DISCLOSURE

REDACTED PROTOCOL AMENDMENT 1

ABI-007-NSCL-006

A PHASE 2, RANDOMIZED, OPEN-LABEL, MULTICENTER STUDY TO ASSESS SAFETY AND EFFICACY OF NAB®-PACLITAXEL (ABI-007) WITH EPIGENETIC MODIFYING THERAPY OF CC-486, AND NAB®-PACLITAXEL MONOTHERAPY AS SECOND-LINE TREATMENT IN SUBJECTS WITH ADVANCED NONSQUAMOUS NONSMALL CELL LUNG CANCER (NSCLC): ABOUND.2L

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A PHASE 2, RANDOMIZED, OPEN-LABEL, MULTICENTER STUDY TO ASSESS SAFETY AND EFFICACY OF NAB®-PACLITAXEL (ABI-007) WITH EPIGENETIC MODIFYING THERAPY OF CC-486, AND NAB®-PACLITAXEL MONOTHERAPY AS SECOND-LINE TREATMENT IN SUBJECTS WITH ADVANCED NONSQUAMOUS NON-SMALL CELL LUNG CANCER (NSCLC): ABOUND.2L

INVESTIGATIONAL PRODUCTS:	**CC-486, *nab*-Paclitaxel (ABI-007)**
PROTOCOL NUMBER:	**ABI-007-NSCL-006**
DATE FINAL:	**29 May 2014**
AMENDMENT 1 FINAL:	**24 June 2014**
EudraCT NUMBER	**2014-001105-41**
IND NUMBER	**123160**
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PROTOCOL SUMMARY

Study Title

A Phase 2, randomized, open-label, multicenter study to assess safety and efficacy of *nab*-paclitaxel (ABI-007) with epigenetic modifying therapy of CC-486, and *nab*-paclitaxel monotherapy as second-line treatment in subjects with advanced nonsquamous non-small cell lung cancer (NSCLC): ABOUND.2L

Indication

Second-line treatment of advanced nonsquamous NSCLC.

Objectives

Primary

- To assess the efficacy of *nab*-paclitaxel[1] administered intravenously (IV) on Days 8 and 15 with epigenetic modifying therapy of CC-486 once daily (QD) on Days 1 to 14 every 21 days, and *nab*-paclitaxel monotherapy administered IV on Days 1 and 8 every 21 days as second-line treatment for advanced nonsquamous NSCLC, and the relative efficacy of these two treatment regimens.

Secondary

- To evaluate the safety and tolerability of *nab*-paclitaxel administered IV on Days 8 and 15 in combination with epigenetic modifying therapy of CC-486 once daily (QD) on Days 1 to 14 every 21 days, and *nab*-paclitaxel monotherapy administered IV on Days 1 and 8 every 21 days as second-line treatment for advanced nonsquamous NSCLC.

Exploratory

- To assess healthcare resource utilization for the two treatment arms.
- To assess the quality of life (QoL) for the two treatment arms.
- To determine baseline tumor characteristics which predict response to *nab*-paclitaxel as a single agent and in combination with epigenetic modifying therapy of CC-486.
- To evaluate genomic correlates of response to *nab*-paclitaxel as a single agent and in combination with epigenetic modifying therapy of CC-486.

Study Design

This is a Phase 2, randomized, open-label, multicenter study to assess efficacy and safety of *nab*-paclitaxel in combination with epigenetic modifying therapy of CC-486, and *nab*-paclitaxel monotherapy as second-line treatment in subjects with advanced nonsquamous NSCLC who have received one platinum-containing chemotherapy regimen. Approximately 160 subjects with advanced nonsquamous NSCLC will be randomized 1:1 into one of the two treatment arms: *nab*-paclitaxel / CC-486 combination therapy or *nab*-paclitaxel monotherapy prior to receiving first

[1] *nab*® is a registered trademark of Celgene Corporation.

dose of investigational product (IP). Randomization will be centralized and stratified by Eastern Cooperative Oncology Group (ECOG) performance status (0 versus 1, see Appendix A), gender (males versus females), and smoker (yes versus no).

The study will consist of up to a 28-day Screening Period, a Treatment Period and a Follow-up Period.

The Screening Period for eligibility determination begins upon subject written informed consent. All screening assessments must be completed within 28 days prior to first dose of IP.

The Treatment Period begins with the first dose of IP as described in Section 8. Subjects will receive one of the following treatments based on the randomization assignment:

- *nab*-Paclitaxel 100 mg/m^2 IV infusion over 30 minutes on Days 8 and 15 and CC-486 200 mg orally QD on Days 1 to 14 of each 21-day treatment cycle, or
- *nab*-Paclitaxel 100 mg/m^2 IV infusion over 30 minutes on Days 1 and 8 of each 21-day treatment cycle

No additional anticancer agents are allowed during study treatment. All supportive care (including but not limited to growth factors, antiemetics, analgesics, zolendronic acid, denosumab) is permitted as per the investigator's discretion and should be administered according to local institutional practice. Subjects will continue treatment until disease progression, development of an unacceptable toxicity, death, lost to follow-up, withdrawal of consent, or termination of the study by the sponsor.

Tumor evaluations will be assessed by the investigative sites and response will be determined according to Response Evaluation Criteria in Solid Tumors (RECIST) guidelines, Version 1.1 (Eisenhauer, 2009).

All scheduled laboratory samples will be sent to a central laboratory for analysis. Local hematology and chemistry tests may be performed as required for subject management/treatment decisions. Local laboratory values that are considered abnormal and clinically significant will be recorded as an adverse event (AE)/serious adverse event (SAE) and also recorded on the laboratory electronic Case Report Form (eCRF) (see Section 11.3).

All subjects who discontinue from treatment for any reason other than withdrawal of consent, lost to follow-up, death, or termination of the study by the sponsor will enter the Follow-up Period. It will consist of a visit 28 days after treatment discontinuation. Thereafter, subjects will be followed for survival by phone call contact approximately every 90 days (+/- 14 days) for 12 months after the last subject is randomized or 120 progression-free survival (PFS) events have been observed, whichever comes later.

During the study, subjects will have computed tomography (CT) scans every 42 days (-3/+7 days) until documented progression of disease, withdrawal of consent, lost to follow-up, death, or termination of the study by the sponsor. Those subjects entering the Follow-up Period without documented progression will continue to have CT scans in accordance with local standard of care (or approximately every 90 days) until documented progression of disease, withdrawal of consent, lost to follow-up, death, or termination of the study by the sponsor. All posttreatment anticancer therapies will be recorded during the Follow-up Period.

Study Population

Male and female subjects with advanced nonsquamous NSCLC who have received one platinum-containing chemotherapy regimen for their advanced disease will be eligible for this study.

Length of Study

The enrollment of 160 subjects on this study will take approximately 24 months. The total length of this Phase 2 study with follow-up is estimated to be approximately 3 years.

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

Study Treatments

Subjects will receive *nab*-paclitaxel in combination with CC-486 or *nab*-paclitaxel monotherapy during the study. The CC-486 and *nab*-paclitaxel for both arms are designated as IP and will be packaged and supplied by Celgene Corporation.

Overview of Statistical Methods

The primary objective of this study is to evaluate the efficacy of the CC-486 and *nab*-paclitaxel combination therapy and that of the *nab*-paclitaxel monotherapy, and the relative efficacy of these two treatment regimens.

Approximately 160 subjects will be randomized to the two treatment arms in a 1:1 ratio. A permuted-block randomization method will be employed, and the randomization will be carried out centrally using an Interactive Response Technology (IRT) system. The randomization will be stratified based on the following baseline factors: ECOG performance status (0 versus 1), gender (males versus females), and smoker (yes versus no).

Evaluations of the study endpoints will be based primarily on the point estimates and the associated 95% confidence intervals of the within- and between-treatment differences. However, nominal p-values from statistical tests may be provided in the clinical study report to indicate the strength of the treatment differences evaluated.

An independent Data Monitoring Committee (DMC) will be established to review the interim safety and efficacy data.

Efficacy Analyses

The intent-to-treat population, which includes all randomized subjects regardless of whether the subject receives any IP or has any efficacy assessments performed, will be used for all efficacy analyses. The primary efficacy endpoint is PFS, which is defined as the time from the date of randomization to the date of disease progression or death (from any cause) on or prior to the data cutoff date for analyses, whichever occurs first, based on the investigator's assessment of the data from CT scans using RECIST 1.1 guidelines. Baseline tumor measurements will be determined from the radiologic evaluation performed within 28 days before the start of study therapy.

Progression-free survival will be summarized using Kaplan-Meier methods with median PFS time (including two-sided 95% confidence interval [CI]) for each treatment arm. The relative treatment effect between the combination and monotherapy arms with respect to PFS will be estimated by the hazard ratio (HR) and the associated two-sided 95% CIs using the stratified Cox proportional hazard model with ECOG performance status (0 versus 1), gender (males versus females), and smoker (yes versus no) as the stratification factors. No statistical inferential tests will be performed.

The secondary endpoints include disease control rate (DCR), overall response rate (ORR), and overall survival (OS). Disease control rate and ORR will be summarized within each treatment arm by the observed rates and the associated 95% CIs. The relative treatment effect will be summarized by the absolute difference and the ratio of the observed rates. Overall survival will be analyzed using similar statistical method as that for the PFS endpoint.

Safety Analyses

The treated population, which includes all randomized subjects who receive at least one dose of IP, will be the analysis population for all safety analyses.

Adverse events will be analyzed in terms of treatment-emergent adverse events (TEAEs), defined as any AE or SAE occurring or worsening on or after the day of the first dose of the IP through 28 days after the last dose of IP. In addition, any SAE with an onset date more than 28 days after the last dose of IP that is assessed by the investigator as related to IP will be considered a TEAE.

Treatment-emergent adverse events, Grade 3 or higher TEAEs, SAEs, TEAEs leading to dose reduction, dose delay, and dose interruption, TEAEs leading to treatment discontinuation, and TEAEs with an outcome of death will be summarized by treatment arms using MedDRA system organ class and preferred terms.

Sample Size

This study is designed to estimate the treatment effect within each of the combination and monotherapy arms and the relative effect between the two arms with respect to the primary and secondary efficacy endpoints. The sample size was chosen to support the estimation of the within- and between-treatment effects with reasonable precision. Table 1 below summarizes the precisions that can be achieved given different scenarios of hypothetical observed hazard ratios between the two treatment arms for PFS events, assuming a total of 120 events are observed, and the time to PFS has an exponential distribution.

Table 1: Progression-Free Survival – Two-side 95% Confidence Interval of Hypothetical Observed Hazard Ratio between Treatment Arms

Hypothetical Number of Events Observed	Hypothetical Observed Hazard Ratio of PFS Events	95% Confidence Interval of Hazard Ratio[a]
120	0.60	(0.42, 0.86)
	0.65	(0.45, 0.93)
	0.70	(0.49, 1.00)

[a] Assuming a standard error of 0.18 for the log hazard ratio.

Assuming the median times of PFS are 4.17 and 2.5 months, respectively, for the *nab*-paclitaxel/CC-486 combination therapy and *nab*-paclitaxel monotherapy arms, and an approximate 24 months accrual period for a total of 160 subjects, it is estimated that a total of 120 PFS events will be observed approximately 2 months after the last subject is randomized, assuming an exponential distribution for PFS.

One nonbinding interim analysis for PFS with early stopping rule for futility will be conducted when approximately 60 events are observed.

Data Monitoring Committee

An independent Data Monitoring Committee (DMC) will be established with the responsibilities for safeguarding the interests of study participants and monitoring the overall conduct of the study. Final recommendations of the DMC will reflect the judgment of the DMC members and will be considered advisory in nature to the sponsor. The decision to implement the recommendations of the DMC will be made by the sponsor, following consultation with the trial Coordinating Investigator and Steering Committee. A DMC charter will be established.

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1. INTRODUCTION

1.1. Non-small Cell Lung Cancer

Lung cancer is the leading cause of cancer-related deaths among men and women worldwide, with 1.2 million new cases diagnosed each year. Non-small cell lung cancer (NSCLC) is the most common type of lung cancer, accounting for 80% of all new cases. There are an estimated 1.1 million lives lost per year (approximately 500,000 in the United States [US] and European Union [EU] alone) due to NSCLC. Smoking is the causative factor for up to 85% of cases (http://www.lungcancercoalition.org/en/pages/about/awareness).

The majority of patients are not diagnosed until the tumor has progressed beyond the primary site. Despite step-wise advances in patient selection, targeted agents, and optimizing chemotherapy regimens, patients with advanced NSCLC continue to have an unmet medical need (Schiller, 2013).

Platinum-containing chemotherapy regimens remain the standard first-line treatment in the majority of patients in the US and Japan. In the EU, a third-generation chemotherapeutic agent (docetaxel, gemcitabine, paclitaxel, or vinorelbine), most commonly gemcitabine or vinorelbine, plus a platinum drug is used for advanced NSCLC (NICE, 2011). For first-line therapy in patients with Stage IV NSCLC and good performance status, the American Society of Clinical Oncology (ASCO) clinical practice guideline recommends treatment with a platinum-based two-drug combination of cytotoxic drugs (Azzoli, 2009). For patients without disease progression, the option of maintenance monotherapy with pemetrexed or erlotinib could also be considered (Gerber, 2013; Schiller, 2013). A trend that is becoming more prevalent is personalized NSCLC treatment based on tumor histology (squamous versus nonsquamous), on molecular characteristics of the tumor, and on the patient's clinical status using agents targeting specific receptors, kinases and pathways (ie, epidermal growth factor receptor [EGFR], echinoderm microtubule-associated protein-like 4 [EML4] and anaplastic lymphoma kinase [ALK] fusion protein).

Single agent chemotherapy (pemetrexed, EGFR-inhibitors and taxanes) are standards of care for second-line treatment of patients with locally advanced or metastatic NSCLC after failure of prior platinum-based chemotherapy. Docetaxel has been widely evaluated in this setting, and is currently approved by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) as a single agent for the treatment of patients with locally advanced or metastatic NSCLC after failure of prior chemotherapy (the US label specifies prior platinum-based chemotherapy). For patients with a good performance status at the time of disease progression following first-line chemotherapy, docetaxel, despite a low response rate, was associated with a 10% to 20% prolongation of 1-year survival and an improved quality of life when compared with ifosfamide, vinorelbine, or best supportive care (BSC) alone (Hanna, 2004). Erlotinib is indicated in the US and EU for the treatment of patients with locally advanced or metastatic NSCLC after failure of at least one prior chemotherapy regimen, although no survival benefit has been demonstrated in patients with EGFR-IHC negative tumors. Pemetrexed is indicated in the US and EU as a single agent for the treatment of patients with locally advanced or metastatic nonsquamous NSCLC after prior chemotherapy. However, the

approval and subsequent increased use of pemetrexed and erlotinib in the first-line setting poses an unmet need in the second-line setting, whereby new therapeutic options are needed.

1.2. *nab*-Paclitaxel in NSCLC

nab-Paclitaxel is approved in the first-line setting in combination with carboplatin for patients with NSCLC in the US, Japan, Argentina, Australia, and New Zealand. The approval was based on the evaluation of Phase I and II data (Belani, 2008; Rizvi, 2008; Socinski, 2010), as well as the pivotal Phase 3 study (CA031), (Socinski, 2012). The pivotal Phase 3 study was a multicenter, randomized, open-label study conducted in 1052 chemo-naïve subjects with Stage IIIB/IV NSCLC to compare *nab*-paclitaxel in combination with carboplatin to paclitaxel injection in combination with carboplatin as first-line treatment in patients with advanced NSCLC. *nab*-Paclitaxel was administered as an IV infusion over 30 minutes at a dose of 100 mg/m^2 on Days 1, 8, and 15 of each 21-day cycle. Paclitaxel injection was administered as an IV infusion over 3 hours at a dose of 200 mg/m^2, following premedication. In both treatment arms carboplatin at a dose of area under the curve (AUC) = 6 mg*min/mL was administered IV on Day 1 of each 21-day cycle after completion of *nab*-paclitaxel/paclitaxel infusion. Treatment was administered until disease progression, development of an unacceptable toxicity or patient withdrawal. The primary efficacy outcome measure was overall response rate (ORR) as determined by a central independent review committee using RECIST guidelines (Version 1.0). In the intent-to-treat (all-randomized) population, the median age was 60 years, 75% were men, 81% were white, 49% had carcinoma/adenocarcinoma, 43% had squamous cell lung cancer, 76% were ECOG performance status (PS) 1, 15% were ≥70 years of age and 73% were current or former smokers. Patients received a median of 6 cycles of treatment in both study arms. Patients in the *nab*-paclitaxel/carboplatin arm had a statistically significantly higher overall response rate compared to patients in the paclitaxel injection/carboplatin arm [(33% versus 25%; response rate ratio, 1.313; 95% CI, 1.082 to 1.593; p=0.005), see Table 2].

Non-inferiority analysis of overall survival (OS) demonstrated that *nab*-paclitaxel/carboplatin (nab-p/C) treatment is not inferior to paclitaxel/carboplatin (P/C) treatment. Overall survival in the *nab*-paclitaxel arm was 12.1 months versus 11.2 months in the control arm (p = 0.271; HR = 0.922). There was an approximately 10% increase in PFS in the *nab*-p/C versus P/C arm and PFS in the nab-p/C arm was noninferior to PFS in the P/C arm ($HR_{nab\text{-}p/C/P/C}$ 95% CI upper bound, 1.086).

Table 2: Blinded Radiology Assessment of Overall Response Rate (Intent-to-treat Population)

Variable Category/Statistic	*nab*-Paclitaxel/ carboplatin (N=521)	Paclitaxel/ carboplatin (N=531)	Response Rate Ratio (p_A/p_T)	p-value
Patients with Confirmed Complete or Partial Overall Response				
n (%)	170 (33%)	132 (25%)	1.313	0.005*
Confidence Interval (CI) [a]	28.6, 36.7	21.2, 28.5	1.082, 1.593	
Complete Response, n (%)	0	1 (< 1%)		
Partial Response, n (%)	170 (33%)	131 (25%)		

P_A/P_T: response rate of *nab*-paclitaxel/response rate of paclitaxel.
[a] 95% CI of response rate and 95.1% CI of response rate ratio.
* Indicates p-value < 0.049.
Note: p-value is based on a chi-square test.
Source: Data on File.

Adverse events (AEs) were assessed in 514 *nab*-paclitaxel/carboplatin-treated patients and 524 paclitaxel injection/carboplatin-treated patients. The following common (≥ 10% incidence) AEs were observed at a similar incidence in *nab*-paclitaxel/carboplatin and paclitaxel/carboplatin arms: alopecia 56%, nausea 27%, fatigue 25%, decreased appetite 17%, asthenia 16%, constipation 16%, diarrhea 15%, vomiting 12%, dyspnea 12%, and rash 10% (incidence rates are for the *nab*-paclitaxel plus carboplatin treatment group). Toxicities, particularly neuropathy and Grade 3/4 neutropenia were less pronounced using *nab*-paclitaxel in the dose and schedule employed. Laboratory-detected abnormalities which occurred with a difference ≥ 5% for nab-paclitaxel plus carboplatin versus paclitaxel injection plus carboplatin (Grades 1 to 4 [and Grade 3/4]) were: anemia (98% vs 91% [28% vs 7%]), neutropenia (85% vs 83% [47% vs 58%]) and thrombocytopenia (68% vs 55% [18% vs 9%]).

1.3. Rationale for *nab*-Paclitaxel as Second-line Treatment in Subjects with Advanced Nonsquamous NSCLC

Patients who fail first-line chemotherapy are eligible for second-line treatment with single agent docetaxel, pemetrexed or erlotinib. In patients with good performance (eg, ECOG PS 0 or 1) and general health status, further treatment with chemotherapy is an important consideration that has been shown to extend overall survival. Despite the availability of second-line therapy, the trend of increased use of pemetrexed, as well as erlotinib (in selected patients) in the first-line and maintenance settings, potentially limits the number of available second-line treatment options for many patients. Furthermore, the tolerability issues associated with the administration of docetaxel once every 3 weeks (q3w) has prompted active research in the past decade to evaluate whether weekly regimens of taxanes could be optimized to improve the toxicity profile. The availability of an effective second-line cytotoxic chemotherapy with an improved efficacy/safety profile over current available options would be a valuable addition for both the patient and the treating physician. Paclitaxel has also demonstrated potential activity in second-line NSCLC in a

few studies (Socinski, 1999; Juan, 2002; Socinski, 2002; Sculier, 2002; Buccheri, 2004; Ceresoli, 2004; Yasuda, 2004).

nab-Paclitaxel exhibits 10-fold higher mean C_{max} of free paclitaxel, delivers 33% higher drug concentration to tumors in preclinical xenograft models, and demonstrates enhanced transport across endothelial cell monolayers, when compared with paclitaxel (Desai, 2006; Gardner, 2008). The Cremophor EL-free medium enables *nab*-paclitaxel to be given over a shorter duration without the need for premedication to prevent solvent-related hypersensitivity reactions. When administered with carboplatin in the first-line setting, weekly *nab*-paclitaxel has demonstrated a more favorable efficacy:safety profile compared to the every 3 weeks schedule. This weekly schedule schedule of *nab*-paclitaxel allows the opportunity for closer (ie, shorter interval) monitoring of side effects and optimizing dose-intensity through timely adjustments.

As previously noted, *nab*-paclitaxel 100 mg/m^2 weekly (Days 1, 8 and 15) in combination with carboplatin (21 day cycle) is approved in the US, Japan, Argentina, Australia, and New Zealand for the treatment of locally advanced or metastatic NSCLC in the first-line setting. However, there is limited data of monotherapy *nab*-paclitaxel in the second-line setting; hence, this study will assess the efficacy and tolerability of weekly *nab*-paclitaxel, when administered on Days 1 and 8 of each 21-day cycle. The allowance of a one week rest period in this study (ie, no treatment on Day 15), takes into account research findings from other taxanes, whereby patients in the second-line setting are unlikely to tolerate the same dose-intensity compared to chemo-naïve patients (eg, sharper dose reduction in the second-line setting). Therefore, the proposed *nab*-paclitaxel schedule (2 weeks treatment, 1 week rest) could offer the option of maintaining consistent dose-intensity for NSCLC patients in this setting.

1.4. Rationale for *nab*-Paclitaxel in Combination With Epigenetic Modifying Therapy of CC-486 as Second-line Treatment in Subjects with Advanced Nonsquamous NSCLC

CC-486 is an orally bioavailable formulation of the nucleoside analog 5-azacitidine (AZA). After its incorporation into a cell's DNA during the S-phase of the cell cycle, CC-486 forms covalent adducts with DNA Methyltransferase 1 (DNMT1) and depletes this enzyme required for the maintenance of DNA methylation patterns, thereby altering the epigenetic status of the cell.

Epigenetic changes are covalent modifications of chromatin (DNA and histone proteins) that mediate the stable transmission of a gene's transcriptional status through cell division. One of the first recognized epigenetic alterations in cancer was DNA methylation. The addition of a methyl group to cytosine in the dinucleotide CpG is catalyzed by DNA methyltransferases (DNMTs) and is associated with transcriptional repression of genes with high density of CpGs (CpG islands) in the vicinity of their promoters (Jones, 2007). Genomic methylation patterns are precisely regulated during normal embryonic development and differentiation and have been found to be altered in specific ways in cancer. Specifically, cancer cell genomes are typified by reduced methylation globally with focal areas of aberrant hypermethylation in the CpG islands of genes encoding known tumor suppressors such as PTEN and BRCA1 as well as genes encoding proteins required for apoptosis, including caspase 8, DAPK and Apaf-1. DNA methylation-based silencing can thus contribute to the establishment and maintenance of the transformed state and limit the effectiveness of anti-cancer therapies. The recognition of the role of aberrant methylation in carcinogenesis and its reversibility has led to the development of DNMT

inhibitors for cancer. Subcutaneous (SC) AZA was the first DNMT inhibitor to be approved in myelodysplastic syndromes (MDS) in 2004 (Kaminskas, 2005).

The notion that sequential treatment with an epigenetic modifying agent followed by a cytotoxic agent can result in improved response to the latter is supported by numerous preclinical experiments and now by early clinical results. In breast cancer cell lines, restoring expression of the aberrantly methylated pro-apoptotic gene TMS1 with azacitidine can restore taxane sensitivity (Gordian, 2009). In a model of platinum resistant ovarian cancer, azacitidine reversed resistance to carboplatin (Li, 2009). This effect required pretreatment of the cells with noncytotoxic levels of azacitidine for 24 hours before the addition of carboplatin and was not observed with concurrent exposure to both agents. More recently, Juergens and colleagues observed an unusually high ORR of approximately 20% in multiple-relapsed NSCLC patients treated with a variety of regimens after being treated with a combination of SC AZA and another epigenetic agent, entinostat, a histone deacetylase inhibitor (Juergens, 2011). In one case, a patient who had previously progressed on a regimen of paclitaxel, carboplatin and bevacizumab responded to the same triplet after treatment with SC AZA and entinostat, suggesting that the epigenetic modifying agents had reversed acquired resistance to the cytotoxic/anti-angiogenic regimen. In a Phase 1/2 study of SC AZA with *nab*-paclitaxel in subjects with advanced metastatic solid tumors and breast cancer (Dumlao, 2011), escalating doses of SC AZA (75 to 100 mg/m^2) were administered on Days 1 through 5, followed by *nab*-paclitaxel (100 mg/m^2) intravenous (IV) on Days 8, 15, and 22 of a 28-day cycle. Of 16 subjects treated at the time of publication, clinical activity has included 3 complete responses (CR, 1 Diffuse Large B-cell Lymphoma [DLBCL], 2 ovarian), 4 partial responses (PR) in ovarian and endometrial cancer and 4 stable diseases (SD, 2 lung, 1 pancreatic, and 1 sarcoma).

CC-486 entered clinical testing in 2006 in subjects with MDS, chronic myelomonocytic leukemia [CMML], and acute myeloid leukemia [AML], with daily extended dosing schedules of 14 and 21 out of 28 days in a non-crossover fashion. Daily doses of 300 mg CC-486 have proven to be tolerated on both the 14 and 21 out of 28-day schedules with myelosuppression, gastrointestinal symptoms, and fatigue being the most common toxicities (Garcia-Manero, 2011). Subjects treated with CC-486 for 14 or 21 days had DNA hypomethylation that persisted through the end of cycle. This contrasts with the lack of persistent hypomethylation at the end of cycle when subjects were treated with SC AZA for 7 out of 28 days.

This Phase 2 study will test the hypothesis that epigenetic modifying therapy with CC-486 can improve the anti-tumor activity of *nab*-paclitaxel in second-line NSCLC patients (see Section 4.2 for study rationale). Although docetaxel has been assessed in other randomized studies as a chemotherapy backbone, the considerable neutropenia-related toxicity could potentially pose safety concerns if combined with CC-486, and the steroid premedication could confound the epigenetic impact of CC-486. In addition, the q3w dosing schedule of docetaxel restricts dose adjustment options, thus potentially yielding lower chemotherapy dose-intensity.

Please refer to the Investigator's Brochures (IBs) of CC-486 and *nab*-paclitaxel (ABI-007) for detailed information concerning the available pharmacology, toxicology, drug metabolism, clinical studies, and adverse event profile of the IPs.

2. STUDY OBJECTIVES

2.1. Primary Objective

The primary objective of the study is:

- To assess the efficacy of *nab*-paclitaxel administered intravenously (IV) on Days 8 and 15 with epigenetic modifying therapy of CC-486 once daily (QD) on Days 1 to 14 every 21 days, and *nab*-paclitaxel monotherapy administered IV on Days 1 and 8 every 21 days as second-line treatment for advanced nonsquamous NSCLC, and the relative efficacy of these two treatment regimens.

2.2. Secondary Objective

The secondary objective of the study is:

- To evaluate the safety and tolerability of *nab*-paclitaxel administered IV on Days 8 and 15 with epigenetic modifying therapy of CC-486 QD on Days 1 to 14 every 21 days, and *nab*-paclitaxel monotherapy administered IV on Days 1 and 8 every 21 days as second-line treatment for advanced nonsquamous NSCLC.

2.3. Exploratory Objectives

The exploratory objectives of the study are:

- To assess healthcare resource utilization for the two treatment arms.
- To assess the QoL for the two treatment arms.
- To determine baseline tumor characteristics which predict response to *nab*-paclitaxel as a single agent and with epigenetic modifying therapy of CC-486.
- To evaluate genomic correlates of response to *nab*-paclitaxel as a single agent and with epigenetic modifying therapy of CC-486.

3. STUDY ENDPOINTS

Study efficacy endpoints will be assessed by the investigator using RECIST 1.1 guidelines.

3.1. Primary Endpoint

The primary endpoint is:

- Progression free survival.

3.2. Secondary Endpoints

The secondary endpoints are:

3.2.1. Efficacy

- Disease control rate.
- Overall response rate.
- Overall survival.

3.2.2. Safety

- The type, frequency, and severity of AEs and SAEs graded using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE, Version 4.0).
- Discontinuation rate.
- The median dose intensity.
- The incidence of dose reduction.

3.3. Exploratory Endpoints

- Healthcare resource utilization during the study using a questionnaire.
- Changes in the Lung Cancer Symptom Scale (LCSS), European Organisation for Research and Treatment of Cancer (EORTC) QLQ C30, and EuroQoL 5D-5L (EQ-5D-5L).
- The correlation between pretreatment tumor characteristics and response to the study treatment determined using next-generation sequencing methods, immunohistochemistry, or other analysis methods.

4. OVERALL STUDY DESIGN

4.1. Study Design

This is a Phase 2, randomized, open-label, multicenter study to assess safety and efficacy of *nab*-paclitaxel in combination with epigenetic modifying therapy of CC-486, and *nab*-paclitaxel monotherapy as second-line treatment in subjects with advanced nonsquamous NSCLC who have received one platinum-containing chemotherapy regimen. Approximately 160 subjects with advanced nonsquamous NSCLC will be randomized 1:1 into one of the two treatment arms: *nab*-paclitaxel / CC-486 or *nab*-paclitaxel monotherapy prior to receiving first dose of investigational product (IP). Randomization will be centralized and stratified by ECOG performance status (0 versus 1), gender (males versus females), and smoker (yes versus no).

The study will consist of up to a 28-day Screening Period, a Treatment Period and a Follow-up Period.

4.1.1. Screening Period

The Screening Period for eligibility determination begins upon subject written informed consent. All screening assessments must be completed within 28 days prior to first dose of IP.

4.1.2. Treatment Period

The Treatment Period begins with the first dose of IP as described in Section 8. Subjects will receive one of the following treatments based on the randomization assignment:

- *nab*-Paclitaxel 100 mg/m^2 IV infusion over 30 minutes on Days 8 and 15 and CC-486 200 mg orally QD on Days 1 to 14 of each 21-day treatment cycle, or
- *nab*-Paclitaxel 100 mg/m^2 IV infusion over 30 minutes on Days 1 and 8 of each 21-day treatment cycle.

No additional anticancer agents are allowed during study treatment. All supportive care (including but not limited to growth factors, antiemetics, analgesics, zolendronic acid, denosumab) is permitted as per the investigator's discretion and should be administered according to local institutional practice. Subjects will continue treatment until disease progression, development of an unacceptable toxicity, death, lost to follow-up, withdrawal of consent, or termination of the study by the sponsor.

During the study, subjects will have computed tomography (CT) scans every 42 days (-3/+7 days) until documented progression of disease, withdrawal of consent, lost to follow-up, death, or termination of the study by the sponsor. Tumor evaluations will be assessed by the investigative sites and response will be determined according to RECIST 1.1 guidelines.

All scheduled laboratory samples will be sent to a central laboratory for analysis. Local hematology and chemistry tests may be performed as required for subject management/treatment decisions. Local laboratory values that are considered abnormal and clinically significant will be recorded as an AE/SAE and also recorded on the laboratory eCRF (see Section 11.3).

4.1.3. Follow-up Period

All subjects who discontinue from treatment for reasons other than withdrawal of consent, lost to follow-up, death, or termination of the study by the sponsor will enter the Follow-up Period. It will consist of a visit 28 days after treatment discontinuation followed by phone follow-up for survival approximately every 90 days (+/- 14 days) for up to 12 months after the last subject is randomized or 120 PFS events have been observed whichever comes later.

Those subjects entering the Follow-up Period without documented progression will continue to have CT scans in accordance with local standard of care (or approximately every 90 days) until documented progression of disease, withdrawal of consent, lost to follow-up, death, or termination of the study by the sponsor. All posttreatment anticancer therapies will be recorded during the Follow-up Period.

4.2. Study Design Rationale

This is an open-label, randomized study designed to evaluate the effects of adding CC-486 to *nab*-paclitaxel and *nab*-paclitaxel monotherapy in second-line NSCLC. A placebo-controlled study would not be feasible for this population as blinding would be difficult and would need a double dummy design. A key objective in this study is to determine the chemo-priming effect of CC-486. The inclusion of only patients with nonsquamous NSCLC histology allows for a more homogenous population, hence, reducing the impact of potential confounding factors. Second-line NSCLC enables a unique setting to evaluate epigenetics:

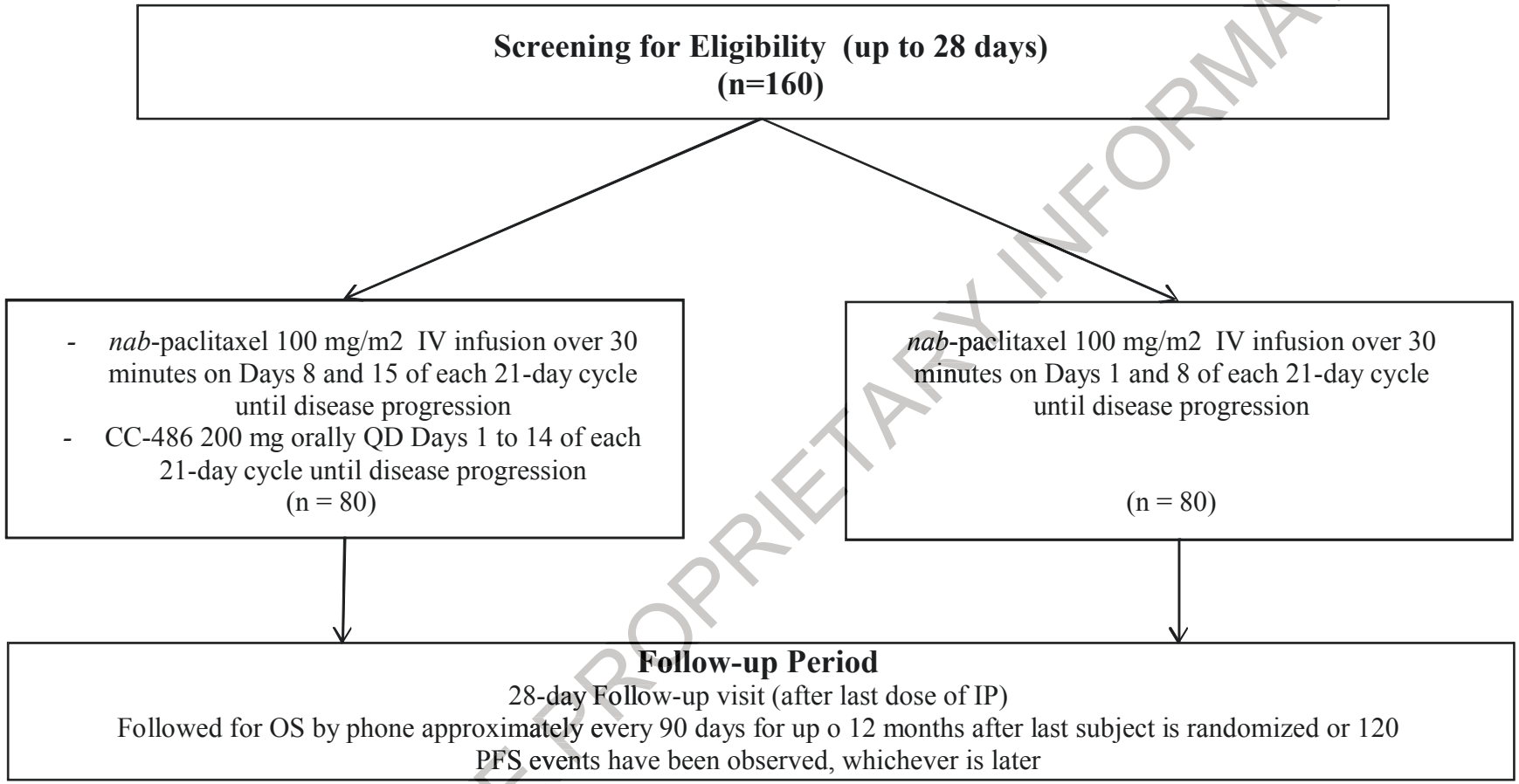
a) compared to more heavily treated patients, patients eligible for second-line treatment have better immune function/reserve which is critical for safety and activation of immune cells that target cancer cells,

b) due to the overlapping (and dose-limiting) toxicities of doublet/triplet chemotherapy regimens in the first-line setting, it would be very challenging to combine epigenetic therapy at a dose level to elicit clinically meaningful benefit.

Although docetaxel has been assessed in other randomized studies as a chemotherapy backbone, the considerable neutropenia-related toxicity could potentially pose safety concerns if combined with CC-486, and the steroid premedication could confound the epigenetic impact of CC-486. In addition, the q3w dosing schedule of docetaxel restricts dose adjustment options, thus potentially yielding lower chemotherapy dose-intensity.

For patients with NSCLC whose disease progressed after initial platinum-based chemotherapy, the goal of therapy is to delay further progression for as long as possible; hence, the use of PFS as the primary endpoint for efficacy evaluation. Furthermore, maintaining quality of life during this period, especially in reducing/managing toxicity is also an important consideration. Therefore, the proposed study is designed to optimize the evaluation of efficacy with a tolerable dose/schedule of chemotherapy, and its combination with an epigenetic modifying therapy.

Figure 1: Overall Study Design



IP = investigational product; PFS = progression-free survival; QD = once daily; OS = overall survival

4.3. Study Duration

Recruitment is expected to take approximately 24 months, and the analysis of PFS will be performed when approximately 120 PFS events have occurred, estimated as approximately 26 months from first subject randomized. The total length of this Phase 2 study with follow-up is estimated to last approximately 3 years.

4.4. End of Trial

The End of Trial is defined as either the:

- date of the last visit of the last subject to complete the study, or
- the date of receipt of the last data point from the last subject that is required for primary, secondary and/or exploratory analysis, as pre-specified in the protocol and/or the Statistical Analysis Plan (SAP), whichever is the later date.

5. TABLE OF EVENTS

Table 3: Table of Events

Assessment	Screening / Baseline	Treatment Period Every 21-day Cycle				End-of-Treatment/ Discontinuation Visit	Follow-up Period	
	Day -28 to Day -1	Day 1 (±2 days)	Day 8 (±2 days)	Day 15 (±2 days)	Every 42 days (-3/+7 days) (starting Day 1 Cycle 1)		28-day Follow-up Visit (after last dose of IP)	Survival Follow-up[a] Every 90 days (+/- 14 days) (after 28-day follow-up visit)
Informed Consent	X	-	-	-	-	-	-	-
Medical History (including Tobacco Exposure History), Prior Medication and Procedures	X	-	-	-	-	-	-	-
Serum β-hCG [b]	X	-	-	-	-	-	-	-
Urine Pregnancy Test [b]	-	X	-	-	-	X	-	-
Complete Chest CT Scan and Any Other Studies Required for Tumor Imaging[c]	X	-	-	-	X	X	-	X
Weight and Height[d]	X	X	X	X	-	-	-	-
ECOG Status	X	X	-	-	-	X	X	-
Concomitant Medication/Procedures	-	X	X	X	-	X	X	X
Peripheral Neuropathy Assessment[e]	X	X	-	-	-	X	X	-
Healthcare Resource Utilization Questionnaire	-	X	-	-	-	X	X	-
Hematology[f]	X	X	X	X	-	X	X	-
Serum Chemistry[f]	X	X	-	-	-	X	X	-
Archived Tumor Tissue Sample for Biomarker (biopsy, surgical specimen, or other diagnostic tumor sample)	-	X (C1D1 only)	-	-	-	-	-	-

Table 3: Table of Events (Continued)

Assessment	Screening/ Baseline	Treatment Period Every 21-day Cycle				End-of-Treatment/ Discontinuation Visit	Follow-Up Period	
	Day -28 to Day -1	Day 1 (±2 days)	Day 8 (±2 days)	Day 15 (±2 days)	Every 42 days (-3/+7 days) (starting Day 1 Cycle 1)		28-day Follow-up Visit (after last dose of IP)	Survival Follow-Up[a] Every 90 days (+/- 14 days) (after 28-day follow-up visit)
Plasma for Biomarker Analyses	-	X (C1D1 only predose)	-	-	-	-	-	-
Blood for Pharmacogenomic Analyses	-	X (C1D1 only predose)	-	-	-	-	-	-
Adverse Event Evaluation	After signing ICF and until 28 days after the last dose of IP							-
nab-Paclitaxel Monotherapy Administration/Accountability[g]	-	X	X		-	-	-	-
nab-Paclitaxel Combination Administration/Accountability[g]	-	-	X	X	-	-	-	-
CC-486 Administration/Accountability[g]	-	X			-	-	-	-
LCSS, EORTC QLQ C30 and EQ-5D-5L	-	X	-	-	-	X	X	-
Survival Phone Call	-	-	-	-	-	-	-	X[a]
Electrocardiogram (ECG)	X	Will be done as per standard of care during the Treatment Period and as clinically indicated; however, results will not be routinely collected in the eCRFs. If CT/bone scans show lesions pertinent for RECIST 1.1 criteria evaluation, data will be collected on the pertinent tumor evaluation eCRFs. If ECGs, physical examinations, and/or vital signs are abnormal and clinically significant, the data will be recorded on the AE/SAE eCRF.						
Vital Signs	X							
Physical Examination	X							
Bone Scan (X-rays if needed)	If clinically indicated							
CT Scan of the Head or Brain Magnetic Resonance Imaging (MRI)	If clinically indicated (mandatory if symptomatic)							

AE = Adverse Event; β-HCG = beta human chorionic gonadotropin; C1D1 = Cycle 1 Day 1; CT = Computed Tomography; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic Case Report Form; EORTC QLQ C30 = European Organisation for Research and Treatment of Cancer QLQ C30; EQ-5D-5L = EuroQol 5D-5L; ICF = informed consent form; IP = investigational product; LCSS = Lung Cancer Symptom Scale; QD = once daily; RECIST = Response Evaluation Criteria in Solid Tumors; SAE = Serious Adverse Event.

[a] Every 90 (+/-14) days (from 28-day Follow-up Visit) for up 12 months after the last subject is randomized or 120 PFS events have been observed whichever comes later.

[b] A pregnancy test is required for women of child-bearing potential only. For women of child-bearing potential a Serum β-hCG pregnancy test must be performed to assess eligibility at Screening/Baseline. Note: the screening serum pregnancy test can be used as the Cycle 1 Day 1 test prior to study therapy if it is performed within the 72-hour timeframe. A urine pregnancy test must be performed prior to administration of IP before beginning each new cycle and at the End-of-Treatment Visit.

[c] All subjects must have a radiographically documented measurable tumor(s) by RECIST 1.1 criteria: Complete chest CT scan (including base of neck and adrenal gland) will be performed at Screening, every 42 days (-3/+7 days) (starting from Day 1 Cycle 1) until disease progression, withdrawal of consent, lost to follow-up, death, or termination of the study by the sponsor. The results of a complete chest CT scan (including base of neck and adrenal gland) performed per Standard of Care may be accepted and not repeated during Screening provided it was performed within 28 days of the first dose of study drug (Cycle 1 Day 1). The methods of assessment chosen at baseline to follow tumors are to remain consistent throughout study duration. Those subjects entering the Follow-up Period without documented progression will continue to have CT scans in accordance with local standard of care (or approximately every 90 days) until documented progression of disease, withdrawal of consent, lost to follow-up, death, or termination of the study by the sponsor.

[d] Height will only be obtained at screening visit. Weight will be obtained at Screening and every visit during the Treatment Period before administration of IP.

[e] The occurrence of peripheral neuropathy will be reported by the investigator per protocol as an AE or SAE.

[f] All scheduled laboratory samples will be sent to a central laboratory for analysis. Local hematology and chemistry tests may be performed as required for subject management/treatment decisions. Local laboratory values that are considered abnormal and clinically significant will be recorded as an AE/SAE and also recorded on the laboratory eCRF (see Section 11.3).

[g] nab-Paclitaxel 100 mg/m2 IV infusion over 30 minutes on Days 8 and 15 and CC-486 200 mg orally QD on Days 1 to14 of each 21-day treatment cycle or nab-paclitaxel 100 mg/m^2 IV infusion over 30 minutes on Days 1 and 8 of each 21-day treatment cycle.

6. PROCEDURES

Subjects will be provided with a written Informed Consent Form (ICF), given the opportunity to ask any questions concerning the study and will sign an ICF prior to participating in any study procedures. After giving written informed consent, subjects will undergo a Screening Period to be assessed for eligibility. All subjects who sign an ICF must be entered into the Integrated Response Technology (IRT) immediately upon signature on the document. Subjects who do not meet the eligibility criteria will be considered screening failures and will not be eligible for the study. Subjects who fail initial screening may undergo re-screening up to 2 times at any time and an ICF will need to be resigned, as well as all screening procedures repeated (some procedures may not need to be done if previously done within 28 days prior to screening again). Subjects that have met all eligibility criteria after the Screening Period will be eligible for randomization.

6.1. Medical History

A complete medical history including, but not limited to, evaluation for past (up to 5 years) or present cardiovascular, respiratory, gastrointestinal, renal, hepatic, neurological, endocrine, lymphatic, hematological, immunologic, dermatological, psychiatric, genitourinary, obstetrical, surgical history or any other diseases or disorders will be performed at Screening. All NSCLC-related medical history should be recorded regardless of time. Smoking status/tobacco exposure history will be captured on the eCRF.

6.2. Prior and Concomitant Medications and Procedures

Prior medications are defined as any medications started before the first dose of IP and stopped either prior to the date of the first dose of IP or continued after study treatment. All prior medications/procedures of clinically significant or ongoing medical conditions taken up to 28 days of time of signature on the ICF should be recorded. All NSCLC-related prior medications/procedures should be recorded regardless of time.

Concomitant medication is defined as the medication that was either initiated before the first dose of IP and continued during the study treatment, or initiated on/after the date of the first dose of IP but on or before 28 days after the last dose of IP. All subjects will have concomitant medications and procedures (including radiation therapy) recorded at each visit from the time of signature on the ICF until the 28-day Follow-up Visit, for conditions that are clinically significant or ongoing. During the Follow-up Period only NSCLC-associated concomitant medications/procedures (including radiation therapy) will be recorded, ie, subsequent-line(s) of anti-cancer therapy.

6.3. Pregnancy Testing

A pregnancy test is required for women of child-bearing potential only. For women of child-bearing potential a serum β-hCG pregnancy test with sensitivity of at least 25 mIU/mL must be performed to assess eligibility at Screening/Baseline. Note: the screening serum pregnancy test can be used as the Cycle 1 Day 1 test prior to study therapy if it is performed within the 72-hour timeframe. A urine pregnancy test must be performed prior to administration of IP before

beginning each new cycle and at the End-of-Treatment Visit. The subject may not receive treatment until the investigator has verified that the result of the pregnancy test is negative. See inclusion criteria for pregnancy testing requirements. Any pregnancies that occur in women who have received IP must be immediately reported to Celgene Drug Safety (See Section 11.4).

6.4. Complete Chest Computed Tomography (CT) Scan

A complete chest CT scan (including base of neck and adrenal gland) and any other studies required for tumor imaging will be done at Screening, every 42 days (-3/+7 days) (starting from Day 1 Cycle 1), and End-of-Treatment, until documented progression of disease, withdrawal of consent, lost to follow-up, death, or termination of the study by the sponsor. The results of a complete chest CT scan (including base of neck and adrenal gland) performed per Standard of Care may be accepted and not repeated during Screening provided it was performed within 28 days of the first dose of study drug (Cycle 1 Day 1). Those subjects entering the Follow-up Period without documented progression will continue to have CT scans in accordance with local standard of care (or approximately every 90 days) until documented progression of disease, withdrawal of consent, lost to follow-up, death, or termination of the study by the sponsor. Additional CT scans may be done at any time during the study if clinically indicated. All CT scans and reports should be archived at the site according to site regulations and copies provided to sponsor if requested. All posttreatment anticancer therapies will be recorded during the Follow-up Period.

6.5. Weight and Height

Weight will be obtained at Screening and at every visit during the Treatment Period before administration of IP. Additional measurements of weight may be collected per local standards at any time during the study as needed. Height will only be collected at Screening. All weight and height data will be collected on eCRFs.

6.6. ECOG Performance Score

Eastern Cooperative Oncology Group performance status score will be collected at Screening, Day 1 of every treatment cycle, at the End-of-Treatment Visit and at the 28-day Follow-up Visit. Additional ECOG assessments may be performed at any time during the study as clinically indicated.

6.7. Peripheral Neuropathy Assessment

Peripheral neuropathy (sensory or motor) assessment will be done at Screening, Day 1 of every treatment cycle, at the End-of-Treatment Visit and at the 28-day Follow-up Visit. Changes in neuropathy grade from baseline will be reported as an AE as per Section 11. Additional peripheral neuropathy assessments may be done at any time during the study as clinically indicated.

6.8. Adverse Event Reporting

Adverse events will be recorded from time of signature on the ICF until 28 days after the last dose of IP, including any unscheduled visits. See Section 11 for details.

6.9. Quality of Life Questionnaires

The LCSS, EORTC QLQ C30 and EQ-5D-5L questionnaires will be used to measure quality of life (QoL) for subjects in the study. The LCSS is comprised of 9 questions to be completed by the subject using a visual analogue scale (VAS) to denote intensity of a symptom. The EQ-5D-5L comprises 5 questions on mobility, self-care, usual activities, pain/discomfort, anxiety/depression and a VAS for overall QoL. These questionnaires will be completed by the subject prior to interaction with study personnel, at Day 1 of every Cycle, at the End-of-Treatment Visit and at the 28-day Follow-up Visit.

6.10. Healthcare Resource Utilization Questionnaire

A healthcare resource utilization questionnaire will be used to capture the additional use of healthcare resources, including hospitalizations, emergency room visits, doctor or nurse visits, procedures, and/or additional medication during the study period. The assessment will be completed on Day 1 of every treatment cycle, at the End-of-Treatment Visit and at the 28-day Follow-up Visit.

6.11. Laboratory Assessments

Blood for hematology and chemistry evaluation will be collected as per Table 3, Table of Events. Blood for hematology will be collected at Screening, Days 1, 8, and 15 of every treatment cycle, at the End-of-Treatment Visit and at the 28-day Follow-up Visit. Blood for serum chemistry will be collected at Screening, Day 1 of every treatment cycle, at the End-of-Treatment Visit and at the 28-day Follow-up Visit. Additional laboratory samples for safety may be collected as clinically indicated.

All scheduled laboratory samples will be sent to a central laboratory for analysis. Local hematology and chemistry tests may be performed as required for subject management/treatment decisions. Local laboratory values that are considered abnormal and clinically significant will be recorded as an AE/SAE and also recorded on the laboratory eCRF (see Section 11.3).

Abnormal and clinically significant laboratory assessments at Screening will be recorded as medical history, and after Screening, as AE or SAE (clinically significant laboratory abnormalities at Screening may result in a subject being ineligible for the study and should not be captured as an AE).

Any abnormal values that persist should be followed at the discretion of the investigator. The investigator should file all copies of the reports, including faxes with the subject's medical chart.

6.12. Tumor Tissue Sample Collection and Peripheral Blood Collection (Exploratory Assessments)

Histologically or cytologically confirmed advanced nonsquamous NSCLC is a required inclusion criteria for entry into this study. If a subject's previously collected tumor tissue (also known as archival tumor) is available, these samples will be collected for biomarker testing as detailed below at Cycle 1 Day 1. If such samples do not exist, have been depleted, or do not contain sufficient tumor material to be analyzed, this will not preclude participation in the study and a

new biopsy or other procedure to collect tumor tissue will not be required. Table 4 delineates the specific requirements for commonly encountered archival tumor types.

Table 4: Requirements for Collection Based on Archival Tumor Sample Type

Sample Type	Amount to Collect	Collection Requirement for Biomarkers	Comments/ Exceptions
Core biopsy or surgical specimen	10 slides ≥4 μM thickness. If a block is provided, a core of viable tumor will also be collected.	Mandatory if the sample exists.	If the quantity of material is not sufficient, the available amount will be collected.
Fine needle aspirates (FNA)	10 slides ≥4 μM. If a block is provided, a core of viable tumor will also be collected.	Mandatory if the sample exists, unless a core biopsy or surgical sample was provided.	If the quantity of material is not sufficient, the available amount will be collected.
Transbronchial endoscopy samples	10 slides ≥4 μM. If a block is provided, a core of viable tumor will also be collected.	Mandatory if the sample exists, unless a core biopsy or surgical sample was provided.	If the quantity of material is not sufficient, the available amount will be collected.
Bronchial lavage, sputum, or other sample types	Slides or blocks representing >100,000 tumor cells	Collection is strongly encouraged when these samples contain sufficient material.	Collection is strongly encouraged when these samples contain sufficient material.

In addition, test results for tumor mutational status of genes, including but not limited to EGFR, ALK, and KRAS will be collected and recorded on eCRF if these tests have been performed.

Plasma for cell-free nucleic acids analyses will be collected on Cycle 1 Day 1 prior to first dose of IP, as will a sample of whole blood or peripheral blood mononuclear cells for a germ-line reference comparison. Types of techniques planned to be used for tumor and plasma analyses include:

- Gene expression by RNA sequencing
- Immunohistochemistry
- DNA sequencing
- DNA methylation profiling

Details regarding the collection, storage, and shipment of the samples are given in the Laboratory Manual.

6.13. Electrocardiogram

Electrocardiograms (ECGs) will be done at Screening and as per standard of care during the Treatment Period, and as clinically indicated. Results will be collected in the eCRFs as AE or

SAE only if results are abnormal, changed and clinically significant, unless the finding is already documented in medical history.

6.14. CT Scan of the Head or Brain Magnetic Resonance Imaging (MRI)

A CT scan of the head, or preferably brain MRI, will be done as per standard of care at Screening, during the Treatment Period, and as clinically indicated. If CT scans show lesions pertinent for RECIST 1.1 criteria evaluation, data will be collected on the pertinent tumor evaluation eCRFs.

6.15. Bone Scans and X-rays

Bone scans and x-rays will be done as per standard of care at Screening, during the Treatment Period, and as clinically indicated. Results will be collected in the eCRFs. If bone scans or X-rays show lesions pertinent for RECIST 1.1 criteria evaluation, data will be collected on the pertinent tumor evaluation eCRFs.

6.16. Physical Examinations

Physical examinations will be done at Screening and as per standard of care during the Treatment Period, and as clinically indicated. Results will be collected in the eCRFs as AE or SAE only if results are abnormal and clinically significant.

6.17. Vital Signs

Vital signs will be done at Screening and as per standard of care during the Treatment Period, and as clinically indicated. Results will be collected in the eCRFs as AE or SAE only if results are abnormal and clinically significant.

6.18. Survival

After the End-of-Treatment Visit, the subjects will have a 28-day Follow-up Visit followed by a phone call approximately every 90 days (+/- 14 days) for at least 12 months after the last subject is randomized or 120 PFS events have been observed whichever comes later. The subjects will also be asked questions about other medications they may be taking for their NSCLC. Those subjects entering the Follow-up Period without documented progression will continue to have CT scans in accordance with local standard of care (or approximately every 90 days) until documented progression of disease, withdrawal of consent, lost to follow-up, death, or termination of the study by the sponsor.

7. STUDY POPULATION

7.1. Number of Subjects and Sites

Male and female subjects with advanced nonsquamous NSCLC who have received one platinum-containing chemotherapy regimen for their advanced disease will be eligible for this study. The study will randomize approximately 160 subjects. The study will be conducted at approximately 30 to 60 sites in the United States, Canada, and Europe.

7.2. Inclusion Criteria

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

1. Age ≥ 18 years at the time of signing the ICF.
2. Understand and voluntarily provide written informed consent prior to the conduct of any study related assessments/procedures.
3. Able to adhere to the study visit schedule and other protocol requirements
4. Histologically or cytologically confirmed advanced nonsquamous NSCLC.
5. No other current active malignancy requiring anticancer therapy.
6. Radiographically documented measurable disease (defined by the presence of ≥ 1 radiographically documented measurable lesion).
7. One prior platinum-containing chemotherapy for the treatment of advanced disease.
8. Absolute neutrophil count (ANC) ≥ 1500 cells/mm^3.
9. Platelets ≥ 100,000 cells/mm^3.
10. Hemoglobin (Hgb) ≥ 9 g/dL.
11. Aspartate transaminase (AST/serum glutamic oxaloacetic transaminase [SGOT]) and alanine transaminase (ALT/serum glutamic pyruvic transaminase [SGPT]) ≤ 2.5 × upper limit of normal range (ULN) or ≤ 5.0 × ULN if liver metastases.
12. Total bilirubin ≤ 1.5 ULN (unless there is a known history of Gilberts Syndrome).
13. Serum creatinine ≤ 1.5 x ULN, or calculated creatinine clearance ≥ 60 mL/min (if renal impairment is suspected 24-hour urine collection for measurement is required).
14. Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1.
15. Females of childbearing potential [defined as a sexually mature woman who (1) have not undergone hysterectomy (the surgical removal of the uterus) or bilateral oophorectomy (the surgical removal of both ovaries) or (2) have not been naturally postmenopausal for at least 24 consecutive months (ie, has had menses at any time during the preceding 24 consecutive months)] must:
    a. Have a negative pregnancy test (ß-hCG) as verified by the study doctor within 72 hours prior to starting study therapy. She must agree to ongoing pregnancy testing

during the course of the study, and after end of study therapy. This applies even if the subject practices true abstinence* from heterosexual contact.

b. Either commit to true abstinence* from heterosexual contact (which must be reviewed on a monthly basis) or agree to use, and be able to comply with, effective contraception without interruption, 28 days prior to starting IP, during the study therapy (including dose interruptions), and for 3 months after discontinuation of study therapy.

Male subjects must:

a. Practice true abstinence* or agree to use a condom during sexual contact with a pregnant female or a female of childbearing potential while participating in the study, during dose interruptions and for at least 6 months following IP discontinuation, even if he has undergone a successful vasectomy.

16. Females must abstain from breastfeeding during study participation and 3 months after IP discontinuation.

7.3. Exclusion Criteria

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

1. Squamous cell NSCLC.
2. Prior taxane therapy.
3. Evidence of active brain metastases, including leptomeningeal involvement (prior evidence of brain metastasis are permitted only if asymptomatic and clinically stable for at least 8 weeks following completion of therapy). MRI of the brain (or CT scan w/contrast) is preferred.
4. Only evidence of disease is non-measurable.
5. Known EGFR mutation.
6. Known EML4-ALK mutation.
7. Preexisting peripheral neuropathy of Grade $\geq$ 2 (per NCI CTCAE v4.0).
8. Venous thromboembolism within 1 month prior to Cycle 1 Day 1.
9. Current congestive heart failure (New York Heart Association Class II-IV).
10. History of the following within 6 months prior to Cycle 1 Day 1: a myocardial infarction, severe/unstable angina pectoris, coronary/peripheral artery bypass graft, New York Heart Association (NYHA) Class III-IV heart failure, uncontrolled hypertension, clinically significant cardiac dysrhythmia or clinically significant electrocardiogram (ECG) abnormality, cerebrovascular accident, transient ischemic attack, or seizure disorder.
11. Known hepatitis B or C virus (HBV/HCV) infection, known history of human immunodeficiency virus (HIV) infection, or receiving immunosuppressive or

* 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].

myelosuppressive medications that would in the opinion of the investigator, increase the risk of serious neutropenic complications.

12. Active, uncontrolled bacterial, viral, or fungal infection(s) requiring systemic therapy, defined as ongoing signs/symptoms related to the infection without improvement despite appropriate antibiotics, antiviral therapy, and/or other treatment.
13. History of interstitial lung disease, sarcoidosis, silicosis, idiopathic pulmonary fibrosis, or pulmonary hypersensitivity pneumonitis.
14. Subject has a clinically significant malabsorption syndrome, persistent diarrhea, or known sub-acute bowel obstruction $\geq$ NCI CTCAE Grade 2, despite medical management.
15. Treatment with any investigational product within 28 days prior to signing the ICF.
16. History of or suspected allergy to *nab*-paclitaxel, azacitidine, human albumin or mannitol.
17. Currently enrolled in any other clinical protocol or investigational trial that involves administration of experimental therapy and/or therapeutic devices.
18. Any other clinically significant medical condition, psychiatric illness, and/or organ dysfunction that will interfere with the administration of the therapy according to this protocol or which, in the views of investigator, preclude combination chemotherapy.
19. Any other malignancy within 5 years prior to randomization, or advanced malignant hepatic tumors, with the exception of adequately treated squamous cell carcinoma of the skin, in-situ carcinoma of the cervix, uteri, non-melanomatous skin cancer, carcinoma in situ of the breast, or incidental histological finding of prostate cancer (TNM Classification of Malignant Tumours (TNM) stage of T1a or T1b). (All treatment of which should have been completed 6 months prior to signing ICF).
20. Any condition including the presence of laboratory abnormalities, which places the subject at unacceptable risk if he/she were to participate in the study.
21. Any medical condition that confounds the ability to interpret data from the study.
22. Pregnant or breastfeeding females.

8. DESCRIPTION OF STUDY TREATMENTS

8.1. Description of Investigational Products

Subjects will receive open-label *nab*-paclitaxel / CC-486 or *nab*-paclitaxel monotherapy during the Treatment Period of the study. The *nab*-paclitaxel and CC-486 are designated as IP and will be packaged and supplied by Celgene Corporation.

The reconstitution and IV administration of *nab*-paclitaxel should follow the local Prescribing Information for Abraxane.

8.1.1. *nab*-Paclitaxel

nab-Paclitaxel will be supplied by the sponsor, Celgene Corporation, in single-use vials in single count cartons. Each single-use 50 mL vial will contain paclitaxel (100 mg) and human albumin as a stabilizer.

Please see local prescribing information for Abraxane for detailed instructions on the reconstitution, storage conditions and IV administration of *nab*-paclitaxel. Reconstituted *nab*-paclitaxel should be stored in an area accessible only to study personnel.

Temperature records for *nab*-paclitaxel must be made available to Celgene or other sponsor-nominated monitoring teams for verification of proper IP storage.

8.1.2. CC-486 (Azacitidine for Oral Administration)

Celgene Corporation will supply azacitidine 100 mg tablets for oral administration. Each tablet is formulated using excipients that are generally regarded as safe and are used in marketed drug products.

All tablets will be packaged in blister cards. Only sufficient IP for one cycle of treatment will be provided to each subject at the start of each treatment cycle. All tablets should be swallowed whole, and should not be broken or chewed. CC-486 may be taken on an empty stomach or with food. Subjects should drink 8 ounces (240 mL) of room temperature water with each dose. It is strongly recommended that all subjects receive a dose of a prophylactic antiemetic, preferably a 5-HT3 antagonist, approximately 30 minutes prior to each dose of CC-486.

The IP must be stored as directed on package label at controlled temperature and a temperature log must be maintained in the source documents The storage area should be secure and have access limited to study personnel.

8.2. Treatment Administration and Schedule

Approximately 160 subjects will be treated with *nab*-paclitaxel / CC-486 or *nab*-paclitaxel monotherapy until disease progression, development of an unacceptable toxicity, death, lost to follow-up, withdrawal of consent, or termination of the study by the sponsor:

- *nab*-Paclitaxel 100 mg/m^2 IV infusion over 30 minutes on Days 8 and 15 and CC-486 200 mg orally QD on Days 1 to 14 of each 21-day treatment cycle

- *nab*-Paclitaxel 100 mg/m^2 IV infusion over 30 minutes on Days 1 and 8 of each 21-day treatment cycle

8.3. Dose Omissions and Modifications

8.3.1. Rules for Dose Omissions and Modified Schedules

nab-Paclitaxel Monotherapy Arm

If, for administrative reasons, treatment cannot be administered on the planned visit date, IP may be administered plus or minus 2 days from the scheduled date.

- **Day 1 Dose Missed**

  If the dose held or missed was to be given on Day 1 of the next cycle, that next cycle will not be considered to start until the day the first dose is actually administered to the subject (ie, D1-D8-Rest, X-D1-D8-Rest, etc).

- **Day 8 Dose Missed**

  That dose will be skipped. Next dose (if laboratory results permit) will be Day 1 of the next scheduled cycle (ie, D1-X-Rest, D1-D8-Rest, etc).

nab-Paclitaxel/CC-486 Combination Arm

If, for administrative reasons, treatment cannot be administered on the planned visit date, IP may be administered plus or minus 2 days from the scheduled date.

If any doses of CC-486 are missed, skip that day and resume as appropriate, do not double up on subsequent days.

For *nab*-paclitaxel:

- **Day 8 Dose Missed**

  That dose will be skipped. Next dose (if laboratory results permit) will be at Day 15 (ie, Rest-X-D15, Rest-D8-D15, etc).

- **Day 15 Dose Missed**

  That dose will be skipped. Next dose (if laboratory results permit) will be Day 8 of the next scheduled cycle (ie, Rest-D8-X, Rest-D8-D15, etc).

8.3.2. Rules for Dose Modifications

Subjects who experience any of the adverse drug reactions in Table 5 will be dose reduced as per Table 5 during treatment.

nab-Paclitaxel Monotherapy Arm

- Do not administer *nab*-paclitaxel on Day 1 of a cycle until ANC is at least 1500 cells/mm^3 and platelet count is at least 100,000 cells/mm^3.
- In subjects who develop severe neutropenia or thrombocytopenia withhold treatment until counts recover to an absolute neutrophil count of at least 1500 cells/mm^3 and platelet count of at least 100,000 cells/mm^3 on Day 1 or to an absolute neutrophil count of at least

500 cells/mm^3 and platelet count of at least 50,000 cells/mm^3 on Day 8 of the cycle. Upon resumption of dosing, permanently reduce *nab*-paclitaxel doses as outlined in Table 5.

- Withhold *nab*-paclitaxel for Grade 3 or 4 peripheral neuropathy. Resume *nab*-paclitaxel at reduced doses (Table 5) when peripheral neuropathy improves to Grade 1 or completely resolves.
    - For Grade 2 or 3 cutaneous toxicity, Grade 3 mucositis, or Grade 3 diarrhea, interrupt treatment until the toxicity improves to ≤ Grade 1, then restart treatment according to the guidelines in Table 5. For any other Grade 3 or 4 nonhematologic toxicity or other investigator defined unacceptable toxicity, interrupt treatment until the toxicity improves to ≤ Grade 2, then restart treatment according to the guidelines in Table 5.

Re-escalation is not permitted at any time.

nab-Paclitaxel/CC-486 Combination Arm

- Do not administer *nab*-paclitaxel on Day 8 or CC-486 on Day 1 or 8 of a cycle until ANC is at least 1500 cells/mm^3 and platelet count is at least 100,000 cells/mm^3.
- In subjects who develop severe neutropenia or thrombocytopenia withhold treatment until counts recover to an absolute neutrophil count of at least 1500 cells/mm^3 and platelet count of at least 100,000 cells/mm^3 on Day 1 and 8 for CC-486 and Day 8 for *nab*-paclitaxel or to an absolute neutrophil count of at least 500 cells/mm^3 and platelet count of at least 50,000 cells/mm^3 on Day 15 of the cycle for *nab*-paclitaxel. Upon resumption of dosing, permanently reduce *nab*-paclitaxel and/or CC-486 doses as outlined in Table 5.
- Withhold *nab*-paclitaxel for Grade 3 or 4 peripheral neuropathy (CC-486 does not need to be withheld). Resume *nab*-paclitaxel at reduced doses (Table 5) when peripheral neuropathy improves to Grade 1 or completely resolves.
    - For Grade 2 or 3 cutaneous toxicity, Grade 3 mucositis, or Grade 3 diarrhea, interrupt treatment until the toxicity improves to ≤ Grade 1, then restart treatment according to the guidelines in Table 5. For any other Grade 3 or 4 nonhematologic toxicity or other investigator defined unacceptable toxicity, interrupt treatment until the toxicity improves to ≤ Grade 2, then restart treatment according to the guidelines in Table 5.

Re-escalation is not permitted at any time.

Table 5: Permanent Dose Reductions for Hematologic and Nonhematologic Toxicities and Dosing on the Study

Dose Modification During Treatment			
Adverse Drug Reaction	**Occurrence**	**Monotherapy Arm: *nab*-paclitaxel Dose (mg/m^2)**	**Combination Arm: *nab*-paclitaxel Dose (mg/m^2) / CC-486 Dose (mg)**
Neutropenic Fever (ANC < 500/mm^3 with fever >38°C) OR Delay of next cycle by > 7 days for ANC < 1500/mm^3 OR ANC < 500/mm^3 for > 7 days	First	75	100/100
	Second	50	75/100
	Third	Discontinue Treatment*	50/100
	Fourth	NA	Discontinue Treatment*
Platelet count < 50,000/mm^3	First	75	100/100
	Second	Discontinue Treatment*	75/100
	Third	NA	Discontinue Treatment*
Peripheral Neuropathy Grade ≥ 3	First	75	75/200
	Second	50	50/200
	Third	Discontinue Treatment*	
Grade 2 or 3 Cutaneous toxicity Grade 3 Diarrhea Grade 3 Mucositis Any other Grade 3 or 4 nonhematologic toxicity or other investigator defined unacceptable toxicity	First	75	100/100
	Second	50	75/100
	Third	Discontinue Treatment*	50/100
	Fourth	NA	Discontinue Treatment*
Grade 4 Cutaneous toxicity, Diarrhea or Mucositis	First	Discontinue Treatment*	

ANC = absolute neutrophil count; AUC = area under the curve; NA = not applicable.
* If an adverse event that requires dose reduction recurs after the dose has been reduced according to the table above , the subject should generally have treatment discontinued unless, at the discretion of the investigator, there is evidence of continuing benefit to the subject that outweighs the risk of recurrent toxicity.

8.4. Method of Treatment Assignment

The Treatment Period of the study is open-label. Enrollment/randomization will occur 1:1 via IRT.

8.5. Packaging and Labeling

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

8.6. Investigational Product Accountability and Disposal

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

Celgene will instruct the investigator on the return, disposal and/or destruction of IP. Only completely unused IP vials should be retained by the site until a representative from Celgene or other Celgene-designated personnel have completed an inventory. Partially used and completely used vials should be destroyed according to local guidelines, and disposition should be recorded on the Investigational Drug Accountability Record Form.

The investigator(s) or designee(s) is responsible for accounting for all IP that is issued to and returned by the subject during the course of the study according to applicable regulatory requirements. Any unused CC-486 must be returned by a study subject and retained by the investigative site for accountability to be conducted by a Celgene representative (or designee). If any IP is lost or damaged, its disposition should be documented. At the periodic monitoring visits, a Celgene representative (or designee) will conduct IP accountability and address any discrepancies. Upon unsatisfactory reconciliation of all IP, returned IP may be destroyed. At the conclusion of the study, all remaining IP will be counted, reconciled with dispensing records, documented, and destroyed at the clinic site or allocated drug destruction location after completion of drug accountability by a Celgene representative (or designee). The Celgene representative (or designee) will ensure that a final report of drug accountability to the unit dose level (ie, tablet) is prepared and placed in both the investigator study file and the central clinical study file.

Investigational product will not be loaned or dispensed by the investigator to another investigator or site. Under certain circumstances, and with sponsor permission, cooperative groups may manage IP between locations within their network as clinical trial agreement and local guidelines permit.

8.7. Investigational Product Compliance

All IP will be administered only by study site personnel and accurate recording of all IP administration will be made in the appropriate section of the subject's eCRF and source documents.

8.8. Overdose

Overdose, as defined for this protocol, refers to *nab*-paclitaxel and CC-486 dosing.

On a per dose basis, an overdose is defined as 10% over the protocol-specified dose of *nab*-paclitaxel or CC-486 to a given subject, regardless of any associated adverse events or sequelae.

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

On an infusion rate basis, an overdose is defined as any rate faster than the protocol-specified rate.

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

9. CONCOMITANT MEDICATIONS AND PROCEDURES

9.1. Permitted Concomitant Medications and Procedures

Over the course of this study, additional medications may be required to manage aspects of the disease state of the subjects, including side effects from study treatments or disease recurrence. All supportive care (including but not limited to growth factors, antiemetics, analgesics, zolendronic acid, denosumab) is permitted as per the investigator's discretion and should be administered according to local institutional practice. All concomitant treatments, including blood and blood products, must be reported on the eCRF.

- Antiemetics are not required during the study; however, it is strongly recommended that all subjects receive a dose of a prophylactic antiemetic, preferably a 5-HT3 antagonist, approximately 30 minutes prior to each dose of CC-486.
- Stable, therapeutic doses of anticoagulants are permitted; however, subjects on warfarin should have prothrombin time (PT) or international normalized ratio (INR) and partial thromboplastin time (PTT) monitored as clinically indicated.
- Subjects on erythropoietin or darbepoetin alfa for at least 4 weeks prior to starting the IP may continue their pretreatment doses throughout the study.
  - Note: If the subject is not on a stable dose of an erythropoiesis-stimulating agents (ESA) prior to study entry, the subject may not start an ESA during Cycle 1. However, medications such as ESAs, granulocyte colony-stimulating factors (G-CSFs), etc., may be administered according to standard of care after Cycle 1.
- Use of white blood cell growth factors (eg, filgrastim, G-CSF for the treatment of subjects with neutropenic fever is permitted at the investigator's discretion. Use of filgrastim rather than pegylated-filgrastim is indicated, because of the 14 day delay of the next cycle following treatment with peg-filgrastim.
- Use of white blood cell growth factors (eg, filgrastim, G-CSF) for secondary prophylaxis in subjects who experienced a neutropenic complication from a prior cycle of chemotherapy (for which primary prophylaxis was not received) is permitted.
- Flu vaccination is permitted.
- Suppressive antiviral therapy (eg, entecavir, tenofovir, or lamivudine) is recommended for subjects with chronic HBV infection (eg, those who are HBsAg positive).
- Routine infectious disease prophylaxis is not recommended, however, antibiotic, antiviral, antipneumocystis, antifungal, or other prophylaxis may be implemented during the study at the discretion of the investigator.
- Treatments with bisphosphonates (eg, pamidronate, zolendronate), or other agents (eg, denosumab) to prevent or delay progression of bone metastases are permitted. Maintenance of a stable dosing regimen throughout the study is recommended.

- Subjects may receive physiologic replacement doses of glucocorticoids as maintenance therapy for adrenal insufficiency. Glucocorticoids may be administered as an antiemetic with IV chemotherapy, if directed by local standard of care.
- Treatment with antidiarrheal medications is recommended at the first sign of diarrhea as per the guidelines in Appendix B. Pre-medication with antidiarrheal medication for subsequent doses of CC-486 may be appropriate.

9.2. Prohibited Concomitant Medications and Procedures

Other investigational therapies must not be used while the subject is enrolled in the study. Anticancer therapy (chemotherapy, biologic or investigational therapy, and surgery) other than the study treatments must not be given to subjects during the study. If such treatment is required, the subject must be discontinued from the study. Focal palliative radiotherapy for treatment of cancer-related symptoms is allowed during study treatment at the discretion of the investigator. The administration of either α-interferon and/or ribavirin, or drugs with known renal toxicity is prohibited during study treatment.

9.3. Required Concomitant Medications and Procedures for Patients Receiving CC-486

If a subject experiences ≥ Grade 3 neutropenia, that subject will be treated with G-CSF 5 μg/kg daily until the ANC ≥ 2000/mm^3. In subsequent cycles, that subject should receive G-CSF 5μg/kg daily beginning on Day 16 and continuing until the ANC ≥ 2000/mm^3. In subjects receiving G-CSF, the next cycle should begin no sooner than 48 hours after discontinuation of G-CSF. Data regarding G-CSF administration should be recorded on the eCRF provided for G-CSF administration.

9.3.1. Description of G-CSF

This medication stimulates the blood system (bone marrow) to make white blood cells, helping fight infections. This medication is given to those whose ability to make white blood cells has been reduced. Filgrastim (also known as G-CSF, or granulocyte colony stimulating factor) is a man-made version of a certain natural substance found in the body. It is produced using a certain bacteria. It will be obtained commercially and relabeled as clinical supplies. It should be stored, and administered according to the manufacturer's recommendation.

9.3.2. Administration of G-CSF

For subjects who experience Grade ≥ 3 neutropenia, G-CSF 5 μg/kg daily will be administered subcutaneously. During any cycle when Grade ≥ 3 neutropenia occurs, CC-486 and other cytotoxic agents will be held, and G-CSF will begin immediately (a minimum of 24 hours after the last dose of CC-486 and chemotherapy). In subsequent cycles, G-CSF will begin on Day 16. G-CSF will continue daily until the ANC ≥ 2000/mm^3. For complete details on drug administration, storage, clinical pharmacology, and the human PK of G-CSF (filgrastim), please see the G-CSF(filgrastim) package insert.

10. STATISTICAL ANALYSES

Statistical analyses for the primary and key secondary endpoints of the study are described below. Additional analyses of these endpoints as well as exploratory endpoints or subgroup analyses will be described in detail in the SAP. The SAP supersedes the analyses described in the protocol should there be differences between the two.

Evaluations of the study endpoints will be based primarily on the point estimates and the associated 95% confidence intervals of the within- and between-treatment differences. However, statistical tests may be conducted and the nominal p-values may be provided in the clinical study report to indicate the strength of the treatment differences evaluated.

10.1. Overview

Approximately 160 subjects will be randomized in a 1:1 ratio to two treatment arms (80 subjects per group). Arm A will receive *nab*-paclitaxel with epigenetic modifying therapy of CC-486 and Arm B will receive *nab*-paclitaxel as a monotherapy. Both regimens will be administered in 21-day cycles. All subjects will receive the assigned study treatment until disease progression, unacceptable toxicity, death, lost to follow-up, withdrawal of consent, or termination of the study by the sponsor, in accordance with local standard of care. A permuted-block randomization method will be employed, and the randomization will be carried out centrally using an IRT system. The randomization will be stratified based on the following baseline factors:

- ECOG performance status (0 versus 1)
- Gender (males versus females)
- Smoker (yes versus no)

A DMC will be used to review the safety and efficacy data during the study.

10.2. Study Population Definitions

10.2.1. Intent-to-treat Population

The primary efficacy analysis will be performed on the intent-to-treat (ITT) population, which includes all randomized subjects regardless of whether the subject receives any IP or has any efficacy assessments performed.

10.2.2. Per-protocol (PP) Population

The PP population is defined as all eligible subjects randomized who receive at least one dose of the IP and have been treated in the arm they were assigned. Additional analyses utilizing the PP population will be described in the SAP.

10.2.3. Treated Population

The treated population will consist of all randomized subjects who receive at least one dose of IP. The safety analyses will be based on the treatment as received if different from the assigned treatment by randomization.

10.3. Sample Size and Power Considerations

The primary objective of this study is to evaluate the efficacy of the CC-486/*nab*-paclitaxel combination therapy and that of the *nab*-paclitaxel monotherapy, and the relative efficacy of these two treatment regimens.

The effect of the two treatment regimens with respect to the efficacy endpoints will be based on the point estimates and the associated 95% confidence intervals. The sample size was chosen to support the estimation of the within- and between-treatment effects with reasonable precision.

Table 6 below summarizes the two-sided 95% confidence intervals for a range of hypothetical observed disease control rates given a sample size of 80 subjects in a treatment arm. If the observed disease control rate is 0.30, then the actual width of the 2-sided 95% confidence interval is 0.21 (95% CI is [0.20, 0.41]).

Table 6: Disease Control Rate –Two-Sided 95% Confidence Interval of Hypothetical Disease Control Rate with a Sample Size of 80 Subjects in a Treatment Arm

Hypothetical Observed Disease Control Rate	Half Width of 95% Confidence Interval	95% Confidence Interval[a]
0.20	0.186	(0.119, 0.304)
0.25	0.199	(0.16, 0.359)
0.30	0.21	(0.203, 0.413)
0.35	0.218	(0.247, 0.465
0.40	0.224	(0.292, 0.516)
0.45	0.227	(0.338, 0.565)
0.50	0.228	(0.386, 0.614)

[a] Based on the Clopper-Pearson exact method.

Table 7 below summarizes the precision that can be achieved given different scenarios of hypothetical observed hazard ratios between the two treatment arms for PFS events, assuming a total of 120 events are observed.

Table 7: Progression-Free Survival – Two-Sided 95% Confidence Interval of Hypothetical Observed Hazard Ratio between Treatment Arms

Hypothetical Number of Events Observed	Hypothetical Observed Hazard Ratio of PFS Events	95% Confidence Interval of Hazard Ratio[a]
120	0.60	(0.42, 0.86)
	0.65	(0.45, 0.93)
	0.70	(0.49, 1.00)

[a] Assuming a standard error of 0.18 for the log hazard ratio.

Assuming the median times of PFS are 4.17 and 2.5 months, respectively, for the *nab*-paclitaxel/CC-486 combination therapy and *nab*-paclitaxel monotherapy arms, and an approximate 24 months accrual period for a total of 160 subjects, it is estimated that a total of 120 PFS events will have been observed approximately 2 months after the last subject is randomized, assuming an exponential distribution for PFS.

Of note, with 120 PFS events, this study has an 80% power (1-sided, Type-1 error of 2.5%) to detect a HR of 0.60 for PFS improvement with the *nab*-paclitaxel/CC-486 arm over the *nab*-paclitaxel monotherapy arm.

One nonbinding interim analysis for PFS with an early stopping rule for futility will be conducted when approximately 60 events are observed. The *nab*-paclitaxel/CC-486 combination arm of the study may be stopped early for futility if the observed HR is > 1.10 given an approximate 60 PFS events have occurred at the time of the interim analysis. A HR> 1.10 when half of the target events of 120 have occurred signals a low probability for observing a meaningful difference in favor of the nab-paclitaxel/CC-486 combination therapy should the study continue to the end. With the assumptions stated above, it will take approximately 16 months from the first subject randomized to observe approximately 60 PFS events for the interim analysis.

If futility is declared, enrollment in the monotherapy *nab*-paclitaxel arm will continue up to a total of 80 subjects.

Disease control rate, OS, and ORR will be evaluated within each treatment arm and between the treatment arms at the time of the final analysis of the PFS endpoint when approximately 120 PFS events have been observed.

All subjects will continue to be followed for OS up to 12 months after the last subject is randomized or 120 PFS events have been observed, whichever comes later.

10.4. Background and Demographic Characteristics

The baseline characteristics of all randomized subjects will be summarized. Subject's age, height, weight, and baseline characteristics will be summarized using descriptive statistics, while gender, race and other categorical variables will be provided using frequency tabulations. Selected medical history data will be summarized using frequency tabulations by system organ class and preferred term.

10.5. Subject Disposition

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

10.6. Efficacy Analysis

10.6.1. Primary Efficacy Endpoints

The primary efficacy endpoint is progression-free survival, which is defined as the time from the date of randomization to the date of disease progression or death (any cause) on or prior to the data cutoff date for analyses, whichever occurs first, based on the investigator's assessment of the data from CT scans using RECIST 1.1 guidelines. Baseline tumor measurements will be determined from the radiologic evaluation performed within 28 days before the start of study therapy.

Subjects who do not have disease progression and are alive as of the data cutoff date for the statistical analysis will be censored at the date of the last radiologic assessment prior to the data cutoff date. Similarly, subjects who discontinue from the study prior to disease progression or death will be censored at the date of the last radiologic assessment prior to the data cutoff date. In the event that a new anticancer treatment occurs prior to documented progression, the subject will be censored at the date of the last radiologic assessment where the subject was documented to be progression-free prior to the new anticancer treatment. Subjects with a single missing radiologic assessment prior to a visit with documented disease progression (or death) will be analyzed as a PFS event at the date of the radiologic assessment that shows progression or death (whichever is earlier). Subjects with two or more missing radiologic assessments prior to a visit with documented disease progression (or death) will be censored at the date of the last radiologic assessment where the subject was documented to be progression-free prior to the first of the two missing visits. Subjects who drop out early or die without any postbaseline radiologic tumor assessment will be censored on the date of randomization.

Progression-free survival will be summarized using Kaplan-Meier methods with median PFS time (including two-sided 95% CI) for each treatment arm. The Kaplan-Meier curve for PFS will be presented graphically for each treatment arm. The relative treatment effect between the combination and monotherapy arms on PFS will be estimated by the hazard ratio (HR) and the associated two-sided 95% CIs using the stratified Cox proportional hazard model with ECOG performance status (0 versus 1), gender (males versus females), and smoker (yes versus no) as the stratification factors, given the number of events in each cell is adequate. No statistical inferential tests will be performed.

To assess the impact on PFS of radiologic assessments not occurring at the regularly scheduled assessment times, the frequency of these unscheduled/off-scheduled assessments will be presented for each treatment arm. In addition, confirmatory and sensitivity analyses will be performed to further assess the impact of missed radiologic assessments. An additional analysis of PFS, where death or new treatment will be considered as an event, will be conducted to address the impact of next line therapy.

10.6.2. Secondary Efficacy Endpoints

10.6.2.1. Disease Control Rate

Disease control rate is defined as the percent of subjects who have a radiologic complete response, partial response, or stable disease according to RECIST 1.1 guidelines, as determined by the investigator.

Disease control rate for each treatment arm will be summarized by the observed DCR rate and the associated two-sided 95% CI. The relative treatment effect will be summarized by the absolute difference and ratio of the response rates and the associated two-sided 95% CI.

10.6.2.2. Overall Survival

Overall survival is defined as the time between randomization and death. All deaths, regardless of the cause of death, will be included. All subjects who are lost to follow-up prior to the end of the study or who are withdrawn from the study will be censored at the time of last contact. Subjects who are still receiving treatment as of the data cutoff date will be censored at the cutoff date. Overall survival will be analyzed in a similar manner as that for PFS.

10.6.2.3. Overall Response Rate

Overall response rate is defined as the percent of subjects who have a radiologic complete or partial response according to RECIST 1.1 guidelines determined by the investigator.

Overall response rate will be assessed using the same statistical methods as those for the DCR endpoint.

10.6.3. Exploratory Endpoints

10.6.3.1. HealthCare Utilization

Healthcare utilization will be summarized by treatment. Additional analyses will be described in detail in the SAP.

10.6.3.2. Quality of Life Questionnaires

The score or VAS value and the corresponding change from baseline at each timepoint will be summarized by treatment for the EQ-5D-5L, EORTC QLQ C30 and LCSS questionnaires. Additional analyses will be described in detail in the SAP.

10.6.3.3. Biomarker, Tumor Characteristics, and Genomic Analyses

Statistical analysis of the biomarkers, tumor characteristics, and genomic correlates will be described in a SAP separate from that described above.

10.7. Safety Analysis

The treated population, which includes all randomized subjects who receive at least one dose of IP, will be the analysis population for all safety analyses.

The safety/tolerability of the two treatment arms will be monitored through continuous reporting and evaluated by adverse events and serious adverse events, and incidence of subjects experiencing dose modifications, dose interruptions, and/or premature discontinuation of IP.

10.7.1. Adverse Events

Adverse events will be analyzed in terms of TEAEs, defined as any AE or SAE occurring or worsening on or after the day of the first dose of the IP through 28 days after the last dose of IP. In addition, any serious AE with an onset date more than 28 days after the last dose of IP that is assessed by the investigator as related to IP will be considered a TEAE.

Adverse events will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA). The severity of AEs will be graded based on NCI CTCAE, Version 4.0; http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40.

Treatment-emergent adverse events, Grade 3 or higher TEAEs, serious AEs, TEAEs leading to dose reduction, dose delay, and dose interruption, TEAEs leading to treatment discontinuation, and TEAEs with an outcome of death will be summarized per treatment arms by MedDRA system organ class and preferred terms.

Adverse events of special interest of the *nab*-paclitaxel/CC-486 combination and *nab*-paclitaxel monotherapy regimens identified in previous studies in a similar population may be identified and summarized by worst NCI CTCAE grade, System Organ Class (SOC) and MedDRA preferred terms.

By-subject listings will be provided for all relevant safety data. Graphical displays and figures will be provided where useful to assist in the interpretation of results.

10.7.2. Laboratory Assessments

Treatment group differences in each laboratory parameter with respect to the NCI CTCAE grades will be summarized by the frequency distribution of subjects with the AE grades.

All laboratory parameters will be summarized by descriptive statistics within each treatment arm, as appropriate.

10.7.3. Study Drug Exposure

The extent of exposure to the IPs will be assessed based on the descriptive statistics on the number of cycles and IP doses administered, cumulative dose, average dose intensity, and percentage of protocol dose administered. The incidences of CC-486 and *nab*-paclitaxel dose reductions, dose interruptions, and dose delays will be summarized by treatment arm.

10.8. Study Therapy Termination

Reasons for stopping study therapy will be presented in listings and summarized by frequency of occurrence and corresponding percentage of occurrence.

10.9. Deaths

Deaths reported during treatment (defined as deaths from the first administration of the IP through 28 days post last dose of the IP) and deaths that occur during the Follow-up Period will

be summarized by frequency of occurrence and corresponding percentage by cause of death per period (during treatment or follow-up).

10.10. Interim Analysis

One nonbinding interim analysis for PFS with an early stopping rule for futility will be conducted when approximately 60 events are observed. The *nab*-paclitaxel/CC-486 combination arm of the study may be stopped early for futility if the observed HR is ≥ 1.10 given an approximate 60 PFS events have occurred at the time of the interim analysis. Should this occur, enrollment in the monotherapy *nab*-paclitaxel arm will continue up to a total of 80 subjects.

10.11. Data Monitoring Committee

An independent DMC will be established with the responsibilities for safeguarding the interests of study participants and monitoring the overall conduct of the study. Final recommendations of the DMC will reflect the judgment of the DMC members and will be considered advisory in nature to the sponsor. The decision to implement the recommendations of the DMC will be made by the sponsor, following consultation with the coordinating investigator and Steering Committee.

Operational details for the DMC will be detailed in the DMC charter.

10.12. Scientific Steering Committee

The conduct of this study will be overseen by a Steering Committee. The Steering Committee will serve in an advisory capacity to the sponsor.

11. ADVERSE EVENTS

11.1. Monitoring, Recording and Reporting of Adverse Events

An adverse event (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 11.3), 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 eCRF rather than the individual signs or symptoms of the diagnosis or syndrome.

For the purposes of this study, progressive disease (PD) of NSCLC will not require reporting as an adverse event.

An overdose, accidental or intentional, whether or not it is associated with an AE, or abuse, withdrawal, sensitivity or toxicity to an investigational product should be reported as an AE. If an overdose is associated with an AE, the overdose and adverse event should be reported as separate terms. See Section 8.8 for the definition of overdose.

In the event of overdose, the subject should be monitored as appropriate and should receive supportive measures as necessary. There is no known specific antidote for *nab*-paclitaxel or CC-486 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 appropriate tests and procedures.

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

11.2. Evaluation of Adverse Events

A qualified investigator will evaluate all adverse events as to:

11.2.1. Seriousness

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

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

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

- A standard procedure for protocol therapy administration. However, hospitalization or prolonged hospitalization for a complication of therapy administration will be reported as an SAE.
- Routine treatment or monitoring of the studied indication not associated with any deterioration in condition.
- The administration of blood or platelet transfusion as routine treatment of studied indication. However, hospitalization or prolonged hospitalization for a complication of such transfusion remains a reportable SAE.
- A procedure for protocol/disease-related investigations (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 starting of treatment on study); must be documented in the source document and the eCRF. 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.
- 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 eCRF and the SAE Report Form must be completed.

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

11.2.2. Severity / Intensity

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

The severity/intensity of AEs will be graded based upon the subject's symptoms according to the current active minor version of NCI CTCAE, Version 4.0

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40.

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

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

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

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

11.2.3. Causality

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

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

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

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

11.2.4. Duration

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

11.2.5. Action Taken

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

11.2.6. Outcome

The investigator will report the outcome of the event for both AEs and SAEs. All SAEs that have not resolved upon discontinuation of the subject's participation in the study must be followed until recovered, recovered with sequelae, not recovered or death (due to the SAE).

11.3. Abnormal Laboratory Values

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

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

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

If a laboratory abnormality is one component of a diagnosis or syndrome, then only the diagnosis or syndrome should be recorded on the AE page/screen of the eCRF. 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).

11.4. Pregnancy

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

11.4.1. Females of Childbearing Potential

Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a female subject occurring while the subject is on IP, or within 3 months of the subject's last dose of IP, are considered immediately reportable events. IP is to be discontinued immediately. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to Celgene Drug Safety immediately by facsimile, or other appropriate method, using the Pregnancy Initial Report Form, or approved equivalent form. The female subject should be referred to an obstetrician-gynecologist or another appropriate healthcare professional for further evaluation.

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 IP should also be reported to Celgene Drug Safety by facsimile, or other appropriate method, within 24 hours of the investigator's knowledge of the event using the SAE Report Form, or approved equivalent form.

11.4.2. Male Subjects

If a female partner of a male subject becomes pregnant while the subject is receiving IP or within 6 months of the last dose of IP, the male subject taking IP should notify the investigator, and the pregnant female partner should be advised to call her healthcare provider immediately. If the male subject is receiving IP, the IP may need to be discontinued in the male subject, but may be resumed later at the discretion of the investigator and medical monitor.

11.5. Reporting of Serious Adverse Events

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

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

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

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

Where required by local legislation, the investigator is responsible for informing the Independent 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.

11.5.1. Safety Queries

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

11.6. Expedited Reporting of Adverse Events

For the purpose of regulatory reporting, Celgene Drug Safety will determine the expectedness of events suspected of being related to *nab*-paclitaxel and CC-486 based on the Investigator Brochures.

In the United States, all suspected unexpected serious adverse reactions (SUSARs) will be reported in an expedited manner in accordance with 21 CFR 312.32.

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.

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

- Any AE suspected of being related to the use of IP in this study or in other studies that is both serious and unexpected (ie, 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. (See Section 15.3 for record retention information).

Celgene Drug Safety Contact Information:

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

12. DISCONTINUATIONS

12.1. Study Treatment Discontinuation

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

- Adverse Event(s)
- Disease progression
- Withdrawal of consent
- Death
- Lost to follow-up
- Protocol violation

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

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

All subjects discontinued from IP for any reason will have a treatment discontinuation visit at the time of discontinuation and should undergo treatment discontinuation procedures.

All subjects discontinued from IP will be followed for a period of 28 days after last dose of IP for the collection of AEs.

Additionally subjects who withdraw from or discontinue treatment should be followed for progressive disease (if applicable), survival and any new anticancer therapy given.

12.2. Study Discontinuation

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

- Withdrawal of consent
- Death
- Lost to follow-up

The following events **may be** considered sufficient reasons for discontinuing a subject from the study:

- Adverse events(s)
- Protocol violation

The reason for study discontinuation should be recorded in the eCRF and in the source documents. The investigator must notify the Medical Monitor immediately when a subject has been discontinued/withdrawn due to an AE (any unacceptable toxicity). All subjects who are

withdrawn from the study should complete all protocol-required evaluations scheduled for early termination at the time of withdrawal.

Since follow-up of subjects who discontinue prematurely is of particular importance, every attempt should be made to collect all survival information and NSCLC treatment/therapy, unless the subject has specifically withdrawn consent from further follow-up. The investigator must make every effort to obtain minimal information regarding the subject's survival status before determining that the subject is lost to follow-up.

12.3. Subject Replacement

Subjects who discontinue will not be replaced.

13. EMERGENCY PROCEDURES

13.1. Emergency Contact

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

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

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

13.2. Emergency Identification of Investigational Products

This is an open-label study; therefore, IP will be indentified on the package labeling.

14. REGULATORY CONSIDERATIONS

14.1. Good Clinical Practice

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

14.2. Investigator Responsibilities

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

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

The investigator is responsible for keeping a record of all subjects who sign an 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 eCRFs and queries.

14.3. Subject Information and Informed Consent

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

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

14.4. Confidentiality

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

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

14.5. Protocol Amendments

Any amendment to this protocol must be approved by the Celgene Clinical Research Physician/Medical Monitor. Amendments will be submitted to the IRB/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.

14.6. 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.

14.7. 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.

14.8. Closure of the Study

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

15. DATA HANDLING AND RECORDKEEPING

15.1. Data/Documents

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

15.2. Data Management

Data will be collected via eCRF and entered into the clinical database per Celgene Standard Operating Procedures (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.

15.3. Record Retention

Essential documents must be retained by the investigator for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or at least 2 years have elapsed since the formal discontinuation of clinical development of the IP. 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/Institution should take measures to prevent accidental or premature destruction of these documents.

16. QUALITY CONTROL AND QUALITY ASSURANCE

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

16.1. Study Monitoring and Source Data Verification

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

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

16.2. Audits and Inspections

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

The investigator is required to permit direct access to the facilities where the study took place, source documents, eCRFs and applicable supporting records of subject participation for audits and inspections by IRB/IECs, regulatory authorities (eg, FDA, European Medicines Agency [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.

17. PUBLICATIONS

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

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19. APPENDICES

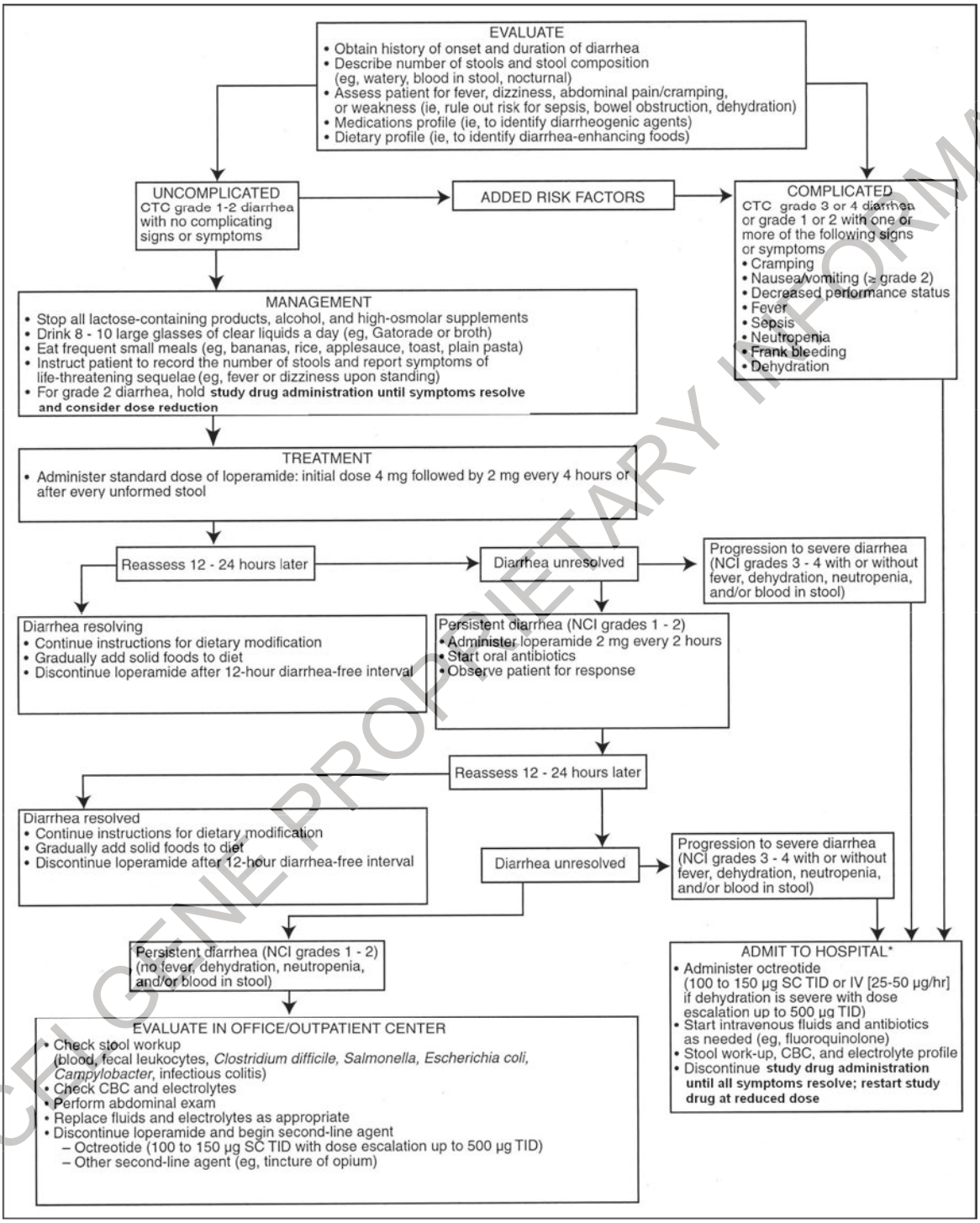
Appendix A: ECOG Performance Status Score

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

Oken, 1982.

Appendix B: Recommendations for Management of Treatment-Induced Diarrhea

The following published guidelines (Benson, 2004) were modified in order to be consistent with the clinical study protocol.



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