), tumor type (Part B) or study period (Part C and Part D) and visit. Shift tables demonstrating the changes from baseline to the worst post-baseline value will be displayed in cross-tabulations by dose cohort (Part A), tumor type (Part B) or study period (Part C and Part D). Vital sign measurements will be listed by subject and by visit.

ECG parameters and changes from baseline will be summarized by dose cohort (Part A) or tumor type (Part B) and visit using descriptive statistics. Post-baseline abnormal QTc (both QTcF and QTcB) values will be summarized using frequency tabulations for the following 5 categories:

- QTc > 450 msec
- QTc > 480 msec
- QTc > 500 msec
- QTc increase from baseline > 30 msec
- QTc increase from baseline > 60 msec

Shift from baseline to worst post-baseline qualitative assessment of abnormality (ie, 'Normal', 'Abnormal, not clinically significant', and 'Abnormal, clinically significant' or 'Normal' and 'Abnormal') will be displayed in cross–tabulations by dose cohort (Part A) , tumor type (Part B) or study period (Part C and Part D). A listing of ECG parameters by subject, by visit will be provided.

9.8. Interim Analysis

No formal interim analysis is planned. Data will be reviewed by the SRC on an on-going basis.

9.9. Other Topics

9.9.1. Statistical Method for Dose Escalation (Part A only)

An adaptive BLRM guided by the escalation with EWOC principle will be used to make dose recommendations and estimate the MTD during the escalation phase of the study (refer to Appendix E for additional details).

The DLT relationship in the escalation part of the study will be described by the following Bayesian logistic regression model:

$$\log\left(\frac{p_j}{1-p_j}\right) = \log\alpha + \beta \cdot \log\left(\frac{d_j}{d^*}\right), \alpha > 0, \beta > 0$$

where p_j's are DLT rates at dose, d_j's are dose levels, d*=30 mg reference dose, α is odds of DLT at d*.

Prior Specifications

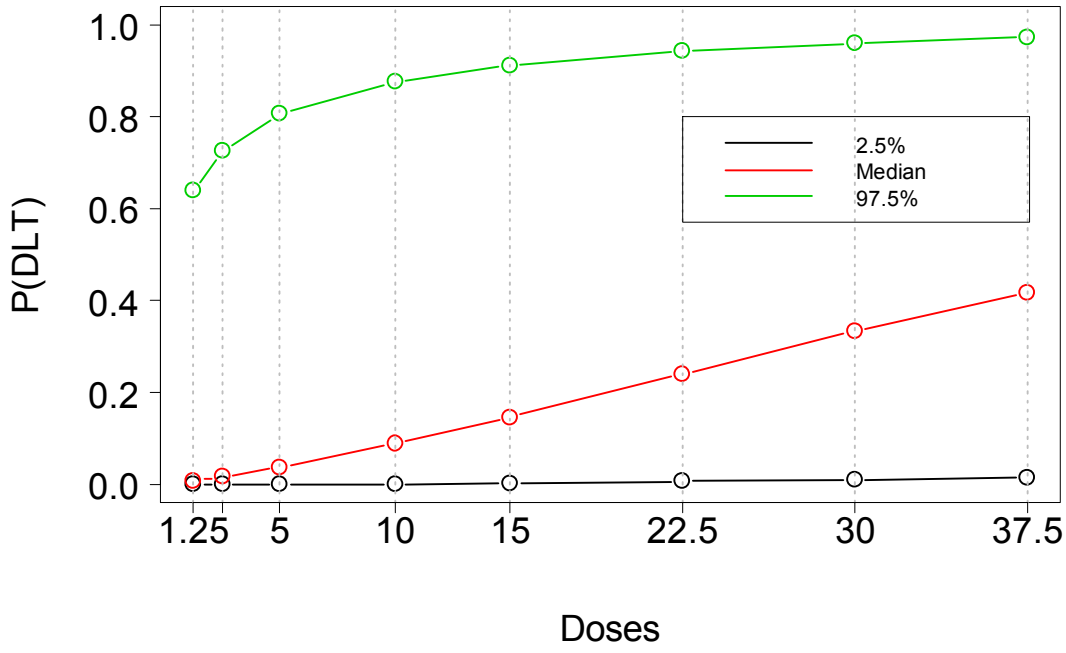
Prior for (log(α), log(β)):

A vague bivariate normal prior for the model parameters (log(α), log(β)) is elicited based on prior estimates (medians) from preclinical data and wide confidence intervals for the probabilities of a DLT at each dose. Prior MTD is assumed to be 30 mg based on preclinical data. The probability of DLT for the first dose is assumed to be low. The parameters of the prior distributions of model parameters are selected based on the method to construct weakly informative prior as described in Neuenschwander et al (2015) and are provided in Table 13. Figure 6 illustrates the resulting prior distribution of DLT rate derived from the prior parameters given in Table 13 .

Table 13: Prior Parameters for Bivariate Normal Distribution of Model Parameters

Parameters	Means	Standard Deviation	Correlation
log(α),log(β)	(-0.693, 0.205)	(2, 0.75)	0

Figure 6: Probability of DLT According to Prior Distribution



Dose Recommendation

The provisional dose levels are: 1.25 mg, 2.5 mg, 5 mg, 10 mg, 15 mg, 22.5 mg, 30 mg, and 37.5 mg.

It is however possible that the actual dose levels selected for the trial may be different from the provisional dose levels, based on emerging safety information.

After each cohort of subjects, the posterior distributions for the probabilities of a DLT rates at different dose levels are obtained. The results of this analysis are summarized in terms of the estimated probabilities that the true rate of DLT at each dose-level will have of lying in each of the following intervals:

- [0, 0.16) under-dosing
- [0.16, 0.33) targeted toxicity
- [0.33, 1.00] excessive toxicity

Following the principle of escalation with EWOC, after each cohort of subjects the recommended dose is the one with the highest posterior probability of the DLT rate falling in the target interval [16%, 33%) among the doses fulfilling EWOC, ie, it is unlikely (<25% posterior probability) that the DLT rate at the dose falls in the excessive toxicity interval.

Note that the dose that maximizes the posterior probability of targeted toxicity is the best estimate of the MTD, but it may not be an admissible dose according to the overdose criterion if the amount of data is insufficient. If vague prior information is used for the probabilities of DLT, in the early stages of the study this escalation procedure will reflect a conservative strategy.

The dose recommended by the adaptive Bayesian logistic model may be regarded as guidance and information to be integrated with a clinical assessment of the toxicity profiles observed at the time of the analysis in determining the next dose level to be investigated.

Details of the dose escalation and determination of the MTD are provided in Section 7.2.

9.9.2. Assessment of Pharmacokinetics

Parts A and B

Plasma PK parameters such as AUC, C_{max}, T_{max}, $t_{1/2}$, CL/F, and Vz/F of CC-90011 will be calculated by the noncompartmental analysis method from the plasma concentration-time profiles of CC-90011. Other PK parameters may be calculated as appropriate.

Summary statistics including number of subjects (N), mean, standard deviation (SD), coefficient of variation (CV%), geometric mean, geometric CV%, median, minimum, and maximum will be provided for CC-90011 concentration by nominal time point, study day, and dose cohort. Mean and individual plots of plasma concentrations will be presented in both original and semi-logarithmic scales. Summary statistics will also be provided for CC-90011 PK parameters by study day and dose cohort and be presented in tabular form.

A population PK analysis for CC-90011 may be conducted to explore the inter-individual variability of plasma drug exposure and the contributing factors (covariates). The relationship between CC-90011 dose, plasma exposures, and selected clinical endpoints (eg., measures of toxicities, effectiveness, and/or biomarkers) will be explored. The population PK model, in combination with the knowledge on exposure-response, may be used to assist identification of the dosing regimen for Part B or Phase 2 studies.

Parts C and D

Plasma CC-90011 concentration will be listed and summarized descriptively (N, mean, SD, coefficient of variation [CV%], geometric mean, geometric CV%, minimum, median, and maximum) by Part and Period for both PK evaluable and DDI evaluable subjects. Individual plots of plasma CC-90011 concentration vs. time will be provided for all PK evaluable subjects and mean plots of CC-90011 plasma concentration vs. time will be provided for both PK evaluable and DDI evaluable subjects by Part and Period.

Plasma CC-90011 PK parameters will be calculated using noncompartmental methods. The following PK parameters will be estimated for CC-90011 in Parts C and D:

- Cmax
- Time to Cmax (Tmax)
- Area under the plasma concentration-time curve (AUC) from time zero to the last quantifiable concentration (AUC0-t)
- AUC from time zero extrapolated to infinity (AUC0-∞)
- AUC from time 0 to 168 hours postdose (AUC0-168)
- Terminal elimination half-life (t1/2)
- Apparent total plasma clearance after oral administration (CL/F)

- Apparent total volume of distribution when dosed orally (Vz/F), based on the terminal phase

The PK parameters will be listed and summarized descriptively (N, mean, SD, coefficient of variation [CV%], geometric mean, geometric CV%, minimum, median, and maximum) by Part and Period for both PK evaluable and DDI evaluable subjects.

Statistical analyses will be conducted using DDI evaluable subjects. To compare PK parameters, an ANOVA model with treatment as a fixed effect and subject as a random effect will be performed separately for each Part on the natural log transformed Cmax and AUC. The geometric means along with ratios of the geometric means (expressed as a percentage) and associated 90% CIs will be presented for the following PK parameter comparisons.

- Part C: CC-90011 plus rifampicin (test) versus CC-90011 alone (reference)
- Part D: CC-90011 plus itraconazole (test) versus CC-90011 alone (reference)

For Tmax, Wilcoxon signed-rank test, Hodges-Lehmann estimate, and its 90% CI will be calculated for the median difference between treatments.

Additionally, exploratory assessments will be conducted to (1) Identify metabolites of CC-90011 in urine, as well as to determine the urinary excretion of CC-90011 (Period 1 of Parts C and D), and (2) To explore the plasma PK of metabolite CC7108272 (M1) and possibly other metabolites after administration of CC-90011 on D1 (Parts C and D) and on D22 (Part C) and on D18 (Part D). Results of all exploratory PK assessments will be reported separately from this CSR.

9.9.3. Assessment of Pharmacodynamics

Descriptive statistics (N, mean, SD, median, min, and max) will be provided for baseline, post-baseline values, and changes from baseline or percent change from baseline for biomarkers including neuroendocrine markers by dose cohort (Part A) or tumor type (Part B) and visit. Subjects' biomarker results over time will be plotted. Comparison of biomarker levels before and during treatment will be performed by Wilcoxon signed rank test. If sufficient and valid results from biomarker assays can be obtained, the relationship between percent changes in biomarker levels and clinical endpoints including ORR and CBR will be explored. The population PK model, in combination with the knowledge on exposure-response, may be used to assist in identification of the dosing regimen for Part B or Phase 2 studies.

10. ADVERSE EVENTS

10.1. Monitoring, Recording and Reporting of Adverse Events

An AE 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 10.3), regardless of etiology. Any worsening (ie, any clinically significant adverse change in the frequency or intensity of a pre-existing 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 7.2.13 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 sequela 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.

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-90011 overdose. Actual treatment should depend on the severity of the clinical situation and the judgment and experience of the treating physician.

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 CC-90011 as well as those SAEs made known to the Investigator at any time thereafter that are suspected of being related to CC-90011. For Part C and Part D, all AEs will be recorded by the Investigator from the time the subject signs informed consent until 28 days after the last dose of CC-90011, or rifampicin or itraconazole as well as those SAEs made known to the Investigator at any time thereafter that are suspected of being related to CC-90011, or to rifampicin or itraconazole. All AEs and SAEs will be recorded on the AE page of the CRF and in the subject's source documents. Refer to Section 10.5 for instructions on how to report SAEs to Drug Safety.

Subjects will be followed for all SAEs and all AEs (SAEs and non-serious AEs) associated with confirmed or suspected SARS-CoV-2 infection until resolution, the condition stabilizes, the event is otherwise explained, the event is deemed irreversible, the participant is lost to follow-up (as defined in Section 6.3), or for suspected cases, until SARS-CoV-2 infection is ruled-out.

10.2. Evaluation of Adverse Events

A qualified Investigator will evaluate all adverse events as to:

10.2.1. Seriousness

An SAE is any AE occurring at any dose that:

- Results in death;
- Is life-threatening (ie, in the opinion of the Investigator, the subject is at immediate risk of death from the AE);
- Requires subject hospitalization or prolongation of existing hospitalization (hospitalization is defined as subject 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 (eg, 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 (ie, planned prior to start 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 pre-existing condition, unrelated to the studied indication, that has not worsened from baseline.
- 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 the IP, action taken regarding the IP, and outcome.

10.2.2. 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 the Common Terminology Criteria for Adverse Events (CTCAE, Version 4.03); http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40

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.

10.2.3. Causality

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

Not suspected:	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:	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 CC-90011 that has not been manufactured or provided by Celgene, please provide the name of the manufacturer when reporting the event.

10.2.4. Duration

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

10.2.5. Action Taken

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

10.2.6. 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 recovered (returned to baseline), recovered with sequelae, or death (due to the SAE).

10.3. 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 CC-90011 dose, or any other therapeutic intervention; or

- is judged to be of significant clinical importance, eg, one that indicates a new disease process and/or organ toxicity, or is an exacerbation or worsening of an existing condition.

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 (eg, record thrombocytopenia rather than decreased platelets).

10.4. Pregnancy

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

The exposure of any pregnant female (eg, caregiver, pharmacist, study coordinator or monitor) to CC-90011 is also an immediately reportable event.

10.4.1. Females of Childbearing Potential:

Pregnancies and suspected pregnancies (including elevated β-hCG or positive pregnancy test in a female subject of childbearing potential regardless of disease state) occurring while the subject is on study treatment, or within 45 days of the subject's last dose of CC-90011(or within 45 days of the last dose of CC-90011,within 1 week of last dose of rifampicin or within 2 months of the last dose of itraconazole, whichever is latest, in Part C and Part D), are considered immediately reportable events. Investigational product is to be discontinued immediately. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to Celgene Drug Safety immediately by email, phone or facsimile, or other appropriate method, using the Pregnancy Initial Report Form, or approved equivalent form.

The female subject should be referred to an obstetrician-gynecologist, preferably one experienced in reproductive toxicity for further evaluation and counseling. 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 (eg, 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 CC-90011 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.

10.4.2. Male Subjects

If a female partner of a male subject taking CC-90011, rifampicin or itraconazole becomes pregnant, the male subject taking IP should notify the Investigator, and the pregnant female partner should be advised to call her healthcare provider immediately. This includes pregnancies occurring within 105 days of the male subject's last dose of CC-90011 and within 1 week after last dose of rifampicin or itraconazole. Where applicable, the CC-90011 may need to be discontinued in the male subject, but may be resumed later at the discretion of the Investigator and Sponsor's study physician.

10.5. Reporting of Serious Adverse Events

Any AE that meets any criterion requires reporting as an SAE within 24 hours of the Investigator's knowledge of the event. This instruction pertains to initial SAE reports as well as any follow-up reports.

This requirement applies to all SAEs (regardless of relationship to CC-90011, rifampicin or itraconazole) that occur during the study (from the time the subject signs informed consent until 28 days after the last dose of CC-90011, rifampicin or itraconazole, whichever is the latest) or any SAE made known to the Investigator at any time thereafter that are suspected of being related to study treatment. Serious adverse events occurring prior to treatment (after signing the ICF) will be captured.

The SAE is reported directly to Celgene Drug Safety by facsimile, or other appropriate method using the SAE Report Form or approved equivalent form. 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, results of the autopsy report and/or 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. Queries pertaining to SAEs will be communicated from Celgene Drug Safety to the site via facsimile or electronic mail. Urgent queries (eg, missing causality assessment) may be handled by phone.

Where required by local legislation, the Investigator is responsible for informing the Institutional Review Board/Ethics Committee (IRB/EC) 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/EC.

10.5.1. 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 (eg, missing causality assessment) may be handled by phone.

10.5.2. Death Reports

Deaths due to progressive disease will not be reported as an SAE unless considered related to IP (if assessed as lack of efficacy by the investigator). Any sign, symptom, or manifestation of progressive disease that meet any of the seriousness criteria and result in death will be reported as individual SAEs. Any other AEs leading to death should be reported as an SAE.

10.6. 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-90011 based on the Investigator Brochure.

For countries within the European Economic Area (EEA), Celgene or its authorized representative will report in an expedited manner to Regulatory Authorities and Ethics Committees concerned, suspected unexpected serious adverse reactions (SUSARs) in accordance with Directive 2001/20/EC and the Detailed Guidance on collection, verification and presentation of adverse reaction reports arising from clinical trials on investigational products for human use (ENTR/CT3) and also in accordance with country-specific requirements.

For the purpose of regulatory reporting in the EEA, Celgene Drug Safety will determine the expectedness of events suspected of being related to rifampicin or itraconazole, based on the summary of product characteristics (SmPC).

Celgene or its authorized representative shall notify the Investigator of the following information:

- Any AE suspected of being related to the use of CC-90011 in this study or in other studies that is both serious and unexpected (eg, SUSAR);
- Any finding from tests in laboratory animals that suggests a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity.

Where required by local legislation, the Investigator shall notify his/her IRB/EC 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/EC (refer to Section 14.3 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.

11. DISCONTINUATIONS

11.1. Treatment Discontinuation

The following events are considered sufficient reasons for discontinuing a subject from the investigational product(s):

- Adverse Event
- Withdrawal by subject
- Lack of efficacy
- Physician decision
- Protocol violation
- Progressive disease
- Death
- Lost to follow-up
- Other (to be specified on the CRF)

The reason for discontinuation of treatment should be recorded in the CRF and in the source documents. In case of treatment discontinuation following an adverse event, every effort will be made to follow subjects for 28 days after the last dose of CC-90011.

The decision to discontinue a subject from treatment 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's study physician and forward appropriate supporting documents for review and discussion.

Note: Any laboratory result, such as neutropenia, thrombocytopenia, other abnormalities, etc., which are felt to be clinically significant should be followed until return to baseline or Grade 1.

11.2. Study Discontinuation

The following events are considered sufficient reasons for discontinuing a subject from the study:

- Screen failure
- Withdrawal by subject
- Lack of efficacy
- Physician decision
- Protocol violation
- Progressive disease
- Death
- Lost to follow-up

- Other (to be specified on the CRF)

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

12. EMERGENCY PROCEDURES

12.1. Emergency Contact

In emergency situations, the Investigator should contact the responsible Sponsor's study 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 Sponsor's study 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 Sponsor's study physician, 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 Sponsor's study physician(s) or Medical Monitor or designee for emergency calls.

12.2. Emergency Identification of Investigational Products

This is an open-label study; therefore, CC-90011 will be identified on the package labeling.

Subjects enrolled in this study will be issued an identification card showing the name of this study and an emergency contact number. This can be used by health care professionals seeking emergency information about a subject's participation in the study.

13. REGULATORY CONSIDERATIONS

13.1. 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 Council for Harmonisation (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/EC 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.

13.2. 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, including obligations of confidentiality of Celgene information. 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 form (ICF) and are screened for entry into the study. Subjects who fail screening must have the reason(s) recorded in the subject's source documents.

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 (eg, medical records, office charts, hospital charts, and study-related charts) for source data verification. The Investigator must ensure timely and accurate completion of CRFs and queries.

The information contained in the protocol and amendments (with the exception of the information provided by Celgene on public registry websites) is considered Celgene confidential information. Only information that is previously disclosed by Celgene on a public registry website may be freely disclosed by the Investigator or its institution, or as outlined in the Clinical Trial Agreement. Celgene protocol, amendment and IB information is not to be made publicly available (for example on the Investigator's or their institution's website) without express written approval from Celgene. Information proposed for posting on the Investigator's or their institution's website must be submitted to Celgene for review and approval, providing at least 5 business days for review.

At the time results of this study are made available to the public, Celgene will provide Investigators with a summary of the results that is written for the lay person. The Investigator is responsible for sharing these results with the subject and/or their caregiver as agreed by the subject.

13.3. 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 ICF 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 ICF must be revised. Study subjects participating in the treatment phase of the study when the amended protocol is implemented must be re-consented with the revised version of the ICF. Only substantial protocol amendments will require revision of the ICF and re-consenting of subjects in active treatment. Once a subject has been discontinued from study drug and is undergoing follow up, re-consenting of subjects should be sought but if the subject declines or is unable to sign, this shall not constitute a deviation from protocol, especially if the amendment(s) contain no safety implication for the particular subject. The revised ICF signed and dated by the study subject and by the person consenting the study subject must be maintained in the Investigator's study files and a copy given to the study subject.

13.4. 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 ICF, it is the responsibility of the Investigator to obtain such permission in writing from the appropriate individual.

13.5. Protocol Amendments

Any amendment to this protocol must be approved by the Sponsor's study physician/Medical Monitor. Amendments will be submitted to the IRB/EC for written approval. Written approval must be obtained before implementation of the amended version occurs. The written signed approval from the IRB/EC 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/IEC approval but will be submitted to the IRB/IEC for information purposes.

In the event of a substantial amendment in the study, the corresponding amendment will be submitted to the Competent Regulatory Authority in each country and will not be implemented until it has been approved.

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

Before the start of the study, the study protocol, ICF, and any other appropriate documents will be submitted to the IRB/EC 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/EC and their occupation and qualifications. If the IRB/EC 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/EC 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/EC 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 ICF should also be revised.

The Investigator must keep a record of all communication with the IRB/EC and, if applicable, between a Coordinating Investigator and the IRB/EC. 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/EC prior to use.

13.7. Ongoing Information for Institutional Review Board/ Ethics Committee

If required by legislation or the IRB/EC, the Investigator must submit to the IRB/EC:

- 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.

13.8. Termination of the Study

Celgene reserves the right to terminate this study prematurely at any time for reasonable medical or administrative reasons. Any premature discontinuation will be appropriately documented according to local requirements (eg, IRB/EC, 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. DATA HANDLING AND RECORDKEEPING

14.1. 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; photographs of clinical lesions; 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 CRFs or CD-ROM.

14.2. Data Management

Data will be collected via CRF and entered into the clinical database per Celgene SOPs. 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 database. An audit trail within the system will track all changes made to the data.

14.3. Record Retention

Essential documents must be retained by the Investigator according to the period of time outlined in the clinical trial agreement. The Investigator must retain these documents for the time period described above or according to local laws or requirements, whichever is longer. Essential documents include, but are not limited to, the following:

- Signed ICFs for all subjects
- Subject identification code list, screening log (if applicable), and enrollment log
- Record of all communications between the Investigator and the IRB/EC
- Composition of the IRB/EC
- 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 Investigator must notify Celgene if he/she wishes to assign the essential documents to someone else, remove them to another location or is unable to retain them for a specified period. The Investigator must obtain approval in writing from Celgene prior to destruction of any records. If the Investigator is unable to meet this obligation, the Investigator 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. Investigator or institution should take measures to prevent accidental or premature destruction of these documents.

15. 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 SOPs.

15.1. 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 Investigators' 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 details describing strategy, including definition of study critical data items and processes (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the 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.

15.2. 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 Investigator is 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 IRB/ECs, regulatory authorities (eg, FDA, EMA, Health Canada) and company authorized representatives. The Investigator should make every effort to be available for the audits and/or inspections. If the Investigator is contacted by any regulatory authority regarding an inspection, he/she should contact Celgene immediately.

15.3. Product Quality Complaint

Issues that call into question IMP safety, purity, potency, quality and identity (e.g., evidence of suspected tampering of product) must be reported as soon as possible to your study Clinical Trial Monitor and/or Clinical Trial Manager or designee. Report an issue or concern with all BMS supplied IMP, NIMP or AxMP suspected to have occurred before the product was transferred to the responsibility of the investigational site (e.g., during manufacturing, packaging and labeling, storage, and/or distribution).

This includes suspected quality issues of components co-packaged with the drug, labelling, and IMP device/drug combination products, and medical devices.

In the event of a suspected product quality issue, the immediate action to be taken by site is to quarantine the affected product. Do not dispose of the product unless retention presents a risk to personnel (e.g., cytotoxic, risk of injury from broken glass or sharps). When reporting, provide as much product information as possible. Suspected IMP quality issues will be investigated and a response will be provided back to the investigational site.

16. PUBLICATIONS

As described in Section 13.2, all protocol- and amendment-related information, with the exception of the information provided by Celgene on public registry websites, is considered Celgene confidential information and is not to be used in any publications. Celgene protocol-related information proposed for use in a publication must be submitted to Celgene for review and approval, and should not be utilized in a publication without express written approval from Celgene, or as described in the Clinical Trial Agreement.

Celgene will ensure Celgene-sponsored studies are considered for publication in the scientific literature in a peer-reviewed journal, irrespective of the results. At a minimum, this applies to results from all Phase 3 clinical studies, and any other study results of significant medical importance. This also includes results relating to investigational medicines whose development programs have been discontinued.

Study results may also be presented at one or more medical congresses, and may be used for scientific exchange and 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.

Eligibility for external authorship, as well as selection of first authorship, will be based on several considerations, including, but not limited to, contribution to protocol development, study recruitment, data quality, participation in data analysis, participation in study steering committee (when applicable) and contribution to abstract, presentation and/or publication development.

17. REFERENCES

Adamo A, Sese B, Boue S, Castano J, Paramonov I, Barrero M, et al. LSD1 regulates the balance between self-renewal and differentiation in human embryonic stem cells. Nat. Cell Biol. 2011;13:652–659.

Ambrosio S, Amente S, Saccà CD, Capasso M, Calogero RA, Lania L, et al. LSD1 mediates MYCN control of epithelial-mesenchymal transition through silencing of metastatic suppressor NDRG1 gene. Oncotarget. 2017 Jan 17;8(3):3854-3869.

Amente S, Bertoni A, Morano A, Lania L, Avvedimento EV, Majello B, et al. LSD1-mediated demethylation of histone H3 lysine 4 triggers Myc-induced transcription. Oncogene 2010;29:3691-3702.

Amente S, Lania L, Barbara M. The histone LSD1 demethylase in stemness and cancer transcription programs. Biochimica et Biophysica Acta (BBA) - Gene Regulatory Mechanisms 2013; 1829 (10):981–986.

Barski A, Cuddapah C, Cui K, Roh TY, Schones DE, Wang Z, et al. High-resolution profiling of histone methylations in the human genome. Cell 2007;129:823-837.

Basso K, Dalla-Favera R. BCL6: master regulator of the germinal center reaction and key oncogene in B cell lymphomagenesis. Adv Immunol. 2010;105:193-210. Review.

Benson AB, Ajani JA, Catalano RB, Engkeling C, Kornblau SM, Martenson JA Jr, et al. Recommended guidelines for the treatment of cancer treatment-induced diarrhea. J Clin Oncol 2004; 22(14):2918-26.

Brambilla E, et al. WHO Classification of Tumours of the Lung, Pleura, Thymus and Heart 2015;63-68. IARC

Cancer Research UK www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/lung-cancer/incidence#heading-Zero)

Campbell AM, Campling B, Algazy K, El-Deiry W. Clinical and Molecular Features of Small cell Lung Cancer. Cancer Biology & Therapy 2002;1(2):105-112.

Caplin ME, Baudin E, Ferolla P, et al. Pulmonary neuroendocrine (carcinoid) tumors: European Neuroendocrine Tumor Society expert consensus and recommendations for best practice for typical and atypical pulmonary carcinoid. Ann Oncol. 2015;26:1604–1620.

Cardenas MG, Yu W, Beguelin W, Teater MR, Geng H, Goldstein RL, et al. Rationally designed BCL6 inhibitors target activated B cell diffuse large B cell lymphoma. J Clin Invest. 2016 Sep 1;126(9):3351-62.

Chen C, Ge J, Lu Q, Ping G, Yang C, Fang X. Expression of Lysine-specific demethylase 1 in human epithelial ovarian cancer. J Ovarian Res. 2015; 8: 28.

Cheson BD, Fisher RI, Barrington SF, Cavalli F, Schwartz LH, Zucca E et al. Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification. J. Clin Oncol. 2014;32(27):3059-68

Chi P, David Allis C, Wang GG. Covalent histone modifications –miswritten, misinterpreted and mis-erased in human cancers. Nat. Rev. Cancer 2010; 10(7):457-469.

Crabtree JS, Singleton CS, Miele L. Notch Signaling in Neuroendocrine Tumors. Front Oncol. 2016 Apr 14;6:94. eCollection 2016. Review.

Chung DC, Smith AP, Louis DN, Graeme-Cook F, Warshaw AL & Arnold A 1997a Analysis of the retinoblastoma tumour suppressor gene in pancreatic endocrine tumours. Clinical Endocrinology 47 523–528.

Ekeblad S, Sundin A, Janson ET, Welin S, Granberg D, Kindmark H, Dunder K, Kozlovacki G, Orlefors H, Sigurd M. Temozolomide as monotherapy is effective in treatment of advanced malignant neuroendocrine tumors. Clin Cancer Res. 2007;13(10):2986–2991.

Elmeliegy M, Vourvahis M, Guo C, Wang DD. Effect of P-glycoprotein (P-gp) Inducers on Exposure of P-gp Substrates: Review of Clinical Drug–Drug Interaction Studies. Clin Pharmacokinet. 2020; 59(6): 699–714

European Medicines Agency (EMA) Guideline on the investigation of drug interactions (CPMP/EWP/560/Rev.1 Corr.2**, 21 June 2012)

European Medicines Agency (EMA) Committee for Medicinal Products for Human Use (CHMP) Guideline on Clinical Trials in small populations. CHMP/EWP/83561/2005/Corr. London, 2006.

Fisseler-Eckhoff A, Demes M. Neuroendocrine tumors of the lung. Cancers (Basel). 2012;4:777–798.

Flossbach L, Antoneag E, Buck M, Siebert R, Mattfeldt T, Möller P, Barth TF. BCL6 gene rearrangement and protein expression are associated with large cell presentation of extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue. Int J Cancer. 2011 Jul 1;129(1):70-7. Food and Drug Administration/CDER. Guidance for industry: clinical drug interaction studies –cytochrome P450 enzyme- and transporter mediated drug interactions. Jan 2020.

Gustafsson BI, Kidd M, Chan A, Malfertheiner MV, Modlin IM. Bronchopulmonary neuroendocrine tumors. Cancer. 2008;113:5–21.

Haines RR, Barwick BG, Scharer CD, Majumder P, Randall TD, Boss JM. The Histone Demethylase LSD1 Regulates B Cell Proliferation and Plasmablast Differentiation. J Immunol. 2018 Nov 1;201(9):2799-2811.

Haines RR, Scharer CD, Lobby JL, Boss JM. LSD1 Cooperates with Noncanonical NF-κB Signaling to Regulate Marginal Zone B Cell Development. J Immunol. 2019 Sep 6.

Harris WJ, Huang X, Lynch JT, Spencer GJ, Hitchin JR, Li Y. The Histone Demethylase KDM1A Sustains the Oncogenic Potential of MLL-AF9 Leukemia Stem Cells. Cancer Cell 2012;21:473–487.

Hatzi K, Maria Nieves CV, Cerchietti L, Melnick A. The Histone Demethylase LSD1 Acts As a BCL6 Corepressor In Germinal Center B Cells[abstract]. 55th ASH Meeting 2013 Abstracts: abstract 781.

Hatzi K, Geng H, Doane AS, Meydan C, LaRiviere R, Cardenas M, et al.. Histone demethylase LSD1 is required for germinal center formation and BCL6-driven lymphomagenesis. Nat Immunol. 2019 Jan;20(1):86-96.

Hayami S, Kelly JD, Cho HS, Yoshimatsu M, Unoki M, Tsunoda T, et al. Overexpression of LSD1 contributes to human carcinogenesis through chromatin regulation in various cancers. Int. J. Cancer 2011;128:574–586.

Hoffmann I, Roatsch M, Schmitt ML, Carlino L, Pippel M, Sippl W, Jung M. The role of histone demethylases in cancer. Molecular Oncology 2012;6:683-703.

Huang J, Sengupta R, Espejo AB, Lee MG, Dorsey JA, Richter M, et al. p53 is regulated by the lysine demethylase LSD1. Nature 2007;449:105-180.

Itraconazole [Summary of Product Characteristics]. Available from: https://www.medicines.org.uk/emc/product/5914/smpc#gref

Jotatsu T, Yagishita S, Tajima K, Takahashi F, Mogushi K, Hidayat M, et al. LSD1/KDM1 isoform LSD1+8a contributes to neural differentiation in small cell lung cancer. Biochem Biophys Rep. 2016 Dec 1;9:86-94. doi: 10.1016/j.bbrep.2016.11.015. eCollection 2017 Mar.

Jin Y, Huo B, Fu X, Hao T, Zhang Y, Guo Y, Hu X. LSD1 collaborates with EZH2 to regulate expression of interferon-stimulated genes. Biomed Pharmacother. 2017 Apr;88:728-737.

Kahl P, Gullotti L, Heukamp LC, Wolf S, Friedrichs N, Vorreuther R, et al. Androgen receptor coactivators lysine-specific histone demethylase 1 and four and a half LIM domain protein 2 predict risk of prostate cancer recurrence. Cancer Res 2006;66:11341-11347.

Kauffman EC, Robinson BD, Downes MJ, Powell LG, Lee MM, Scherr DS, et al. Role of androgen receptor and associated lysine-demethylase coregulators, LSD1 and JMJD2A, in localized and advanced human bladder cancer. Mol. Carcinogen. 2011;50:931–944.

Klimstra D.S. Neuroendocrine neoplasms of the pancreas. WHO Classification of Tumours of the Digestive System IARC 2010:322-326.

Koch LK, Zhou H, Ellinger J, Biermann K, Holler T, von Rucker A, et al. Stem cell marker expression in small cell lung carcinoma and developing lung tissue. Human pathology 2008; 39(11):1597-1605.

Laga AC, Lai CY, Zhan Q, Huang SJ, Velazquez EF, Yang Q, et al. Expression of The Embryonic Stem Cell Transcription Factor SOX2 in Human Skin. Relevance to Melanocyte and Merkel Cell Biology. Am J Pathol. 2010; 176(2): 903–913.

Lencioni R, et al. Modified RECIST (mRECIST) Assessment for Hepatocellular Carcinoma. Semin. Liver Dis. 2010;30:52-60

Llovet JM, et al. Prognosis of hepatocellular carcinoma: The BCLC staging classification. Semin Liver Dis1999; 19:329-338.

Li Y, Wang Z, Shi H, Li H, Li L, Fang R, et al. HBXIP and LSD1 Scaffolded by lncRNA Hotair Mediate Transcriptional Activation by c-Myc. Cancer Res. 2016 Jan 15;76(2):293-304.

Lim S, Janzer A, Becker A, Zimmer A, Schule R, Buettner R, Kirfel J. Lysine-specific demethylase 1 (LSD1) is highly expressed in ER-negative breast cancers and a biomarker predicting aggressive biology. Carcinogenesis 2010;31(3):512-520.

Liu L, et al. Best Practices for the Use of Itraconazole as a Replacement for Ketoconazole in Drug–Drug Interaction Studies. J Clin Pharmacol. 2016;56(2):143-151

Lv T, Yuan D, Miao X, et al. Over-expression of LSD1 promotes proliferation, migration and invasion in non-small cell lung cancer. PLoS ONE 2012;7:e35065.

Lynch, JT, Harris, WJ, and Somervaille, TC (2012). LSD1 inhibition: a therapeutic strategy in cancer? Expert Opin. Ther. Targets 16, 1239–1249.

Maes T, et al. Activity of highly selective LSD1 inhibitors in HCT-116 xenograft mice. Journal of Clinical Oncology, ASCO Annual Meeting Abstracts 2010; 28 (15): e13663.

Maes T, et al., ORY-1001, a Potent and Selective Covalent KDM1A Inhibitor, for the Treatment of Acute Leukemia. Cancer Cell 2018; 33, 1–17. https://doi.org/10.1016/j.ccell.2018.02.002

Magerl C, Elliger J, Braunschweig T, Kremmer E, Koch LK, Holler T, et al. H3K4 dimethylation in hepatocellular carcinoma is rare compared with other hepatobiliary and gastrointestinal carcinomas and correlates with expression of the methylase Ash2 and the demethylase LSD1.Hum Pathol. 2010 Feb;41(2):181-189.

McDonald O, Wu H, Timp W, Doi A, Feinberg AP. Genome-scale epigenetic reprogramming during epithelial to mesenchymal transition. Nat Struct Mol Biol. 2011;18(8): 867–874.

Modlin IM, Lye KD, Kidd M. A 5-decade analysis of 13,715 carcinoid tumors. Cancer. 2003 Feb 15;97(4):934-59.

Modlin IM, Oberg K, Chung DC, Jensen RT, de Herder WW, Thakker RV, et al. Gastroenteropancreatic neuroendocrine tumours. Lancet Oncol. 2008 Jan;9(1):61-72.

Mohammad HP, Smitheman C, Damat C, Johnson N, Hann C, Kruger R. A DNA Hypomethylation Signature Predicts Antitumor Activity of LSD1 Inhibitors in SCLC. Cancer Cell. 2015;28(1):57-69.

Nagasaka M, Tsuzuki K, Ozeki Y, Tokugawa M, Ohoka N, Inoue Y, et al. Lysine-Specific Demethylase 1 (LSD1/KDM1A) Is a Novel Target Gene of c-Myc. Biol Pharm Bull. 2019;42(3):481-488. doi: 10.1248/bpb.b18-00892.

Nguyen L, Papenhausen P, Shao H. The Role of c-MYC in B-Cell Lymphomas: Diagnostic and Molecular Aspects. Genes (Basel). 2017 Apr 5;8(4).

Niebel D, et al. Lysine-specific demethylase 1 (LSD1) in hematopoietic and lymphoid neoplasms Blood 2014 124:151-152.

Oberg K, Knigge U, Kwekkeboom D, Perren A. Neuroendocrine gastro-entero-pancreatic tumors: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology 2012;23 (Supplement 7): vii124–vii130.

Oberg K, Hellman P, Ferrolla P, Papotti M. Neuroendocrine Bronchial and Thymic Tumours: ESMO Clinical Practice Guidelines Annals of Oncology 2012; 23 (Suppl 7): vii120-vii123.

Oken MM, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982; Dec;5(6):649-55.

Park KS, Liang MC, Reiser D, Zamponi R, Roach R, Curtis S, et al. Characterization of the cell of origin for small cell lung cancer. Cell Cycle. 2011;10:2806–2815.

Patta A, Fakih M. First-line cisplatin plus etoposide in high-grade metastatic neuroendocrine tumors of colon and rectum (MCRC NET): review of 8 cases. Anticancer Res. 2011 Mar;31(3):975-8

Peifer M, Fernandez-Cuesta, Sos M, George J, Seidel D, Kasper LH, et al. Integrative genome analyses identify key somatic driver mutations of small-cell lung cancer Nat. Genet. 2012;44(10):1104–1110.

Perros P, Colley S, Boelaert K, Evans C, Evans RM, Gerrard GE, et al. British Thyroid Association Guidelines for the Management of Thyroid Cancer. Clinical Endocrinology 2014;81(1) Chap 17:69-75

Poirier JT, et al. DNA methylation in small cell lung cancer defines distinct disease subtypes and correlates with high expression of EZH2. Oncogene 2015;34:5869-5878.

Pugh RN, et al. Transection of the oesophagus for bleeding oesophageal varices. British Journal of Surgery. 1973; 60(8): 646–649.

Ray S, et al. CtBP and Associated LSD1 Are Required for Transcriptional Activation by NeuroD1 in Gastrointestinal Endocrine Cells. Mol Cell Biol. 2014; 34(12): 2308-2317.

Rechtman N. Neuroendocrine Tumors of the Lung. An Update. Arch Pathol Lab Med. 2010;134:1628–1638.

Rifampicin [Summary of Product Characteristics]. Available from: https://www.medicines.org.uk/emc/product/8789/smpc#gref

Rindi G, et al. Nomenclature and classification of Neuroendocrine neoplasms of the digestive system. WHO Classification of Tumors of the Digestive Tract. WHO IARC 2010;13-14.

Rinske van Oorschot, Marten Hansen, Johanna M. Koornneef, Anna E. Marneth, Saskia M. Bergevoet, et al. Molecular mechanisms of bleeding disorderassociated GFI1BQ287* mutation and its affected pathways in megakaryocytes and platelets. Haematologica. 2019 Jul; 104(7): 1460–1472.

[redacted]

Saleque S, et al. Epigenetic regulation of hematopoetic differentiation by Gfi-1 and Gfi-1b is mediated by the cofactors CoREST and LSD1. Mol. Cell 2007;27:562-572.

Sankar S, et al. Reversible LSD1 Inhibition Interferes with Global EWS/ETS Transcriptional Activity and Impedes Ewing Sarcoma Tumor Growth. Clin Cancer Res 2014; 20:4584.

Sarvi S, et al. CD133+ cancer stem-like cells in small cell lung cancer are highly tumorigenic and chemoresistant but sensitive to a novel neuropeptide antagonist. Cancer Res. 2014;74:1554.

Scoumane A. The lysine-specific demethylase 1 is required for cell proliferation in both p53-dependent and -independent manners. J Biol Chem. 2007;282(21):15471-5.

Scher H, et al. Trial design and objectives for castration-resistant prostate cancer: Updated recommendations from the prostate cancer clinical trials working group 3. J Clin Oncol 2016;34:1402-1418.

Schulte JH, et al. Lysine-specific demethylase 1 is strongly expressed in poorly differentiated neuroblastoma: implications for therapy. Cancer Res 2009;69:2065-71.

Sequist LV, et al. Genotypic and histologic evolution of lung cancers acquiring resistance to EGFR inhibitors. Sci. Transl. Med. 2011;3:75ra26.

Serce N, et al (2012). Elevated expression of LSD1 (lysine-specific demethylase 1) during tumour progression from pre-invasive to invasive ductal carcinoma of the breast. BMC Clin. Pathol.2012; 12:13.

Shi Y, et.al. Coordinated histone modifications mediated by a CtBP co-repressor complex. Nature 2003; 422:735–738. 10.1038/nature01550

Shi Y, et al. Histone demethylation mediated by the nuclear amine oxidase homolog LSD1. Cell 2004;119:941-953.

Sholl LM, et al. Sox2 expression in pulmonary non-small cell and neuroendocrine carcinomas. Appl Immunohistochem Mol Morphol. 2010 Jan;18(1):55-61.

Somervaille T, Salamero O, Montesinos P, Willekens C, Perez Simon JA, Pigneux A, et al. Safety, Pharmacokinetics, Pharmacodynamics and Preliminary Activity in Acute Leukemia of Ory-1001, a First-in-Class Inhibitor of Lysine-Specific Histone Demethylase 1A (LSD1/KDM1A): Initial Results from a First-in-Human Phase 1 Study [abstract]. Presented at: The 58th Annual Meeting of the American Society of Hematology (ASH) and Exposition. 2016 Dec 3-6; San Diego, CA; USA: Abstract 4060.

Sprussel A, et al. Lysine-specific demethylase 1 restricts hematopoetic progenitor proliferation and is essential for terminal differentiation. Leukemia 2012;26:2039-2051.

Srinivas NR. Pharmacokinetic Interaction of Rifampicin with Oral Versus Intravenous Anticancer Drugs: Challenges, Dilemmas and Paradoxical Effects Due to Multiple Mechanisms. Drugs R D. 2016;16:141-148

Stewart CA, et al. Altering the Course of Small Cell Lung Cancer: Targeting Cancer Stem Cells via LSD1 Inhibition. Cancer Cell 2015;28(1):4-6.

Sutherland KD, et al. Cell of origin of small cell lung cancer: inactivation of Trp53 and Rb1 in distinct cell types of adult mouse lung. Cancer Cell. 2011;19:754–764.

Takagi S, Ishikawa Y, Mizutani A, Iwasaki S, Matsumoto S, Kamada Y, et al.LSD1 Inhibitor T-3775440 Inhibits SCLC Cell Proliferation by Disrupting LSD1 Interactions with SNAG Domain Proteins INSM1 and GFI1B. Cancer Res. 2017 Sep 1;77(17):4652-4662.

Thiagalingam A, et al. RREB-1, a novel zinc finger protein, is involved in the differentiation response to ras in human medullary thyroid carcinomas. Mol. Cell. Biol. 1996;16:5335–5345.

Thiesen ER, et al. Reversible inhibition of lysine specific demethylase 1 is a novel anti-tumor strategy for poorly differentiated endometrial carcinoma. BMC Cancer 2014;14:752.

Travis WD, et al. WHO Classification of Tumours of the Lung, Pleura, Thymus and Heart 2015;63-72. IARC

Van Cutsem E.2013
http://oncologypro.esmo.org/content/download/53285/983285/file/Preceptorship-NETs-Epidemiology-clinical-presentation-NETs-Van-Cutsem.pdf

Von Pawel J, et al. Topotecan versus cyclophosphamide, doxorubicin, and vincristine for the treatment of recurrent small-cell lung cancer. JCO 1999;17(2):658-667.

Wang J, et al Opposing LSD1 complexes function in developmental gene activation and repression programmes. Nature 2007;446, 882-887.

Wang J, et al. The lysine demethylase LSD1 (KDM1) is required for maintenance of global DNA methylation. Nat Genet 2009; 41: 125–129.

Yao JC, Phan A, Hoff PM, Chen HX, Charnsangavej C, Yeung SC, et al. Targeting vascular endothelial growth factor in advanced carcinoid tumor: a random assignment phase II study of depot octreotide with bevacizumab and pegylated interferon alpha-2b. J Clin Oncol. 2008 Mar 10;26(8):1316-23.

Yao JC, Hassan M, Phan A, Dagohoy C, Leary C, Mares JE, et al. One hundred years after "carcinoid": epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. J Clin Oncol. 2008 Jun 20;26(18):3063-72.

Yao JC, Voi M, Rouyrre N, Singh S. Everolimus for thetreatment of advanced, non-functional neuroendocrinetumours of the lung or gastrointestinal tract (RADIANT4):a randomised, placebo-controlled, phase 3 study. Lancet. 2016;387:968–977.

Yashiro T, Fulton N, Hara H, Yasuda K, Montag A, Yashiro N, Straus F, II, Ito K, Aiyoshi Y & Kaplan EL 1993 Comparison of mutations of ras oncogene in human pancreatic exocrine and endocrine tumors. Surgery 114 758–763.

Yoshimoto K, Iwahana H, Fukuda A, Sano T, Saito S & Itakura M 1992 Role of p53 mutations in endocrine tumorigenesis: mutation detection by polymerase chain reaction-single strand conformation polymorphism. Cancer Research 52 5061–5064.

Yu HA, et al. Analysis of tumor specimens at the time of acquired resistence to EGFR-TKI therapy in 155 patients with EGFR-mutant lung cancers. Clin Cancer Res. 2013;19:2240 -2247.

Yu X, et al. SOX2 expression in the developing, adult, as well as diseased prostate. Prostate Cancer Prostatic Disease 2014;17(4):301-309.

Zakowski MF, et al. EGFR mutations in small-cell lung cancers in patients who have never smoked. New Engl. J. Med 2006;355:213-215

Zhang Z, et al. Stemness and inducing differentiation of small cell lung cancer NCI-H446 cells. Cell Death and Disease 2013;4:e633.

Zhao ZK, et al. Overexpression of lysine specific demethylase 1 predicts worse prognosis in primary hepatocellular carcinoma patients. World J Gastroenterol. 2012; 18(45): 6651-6656.

Zucca E, Arcaini L, Buske C, Johnson PW, Ponzoni M, Raderer M, et al.; ESMO Guidelines Committee. Marginal zone lymphomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2020 Jan;31(1):17-29. doi: 10.1016/j.annonc.2019.10.010. Epub 2019 Dec 4.

18. APPENDICES

18.1. Appendix A: Table of Abbreviations

Table 14: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
ADL	Activity of daily life
ADR	Adverse drug reaction
AE	Adverse event
ALT	Alanine aminotransferase (SGPT)
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase (SGOT)
AUC	Area under the curve
β-hCG	β-subunit of human chorionic gonadotropin
BDC	Bile duct cannulated
BM	Bone Marrow
BSA	Body surface area
BUN	Blood urea nitrogen
CBC	Complete blood count
CgA	Chromogranin A
CL	Clearance
C_{max}	Maximum plasma concentration of drug
CNS	Central nervous system
CR	Complete response
CRO	Contract research organization
CRF	Case report form
CRP	Clinical Research Physician
CRS	Clinical Research Scientist
CS	Clinically Significant
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
DCR	Disease control rate
DDI	Drug-Drug Interaction

Table 14: Abbreviations and Specialist Terms (Continued)

Abbreviation or Specialist Term	Explanation
DLT	Dose-limiting toxicity
DMC	Data Monitoring Committee
DOR	Duration of response
EC	Ethics Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EEA	European Economic Area
EMA	European Medicines Agency
EMZL	Extranodal Marginal Zone Lymphoma
EOT	End of treatment
FCBP	Females of childbearing potential
FDA	Food and Drug Administration
FDG	Fluorodeoxyglucose
FFPE	Formalin-Fixed, Paraffin Embedded
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMR	Geometric Mean Ratio
HBS	Hepatitis B Surface
HDL	High Density Lipoprotein
HIV	Human immunodeficiency virus
HNSTD	Highest Non-Severely Toxic Dose
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
IHC	Immunohistochemistry
IND	Investigational New Drug
IP	Investigational Product
IRB	Institutional Review Board
IRT	Interactive Response Technology
IV	Intravenous

Table 14: Abbreviations and Specialist Terms (Continued)

Abbreviation or Specialist Term	Explanation
LDH	Lactate dehydrogenase
LSD	Lysine-Specific Demethylase
LVEF	Left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
MRP2	Multidrug resistance-associated protein 2
MUGA	Multi-gated acquisition
MZL	Marginal Zone Lymphoma
NCI	National Cancer Institute
NEC	Neuroendocrine carcinoma
NEN	Neuroendocrine neoplasia
NEPC	Neuroendocrine prostate cancer
NET	Neuroendocrine tumor
NMZL	Nodal Marginal Zone Lymphoma
NSE	Neuron specific enolase
ORR	Overall response rate
OS	Overall survival
PCR	Polymerase Chain Reaction
PCWG3	Prostate Cancer Clinical Trials Working Group 3
PD	Progressive disease
PET	Positron emission tomography
PFS	Progression-free survival
P-gp	P-glycoprotein
PK	Pharmacokinetics
PPK	Population Pharmacokinetic
PR	Partial response
Pro-GRP	Pro-gastrin-releasing peptide
PSA	Prostate-specific antigen
QW	Every week

Table 14: Abbreviations and Specialist Terms (Continued)

Abbreviation or Specialist Term	Explanation
RBC	Red blood cell count
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	Recommended phase 2 dose
R/R	Relapsed and/or refractory
RT-PCR	Reverse Transcription Polymerase Chain Reaction
SAE	Serious adverse event
SAP	Statistical analysis plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SC	Steering committee
SD	Stable disease/Standard deviation
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SmPC	Summary of Product Characteristics
SMZL	Splenic Marginal Zone Lymphoma
SOP	Standard operating procedure
sqNSCLC	Squamous non-small cell lung cancer
SRC	Safety review committee
STD10	Severely Toxic Dose in 10% of the animals
SUSAR	Suspected unexpected serious adverse reaction
SYP	Synaptophysin
$t_{1/2}$	Half-life
TEAE	Treatment-emergent adverse event
TK	Toxicokinetics
UGT	UDP-glucuronyltransferases
ULN	Upper limit of normal
USA	United States of America
USP	United States Pharmacopeia
Vss	Volume of distribution
WBC	White blood cell count
WHO	World Health Organization

18.2. Appendix B: RECIST 1.1

The following information is extracted/summarized from Eisenhauer, 2009, New Response Evaluation Criteria in Solid Tumors: Revised RECIST Guideline (Version 1.1). Please refer to the primary reference for further information.

Definitions

At screening, tumor lesions/lymph nodes will be categorized as measurable or non-measurable.

Measurable Disease

Tumor Lesions. Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm by CT scan (CT scan slice thickness no greater than 5 mm)
- 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable)
- 20 mm by chest X-ray

Malignant Lymph Nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable Disease

All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

Tumor Response Evaluation

Target lesions

When more than one measurable tumor lesion is present at baseline all lesions up to a maximum of 5 lesions total (and a maximum of 2 lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. Note that pathological nodes must meet the measurable criterion of a short axis of ≥ 15 mm by CT scan and only the short axis of these nodes will contribute to the baseline sum. All other pathological nodes (those with short axis ≥ 10 mm but < 15 mm) should be considered non-target lesions. Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed. At baseline, the sum of the target lesions (longest diameter of tumor lesions plus short axis of lymph nodes: overall maximum of 5) is to be recorded.

After baseline, a value should be provided on the eCRF for all identified target lesions for each assessment, even if very small. If extremely small and faint lesions cannot be accurately measured but are deemed to be present, a default value of 5 mm may be used. If lesions are too small to measure and indeed are believed to be absent, a default value of 0 mm may be used.

Non-target lesions

All non-measurable lesions (or sites of disease) plus any measurable lesions over and above those listed as target lesions are considered non-target lesions. Measurements are not required but these lesions should be noted at baseline and should be followed as "present," "absent," or "unequivocal progression."

Response Criteria

Target and non-target lesions are evaluated for response separately, and then the tumor burden as a whole is evaluated as the overall response.

Target Lesion Response

Target lesions will be assessed as follows:

- Complete Response (CR). Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.
- Partial Response (PR). At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
- Progressive Disease (PD). At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).
- Stable Disease (SD). Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum of diameters while on study.

Non-target Lesion Response

Non-target lesions will be assessed as follows:

- Complete Response (CR). Disappearance of all non-target lesions and normalisation of tumor marker level. All lymph nodes must be non-pathological in size (< 10 mm short axis).
- Non-CR/Non-PD. Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.
- Progressive Disease (PD). Unequivocal progression (see comments below) of existing non-target lesions. (Note: the appearance of one or more new lesions is also considered progression).

When the Subject Also Has Measurable Disease: In this setting, to achieve "unequivocal progression" on the basis of the non-target disease, there must be an overall level of substantial

worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest "increase" in the size of one or more non-target lesions is usually not sufficient to quality for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

When the Subject Has Only Non-measurable Disease: This circumstance arises in some Phase 3 trials when it is not a criterion of study entry to have measurable disease. The same general concepts apply here as noted above; however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable) a useful test that can be applied when assessing subjects for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: ie, an increase in tumor burden representing an additional 73% increase in "volume" (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include an increase in a pleural effusion from "trace" to "large," an increase in lymphangitic disease from localized to widespread, or may be described in protocols as "sufficient to require a change in therapy." If "unequivocal progression" is seen, the subject should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so: therefore, the increase must be substantial.

Overall Response

Overall response should be assessed according to Table 15 for subjects with target lesions, and Table 16 for subjects with only non-target lesions.

Table 15: Time Point Response: Subjects With Target (± Non-target) Disease

Target Lesions Response	Non-target Lesion Response	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/ non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, NE = inevaluable.

Table 16: Time Point Response: Subjects With Non-target Disease Only

Nontarget Lesions Response	New Lesions	Overall Response
CR	No	CR
Non-CR/ non-PD	No	Non-CR/ non-PD[a]
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, NE = inevaluable.
[a] "Non-CR/non-PD" is preferred over "stable disease" for non-target disease since SD is increasingly used as endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.

Symptomatic Deterioration

Subjects with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as 'symptomatic deterioration'. Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping study therapy. The objective response status of such subjects is to be determined by evaluation of target and non-target disease.

18.3. Appendix C: The Lugano Classification

Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano Classification (Cheson, 2014) can be accessed online at:

https://ascopubs.org/doi/10.1200/JCO.2013.54.8800

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

18.4. Appendix D: Performance Status Criteria

Table 17: Eastern Cooperative Oncology Group (ECOG) Performance Status

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, eg, light housework, office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

(Oken, 1982)

18.5. Appendix E: Characteristics of the Bayesian Logistic Regression Model

Introduction

An adaptive Bayesian logistic regression model (Neuenschwander, 1998) for dose escalation with overdose control (Babb, 1988) will be used to guide dose escalation in this study. The BLRM and prior specification are described in Section 9.1.

The purpose of this appendix is to present performance metrics (operating characteristics) that illustrate the precision of the design in estimating the MTD under various dose-toxicity relationships through computer simulation. In addition, recommendations of the next dose level by BLRM with overdose control principle are provided under various hypothetical outcome scenarios in early cohorts (assuming exactly 3 evaluable subjects in each cohort for simplicity) to show how it facilitates on-study dose-escalation decisions.

Specifications and results of simulation study

This section presents the operating characteristics that illustrate the precision of the design in estimating the MTD under various assumed true dose-toxicity relationships.

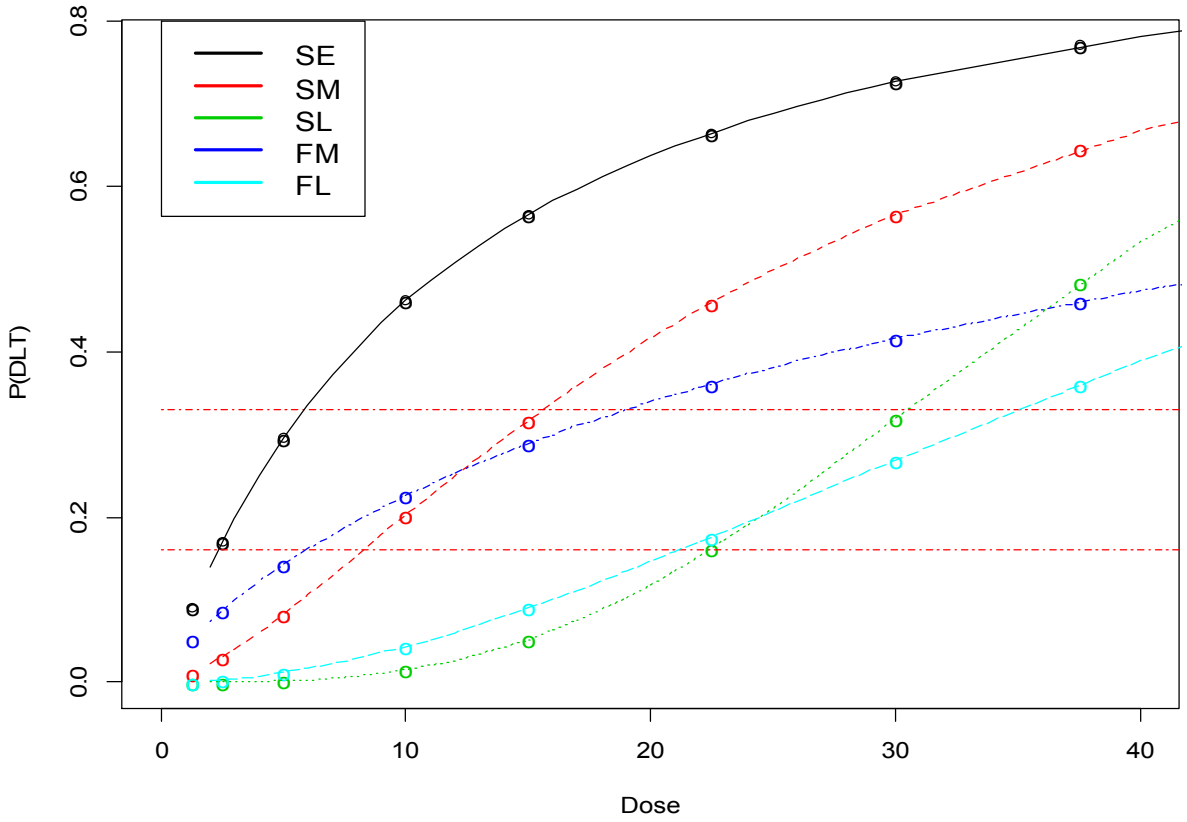
Simulations are performed for the BLRM under a total of 5 scenarios of true dose-DLT relationship (refer to Table 18 and Figure 7):

1. Dose-DLT relationship is a steep curve and MTD is reached at early dose level (SE).
2. Dose-DLT relationship is a steep curve and MTD is reached at middle dose level (SM).
3. Dose-DLT relationship is a steep curve and MTD is reached at late dose level (SL).
4. Dose-DLT relationship is a flat curve and MTD is reached at middle dose level (FM).
5. Dose-DLT relationship is a flat curve and MTD is reached at late dose level (FL).

Table 18: P(DLT) for Five Simulated Scenarios with Numbers in Grey Indicating Doses with True P(DLT) within the Target Toxicity Interval [16%, 33%]

	P(DLT) at Different Dose Levels (mg)							
Scenario	**1.25**	**2.5**	**5**	**10**	**15**	**22.5**	**30**	**37.5**
SE	0.091	0.1699	0.2951	0.4613	0.5655	0.6642	0.7269	0.7702
SM	0.0113	0.031	0.0827	0.2022	0.317	0.4594	0.5663	0.6455
SL	0	0.0002	0.0018	0.0155	0.0522	0.1618	0.3196	0.4836
FM	0.0513	0.0867	0.1428	0.2263	0.289	0.361	0.4165	0.4611
FL	0.0009	0.0033	0.0121	0.0438	0.09	0.176	0.2694	0.3603

Figure 7: Dose Toxicity Curves for Simulation



Operating characteristics are reviewed to investigate overall performance of the BLRM under each true scenario. Table 19 summarizes the results from the simulations performed.

Table 19: Summary Metrics of Simulation for BLRM and Comparison with 3+3

Scenario/ Method	Mean Number of Subjects	Proportion of subjects with DLT	Probability of recommending a dose with true P(DLT)		
			0.16-0.33	≥0.33	<0.16
SE, N-CRM	19.75	0.24	0.80	0.06	0.14
SE, 3+3	14.72	0.24	0.63	0.06	0.31
SM, N-CRM	22.50	0.16	0.72	0.06	0.22
SM, 3+3	20.48	0.16	0.55	0.05	0.40
SL, N-CRM	25.55	0.11	0.75	0.08	0.18
SL, 3+3	26.85	0.11	0.68	0.08	0.24
FM, N-CRM	22.24	0.17	0.48	0.08	0.44
FM, 3+3	20.38	0.18	0.37	0.10	0.52

Table 19: Summary Metrics of Simulation for BLRM and Comparison with 3+3 (Continued)

Scenario/ Method	Mean Number of Subjects	Proportion of subjects with DLT	Probability of recommending a dose with true P(DLT)		
			0.16-0.33	≥0.33	<0.16
FL, N-CRM	25.66	0.10	0.57	0.16	0.27
FL, 3+3	26.80	0.11	0.51	0.16	0.33

Overall the BLRM model with specified prior is performing reasonably. With similar or a little more sample size, BLRM model can select MTD in the target range with higher probability, especially for scenarios 1, 2, and 4.

Hypothetical Dose Escalation Scenarios in Early Cohorts

Aside from the overall operating characteristics studied above, the design should make reasonable decisions during a study based on the observed toxicities. After completion of a given cohort, the decision to dose escalate and actual dose chosen for the subsequent cohort will depend on the recommendation of the BLRM per EWOC principle and medical review of available clinical and laboratory data.

Some scenarios to illustrate the dose escalation up to the third dose cohort are listed in Table 20 using the 2-parameter BLRM. It is assumed that each cohort has exactly 3 evaluable subjects. Dose escalation again follows the rule listed in Section 7.2.3.

Table 20: Possible Scenarios Up to the Third Dosing Cohort with Three Subjects per Cohort

Scenario	Dose History (mg)	Number of DLTs/Number of Subjects	Next dose by N-CRM(mg)
1	1.25	0/3	2.5
2	1.25 2.5	0/3 0/3	2.5 5
3	1.25 2.5	0/3 1/3	2.5 2.5
4	1.25 2.5	0/3 2/3	2.5 1.25
5	1.25 2.5 5	0/3 0/3 0/3	2.5 5 10

Table 20: Possible Scenarios Up to the Third Dosing Cohort with Three Subjects per Cohort (Continued)

Scenario	Dose History (mg)	Number of DLTs/Number of Subjects	Next dose by N-CRM(mg)
6	1.25 2.5 5	0/3 0/3 1/3	2.5 5 5
7	1.25 2.5 5	0/3 0/3 2/3	2.5 5 2.5
8	1.25 2.5 2.5	0/3 1/3 1/3	2.5 2.5 2.5
9	1.25 2.5 2.5	0/3 1/3 2/3	2.5 2.5 1.25
10	1.25 2.5 1.25	0/3 2/3 1/3	2.5 1.25 1.25
11	1.25 2.5 1.25	0/3 2/3 0/3	2.5 1.25 2.5

Again the BLRM model is performing reasonably for the hypothetical dose escalation scenarios.

Discussion

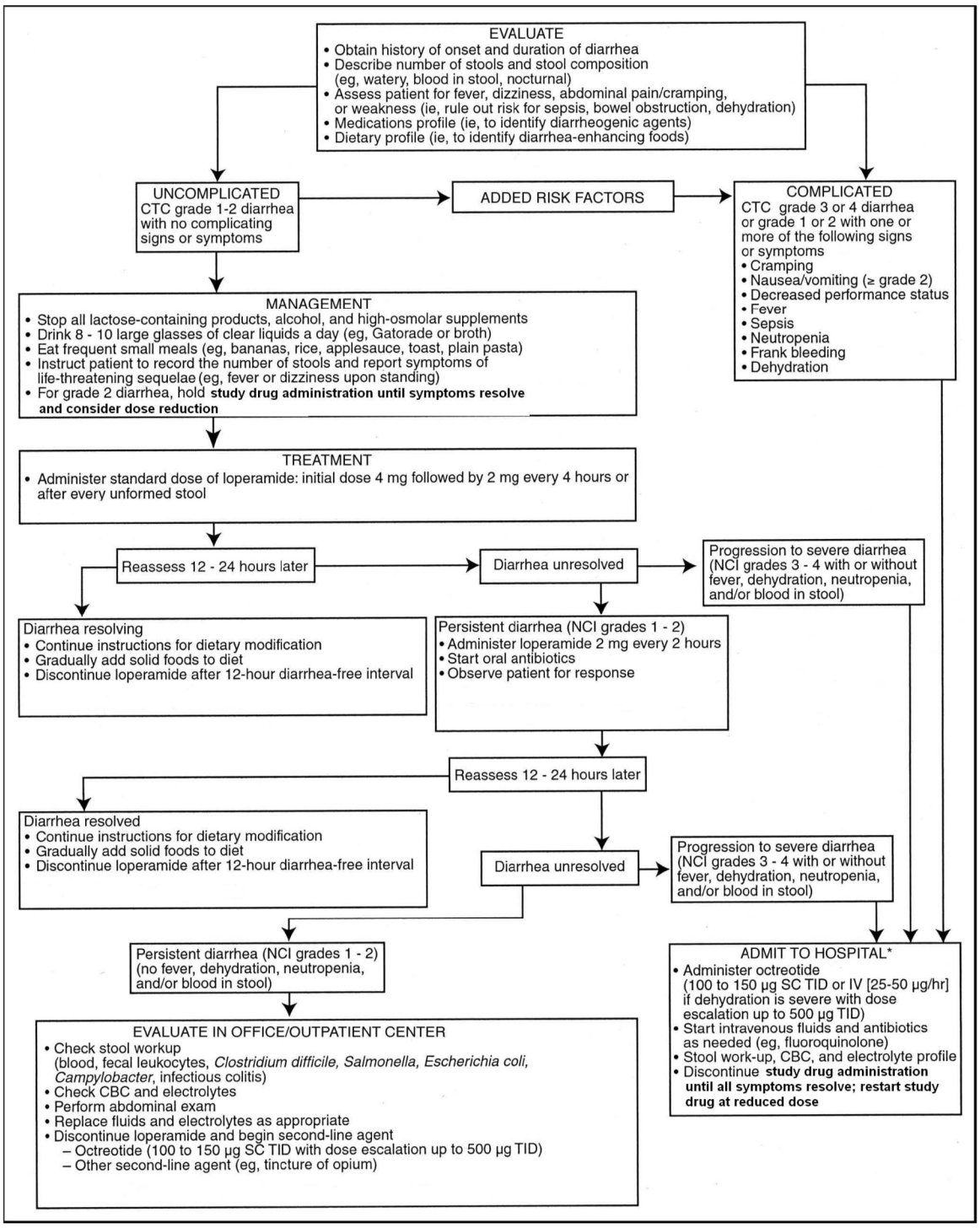
The Bayesian Logistic Regression Model enables us to incorporate the pre-clinical information, as well as to update the recommended dose based on all safety data in the study.

By reviewing the metrics presented in the table, it can be seen that the model is not sensitive to different scenarios of truth. In general, this model is conservative due to the overdose control criteria. In all scenarios, the probability of recommending a dose that is excessively toxic with true P(DLT) $\geq$ 33% is much smaller than that of recommending a dose with true P(DLT) between 16% and 33% as MTD. On-study recommendations based on the model are consistent with the clinical decision making process, and should be considered in conjunction with other available clinical information by the Celgene Clinical Trial Team and study investigators in deciding the dose levels to be tested in order to determine the MTD.

18.6. Appendix F: Recommendations for Management of Treatment-Induced Diarrhea

The following published guidelines (Benson, 2004) were modified in order to be consistent with the study protocol.

Figure 8: Recommendations for management of Treatment-Induced Diarrhea



18.7. Appendix G: Management of Biologic Specimens

This is an addendum to the Laboratory Manual.

Sample Handling and Storage

All blood and tissue samples collected for biomarker and genetic research as part of this study that are not depleted following analysis will be stored for use in research for up to 5 years after the study is completed. With subject consent, the storage period will be extended to 20 years after the study is completed for use in future research to learn more about cancer and other diseases. Samples will be stored in a secure laboratory facility designed for long term sample storage, with appropriate access control, monitoring and back-up systems.

Sample Coding

All biomarker and genetic research samples will be identified only by a code (subject identification number). These samples will not have any other personal information on them. The study doctor will keep the code key. The samples and the code key will be kept confidential and separate. Researchers who perform tests on samples will only see the code and will not see any information that specifically identifies the subject.

Research on Blood & Tissue Samples

Biomarker and genetic research samples will be tested by the sponsor or by companies contracted by the sponsor for use in future research to learn more about cancer and other diseases. This includes determining if biomarkers in blood cells or tumor cells demonstrate that CC 90011 is biologically active.

Reporting and Availability of Biomarker and Genetic Results

Biomarker and genetic research sample test results will not be shared with the subject, insurance companies nor any other third parties not involved in the sample analysis described above. The results will not be filed in the subject's medical records. Test results are for research purposes only and will not be used to make decisions about a subject's routine medical care.

Names of subjects and identifiers will not be mentioned in publications or reports, thereby minimizing the possibility of psychological or social risks that could arise from knowledge of this biomarker and genetic information, such as risk for employability or insurability or the risk of discrimination.

Mechanism to Request Sample Destruction upon Withdrawal of Consent

If subjects withdraw consent to participate in the study, they may additionally request to have their biomarker and genetic research samples destroyed. In such cases, a subject will inform the study doctor that consent has been withdrawn and request to have any stored, unused samples destroyed. Any unused samples will then be destroyed by the sponsor. However, if samples were analyzed before consent was withdrawn, then the sponsor may still use data already available.

If subjects agree to allow biomarker and genetic research samples to be kept 20 years for future research, they are also free to reverse just that decision at any time. The subject will inform the study doctor that permission has been withdrawn for samples to be used for future

research. Any unused samples will then be destroyed by the sponsor. However, if samples were analyzed before consent was withdrawn, then the sponsor may still use data already available.

18.8. Appendix H: Child-Pugh Classification

18.8.1. Child-Pugh Classification of Liver Failure

Subjects with a Child-Pugh A classification without hepatic encephalopathy meet this individual inclusion criterion for the study.

Table 21: Child-Pugh Classification

	1 point	2 points	3 points
Bilirubin (mg/dL)	< 2	2-3	>3
Albumin (g/L)	>3.5	2.8-3.5	<2.8
Prothrombin time prolonged in seconds (INR)	1-4 (<1.7)	4-6 (1.7-2.3)	>6 (>2.3)
Ascites	None	Slight	Moderate
Hepatic encephalopathy	None	Grade 1-2	Grade 3-4
Child A: 5-6 points; Child B: 7-9 points; Child C: ≥ 10 points			

INR = international normalized ratio.
Source: Pugh, 1973.

18.9. Appendix I: Modified RECIST (mRECIST)

mRECIST criteria (Lencioni, 2010) can be accessed online at:

https://www.thieme-connect.com/products/ejournals/html/10.1055/s-0030-1247132

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

18.10. Appendix J: Prostate Cancer Clinical Trials Working Group (PCWG3)

Recommendations of the PCWG3 on the design and end points of clinical trials for subjects with progressive prostate cancer and castrate levels of testosterone (Scher, 2016) can be accessed online at:

http://jco.ascopubs.org/content/34/12/1402

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: Friday, 05 November 2021, 07:48 AM Eastern Daylight Time
Meaning: Approved, no changes necessary.
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