

1.0 Title Page

Clinical Study Protocol M14-360

A Phase 1 Dose Escalation and Phase 2 Randomized, Placebo-Controlled Study of the Efficacy and Tolerability of Veliparib in Combination with Paclitaxel/Carboplatin-Based Chemoradiotherapy Followed by Veliparib and Paclitaxel/Carboplatin Consolidation in Subjects with Stage III Non-Small Cell Lung Cancer (NSCLC)

Incorporating Amendments 1, 2, 3 and 4

AbbVie Investigational
Product: Veliparib/ABT-888

Date: 15 August 2017

Development Phase: 1/2

Study Design: A Phase 1 Dose Escalation and Phase 2 Randomized, Placebo-Controlled Study of the Efficacy and Tolerability of Veliparib in Combination with Paclitaxel/Carboplatin Based Chemoradiotherapy Followed by Veliparib and Paclitaxel/Carboplatin Consolidation in Subjects with Stage III Non-Small Cell Lung Cancer (NSCLC)

Investigator(s): Multicenter Trial: Investigator information is on file at AbbVie

Sponsor: AbbVie

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*The specific contact details of the AbbVie legal/regulatory entity (person) within the relevant country are provided within the clinical trial agreement with the Investigator/Institution and in the Clinical Trial Application with the Competent Authority.

This study will be conducted in compliance with the protocol, Good Clinical Practice and all other applicable regulatory requirements, including the archiving of essential documents.

Confidential Information

No use or disclosure outside AbbVie is permitted without prior written authorization from AbbVie.

1.1 Protocol Amendment: Summary of Changes

Previous Protocol Versions

Protocol	Date
Original	27 August 2014
Amendment 1	24 November 2014
Amendment 2	20 January 2016
Amendment 3	29 September 2016

The primary purpose of this amendment is to update the dose escalation plan, to add pulmonary function testing (PFT) at 12 months post start chemoradiotherapy (CRT), and to include the following changes:

- Update information in Section 1.0, Title Page.
Rationale: Sponsor/Emergency Contact details updated.
- Update information in Section 1.2, Synopsis.
Rationale: Change is to correct previous error so Reference Therapy was updated.
- Update Phase 1 doses in Table 1, Dose Escalation in the consolidation chemotherapy, and throughout protocol.
Rationale: Change is to allow for additional dose level of 240 mg BID to be evaluated in Phase 1 consolidation chemotherapy.
- Update planned number of Phase 1 subjects throughout protocol.
Rationale: Due to additional dose level and over-enrollment in previous cohorts, the previous estimate of approximately 30 subjects to be enrolled in Phase 1 is no longer accurate.
- Update information in Section 1.3, List of Abbreviations and Definition of Terms.
Rationale: Change is to add the "DLCO" abbreviation.
- Update information in Section 5.2, Selection of Study Population, and throughout protocol.

Rationale: Change is to update the DLT period definition for the additional cohort and to describe the roll over process.

- Update information in Section 5.2, Selection of Study Population, and throughout protocol.

Rationale: Inclusion criteria changed for mandating the consent for the archived tissue sample collection.

- Update information in Section 5.3.1, Efficacy and Safety Measurements Assessed and Flow Chart.

Rationale: 12 month post start CRT visit added to include PFT assessment to follow up on late fibrosis events. PFT at 12 months post start of CRT added to the Post Treatment visit to follow up on late fibrosis events.

- Update information in Section 5.3.1, Efficacy and Safety Measurements Assessed and Flow Chart.

Rationale: Archived tissue sample collection changed from optional to mandatory.

- Update information in Section 6.6.3, Reporting Serious Adverse Events.

Rationale: Primary Study Designated Physician details updated.

- Update information in Section 7.0, Protocol Deviations.

Rationale: Medical Monitor details updated; Clinical Monitor details removed.

- Update information in Appendix B, List of Protocol Signatories.

Rationale: Medical Director details updated.

- Other changes to the protocol are minor administrative changes throughout the document for clarification and for typographical and grammatical error corrections.

An itemized list of all changes made to the protocol under this amendment is found in [Appendix F](#).

1.2 Synopsis

AbbVie Inc.	Protocol Number: M14-360
Name of Study Drug: Veliparib/ABT-888	Phase of Development: 1/2
Name of Active Ingredient: Not Applicable	Date of Protocol Synopsis: 15 August 2017
<p>Protocol Title: A Phase 1 Dose Escalation and Phase 2 Randomized, Placebo-Controlled Study of the Efficacy and Tolerability of Veliparib in Combination with Paclitaxel/Carboplatin-Based Chemoradiotherapy Followed by Veliparib and Paclitaxel/Carboplatin Consolidation in Subjects with Stage III Non-Small Cell Lung Cancer (NSCLC)</p>	
<p>Objective(s):</p> <p>The primary objectives of the study are to establish the recommended Phase 2 dose (RPTD) of veliparib in combination with concurrent Paclitaxel/Carboplatin-based chemoradiotherapy and consolidation with Paclitaxel/Carboplatin-based chemotherapy (Phase 1 portion) and to assess whether the addition of oral veliparib versus placebo to Paclitaxel/Carboplatin-based chemoradiotherapy with Paclitaxel/Carboplatin consolidation will improve progression-free survival (PFS) in patients with Stage III non-small cell lung cancer (Phase 2 portion).</p> <p>The secondary objectives of the study are to assess overall survival (OS), objective response rate (ORR), duration of overall response (DOR), safety and tolerability of veliparib versus placebo added to standard therapy (Phase 2 portion).</p> <p>The tertiary objectives are to assess Quality of Life (QoL) (Phase 2 portion) and ECOG performance status. In addition, biomarkers including, but not limited to, defects in DNA-repair genes will be assessed in correlation with safety and efficacy data.</p>	
Investigator(s): Multicenter	
Study Site(s): Approximately 50 – 75	
Study Population: Subjects with Stage III NSCLC suitable for definitive chemoradiotherapy (CRT) who have not received prior therapy for NSCLC	
Number of Subjects to be Enrolled: Approximately 50 in the dose escalation portion and approximately 156 in the randomized portion of the study.	
<p>Methodology:</p> <p>This two-phase study consists of 1) dose-escalation of veliparib to determine an RPTD for combination with concurrent paclitaxel/carboplatin-based CRT; and followed by 2) a randomized, double-blinded study to determine whether veliparib improves outcome relative to placebo when added to Paclitaxel/Carboplatin-based CRT followed by consolidation Paclitaxel/Carboplatin in subjects with previously untreated Stage III NSCLC.</p>	

Methodology (Continued):

In the dose escalation phase of the study, subjects will receive veliparib in combination with carboplatin AUC 2+ paclitaxel 45 mg/m² + thoracic radiotherapy. Radiation delivery will be over no more than 9 weeks by 3-dimensional conformal radiotherapy or intensity modulated radiotherapy (IMRT), and the total dose will be 60 – 63 Gy. The first cohort of at least 3 – 6 subjects will receive veliparib 60 mg BID throughout CRT. Based on tolerability, subsequent cohorts will receive doses of veliparib from 40 mg BID to 240 mg BID. As the CRT RPTD dose is explored (Cohorts 1 – 5), the consolidation RPTD of veliparib will be 120 mg BID + carboplatin AUC 6 + paclitaxel 200 mg/m² for up to two 21-day cycles. The consolidation dose of veliparib in Cohort 6 will be 240 mg BID + carboplatin AUC 6 + paclitaxel 200 mg/m² for up to two 21-day cycles.

Dose limiting toxicity (DLT) events will be collected for each dosing cohort until a new dosing cohort is opened or until the recommended Phase 2 dose is identified. A minimum of 3 subjects will be enrolled in each cohort. Additional eligible subjects may be enrolled at the current dose level at the discretion of the Investigators and the AbbVie Medical Monitor. From each cohort, subjects will be entered into the DLT assessment group of the intended cohort size in order of treatment. For Cohorts 1 – 5, subjects considered evaluable for DLTs will be those that receive treatment through 1 cycle of CRT or have AEs meeting DLT criteria. For Cohort 6, subjects considered evaluable for DLTs will be those that receive treatment through 1 cycle of consolidation chemotherapy. If a subject in the DLT assessment group becomes unevaluable, the subject will be replaced by the next-treated subject in the cohort. The DLT period for each subject participating in Cohorts 1 – 5 will be from start of veliparib dosing through 28 days following completion of CRT or until consolidation chemotherapy is initiated. The DLT period for each subject participating in Cohort 6, will be from the start of Cycle 1 of the consolidation chemotherapy through the start of the Cycle 2 of the consolidation therapy or treatment discontinuation. The DLT period for all subjects at each dose level will end upon initiation of next dose level.

Dose limiting toxicities are the following events that are considered by the investigator group to be related to treatment:

1. Radiation induced Grade 3 or greater cardiac toxicity (e.g., myocarditis, pericarditis, heart failure, ventricular dysfunction, myocardial infarction).
2. Radiation induced myelopathy/myelitis (does not include L'Hermitte's syndrome).
3. Radiation-related pneumonitis resulting in delay in radiotherapy, chemotherapy (CRT or consolidation) or veliparib of more than 3 weeks or early discontinuation of RT (total dose < 50 Gy).
4. G4 or greater esophagitis or esophagitis, dysphagia, and odynophagia requiring treatment interruption of > 7 days despite medical management.
5. G2 or greater seizure.
6. Grade 4 or greater neutropenia for > 7 days or neutropenic fever (defined as ANC < 500 and a temperature of 38.5°C or above).
7. Grade 4 or greater thrombocytopenia.
8. Grade 4 diarrhea or nausea/vomiting despite appropriate antiemetic therapy lasting > 48 hours.
9. Any other toxicity resulting in delay in radiotherapy, chemotherapy, or veliparib of more than 14 days or early discontinuation of RT (total dose < 50 Gy).

Methodology (Continued):

10. All other non-hematologic toxicities of Grade 3 or greater, with the following exceptions:

- a. Anorexia
- b. Fatigue
- c. Grade 3 infection
- d. Grade 3 AST/ALT elevations \leq 7 days
- e. Infusion reactions. Patients with Grade 3 or worse infusion reactions will be removed from study and replaced and will not be considered evaluable for DLT
- f. Grade 3 or 4 lymphopenia
- g. Grade 3 or 4 electrolyte abnormalities that are corrected to Grade 2 or less in less than 48 hours

For Cohort 6, if 3 or fewer subjects were able to take Cycle 2 of consolidation chemotherapy, the reason of dose reduction and treatment discontinuation will be reviewed as part of consideration to determine MTD/RPTD of veliparib for the consolidation phase.

Following the dose escalation portion of the trial, the RPTD will be determined by the sponsor, and at the discretion of the sponsor, the Phase 2 portion of the study will begin with patient randomization in a 1:1:1 ratio to the treatment arms as follows:

- A. Concurrent paclitaxel/carboplatin/radiotherapy/veliparib followed by consolidation paclitaxel/carboplatin/veliparib
- B. Concurrent paclitaxel/carboplatin/radiotherapy/veliparib followed by consolidation paclitaxel/carboplatin/placebo
- C. Concurrent paclitaxel/carboplatin/radiotherapy/placebo followed by consolidation paclitaxel/carboplatin/placebo

Subject randomization will be stratified by tumor volume (≤ 90 versus > 90 cm³) and smoking history (current smoker versus former smoker versus never smoked). Screening procedures, QoL assessment, and baseline radiographic tumor assessments will be performed within 28 days prior to randomization.

Concurrent chemoradiotherapy (CRT) will consist of radiotherapy (RT) using either 3D conformal RT or IMRT plus paclitaxel, (45 mg/m² as a 60 minute infusion), immediately followed by carboplatin, (AUC 2 mg/mL/min as a 30 minute infusion) weekly beginning on Day 1 of radiotherapy. Veliparib (or placebo), will be administered continuously beginning 3 days prior to RT through one day after RT completion.

Consolidation chemotherapy will begin no more than 8 weeks following RT. Subjects who require > 8 weeks to recover from toxicities resulting from CRT should not receive consolidation chemotherapy. Consolidation chemotherapy will consist of paclitaxel, (200 mg/m² as a 3 hour infusion, immediately followed by carboplatin, AUC 6 mg/mL/min as a 30 minute infusion) on Day 1 of each 21-day cycle for up to 2 cycles. Veliparib (or Placebo in the Phase 2 portion), 120 mg (Cohorts 1 – 5) or 240 mg (Cohort 6) BID, will begin on Day -2 (2 days prior to the start of paclitaxel/carboplatin infusion) and will continue through Day 5 of each 21-day cycle.

Subjects who experience toxicities due to carboplatin, paclitaxel, RT, or veliparib/placebo may require a delay in the dosing schedule or a dose modification.

Methodology (Continued):

Radiographic tumor assessments will be conducted at baseline, prior to consolidation chemotherapy, at 24 weeks after start of treatment, every 8 weeks until one year after beginning therapy, then every 12 weeks. Beginning 12 weeks after randomization, progression will be determined based on Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1. Progression prior to that time will be determined by the Investigator. A QoL assessment as measured by the EORTC QLQ-C15-PAL and the companion symptom module EORTC QLQ-LC13 will be performed at Screening, prior to consolidation chemotherapy, at 24 weeks after start of treatment, every 8 weeks until one year after beginning therapy and at the final visit.

After completion of protocol therapy, subjects will be observed without further therapy until progression. The visit at which an investigator identifies disease progression or at which a subject meets other criteria for study discontinuation will be considered the final visit. All subjects with a final visit < 30 days after the last dose of drug will have one Follow-Up Visit approximately 30 days after the Final Visit.

If a subject is discontinued from the study with an ongoing adverse event or an unresolved clinically significant laboratory result, the site will attempt to provide follow-up until a satisfactory clinical resolution of the laboratory results or adverse event is achieved.

To ensure subject safety, an internal data monitoring committee (DMC) will review un-blinded safety data when approximately 45 subjects in the Phase 2 portion of the study have completed CRT, reached an event of disease progression or death, or discontinued the study.

Diagnosis: Stage III NSCLC

Diagnosis and Main Criteria for Inclusion/Exclusion:

Main Inclusion (Phase 1 and Randomized Phase 2):

- Subject must be \geq 18 years of age;
- Subject must have histologically or cytologically confirmed Stage III NSCLC. When pleural fluid is visible on the CT scan or on a chest x-ray, a thoracentesis is required to confirm that the pleural fluid is serous AND cytologically negative. Effusions that are minimal (i.e., not visible on chest x-ray) or that are too small to safely tap are exempted from the requirement for thoracentesis.
- Subjects in the randomized portion of the study must have measurable disease per RECIST version 1.1 criteria;
- Subject must consent to provide archived tissue or cytology sample of NSCLC lesion for analysis;
- Subjects must have V20 (volume of lung to receive 20 Gy radiotherapy according to simulation) < 35%;
- Subject must have an Eastern Cooperative Oncology Group (ECOG) performance score of 0 – 1;

Diagnosis and Main Criteria for Inclusion/Exclusion (Continued):

Main Inclusion (Continued):

- Subject must have adequate hematologic, renal, hepatic, and lung function as follows:
 - Bone marrow: Absolute Neutrophil count (ANC) $\geq 1,500/\mu\text{L}$; Platelets $\geq 100,000/\text{mm}^3$; Hemoglobin ≥ 9.0 g/dL (without transfusion);
 - Renal function: calculated creatinine clearance ≥ 50 mL/min by the Cockcroft-Gault formula;
 - Hepatic function and enzymes: aspartate aminotransferase (AST) and alanine aminotransferase (ALT) $\leq 2.5 \times$ the upper limit of normal (ULN) of institution's normal range; Bilirubin $\leq 1.5 \times$ ULN; subjects with Gilbert's syndrome may have a bilirubin $\geq 1.5 \times$ ULN of central laboratory normal range;
 - Pulmonary function tests (PFTs) including FEV1 within 12 weeks prior to randomization; for FEV1, the best value obtained pre- or post-bronchodilator must be ≥ 1.2 liters/second and/or $\geq 50\%$ predicted.
- Female subjects of childbearing potential (i.e., those who are not postmenopausal for at least 1 year or surgically sterile by bilateral tubal ligation, bilateral oophorectomy or hysterectomy) and their male partner should practice at least one of the methods of birth control listed below for at least 6 months after treatment with chemotherapy. Male subjects and their female partners of childbearing potential should practice at least one of the methods of birth control listed below for at least 6 months after treatment with chemotherapy:
 - Total abstinence from sexual intercourse (if it is the subject's preferred and usual lifestyle; beginning a minimum one complete menstrual cycle prior to study drug administration and to extend 6 months after treatment);
 - Vasectomized subject or partner(s), vasectomy (males);
 - Intrauterine device (females);
 - Double-barrier method (condoms, contraceptive sponge, diaphragm or vaginal ring with spermicidal jellies or creams; both males and females);
 - Hormonal contraceptives (oral, parenteral or transdermal) for at least 90 days prior to study drug administration (females). If hormonal contraceptives are used, the subject and her partner should also use a single barrier method.
 - Subject must voluntarily sign and date an informed consent, approved by an Independent Ethics Committee (IEC)/Institutional Review Board (IRB), prior to the initiation of and Screening for study-specific procedures.

Diagnosis and Main Criteria for Inclusion/Exclusion (Continued):

Main Exclusion:

- Subject with prior chemotherapy or radiotherapy for current NSCLC; subjects curatively treated for past early stage NSCLC greater than 3 years ago may be included;
- Subject with prior exposure to PARP inhibitors;
- Subjects with known hypersensitivity to carboplatin, paclitaxel, or formulations containing polyethoxylated castor oil (Cremophor);
- Subject with prior mediastinal or thoracic radiotherapy. Prior tangential RT to prior breast cancer is acceptable;
- Subject with major surgery in the 4 weeks prior to randomization (VATS and/or mediastinoscopy is not considered major surgery);
- Subject with a previous or concurrent malignancy except for treated basal cell or squamous cell skin cancer, in situ cervical cancer, or other cancer for which the patient received potentially curative treatment and has been disease-free for 3 years or is considered cured by the investigator if has been disease-free for less than 3 years;
- Any medical condition, which in the opinion of the study investigator, places the subject at an unacceptably high risk for toxicities, or any subject circumstance that prohibits trial participation according to local law;
- Subject is pregnant or lactating;
- Subject with sensory peripheral neuropathy of \geq Grade 2 at baseline;
- Subject is unable to swallow medication;
- Subjects with prior history of seizure within the prior 12 months.

Investigational Product:	Veliparib (ABT-888) or Placebo
Dose(s):	60 – 240 mg BID (concurrent chemoradiotherapy); 120 – 240 mg BID (consolidation)
Mode of Administration:	Oral

Reference Therapy:	Carboplatin
Dose(s):	AUC 2 mg/mL/min (concurrent chemoradiotherapy); AUC 6 mg/mL/min (consolidation)
Mode of Administration:	Intravenous

Reference Therapy:	Paclitaxel
Dose(s):	45 mg/m ² (concurrent chemoradiotherapy); 200 mg/m ² (consolidation)
Mode of Administration:	Intravenous

Duration of Treatment:

Subjects without clinical progression of disease and with tolerable side effects should continue to receive treatment until completion of all prescribed cycles (chemoradiotherapy plus 2 cycles of consolidation chemotherapy).

Criteria for Evaluation:

Efficacy:

Progression-free survival (PFS) will be derived according to radiographic progression per RECIST version 1.1 (beginning with the second scan after completion of CRT) or death. Radiographic tumor assessments for response will be conducted at baseline, prior to consolidation chemotherapy, at 24 weeks after start of treatment, every 8 weeks until one year after beginning therapy, then every 12 weeks until radiographic progression or death. Subjects who require additional therapy, withdraw consent, or are lost to follow-up prior to radiographic progression will be censored at that time for the analysis of PFS.

Overall survival (OS) will be determined by the Investigator until radiographic progression. After radiographic progression, survival information will be collected via the electronic CRF at 8-week intervals (or as requested by sponsor to support data analysis).

Objective response rate (ORR), and duration of overall response (DOR) will be derived per RECIST version 1.1. Radiographic tumor assessments for response will be conducted at baseline, prior to consolidation chemotherapy, at 24 weeks after start of treatment, every 8 weeks until one year after beginning therapy, then every 12 weeks until radiographic progression or death. Subjects who require additional therapy, withdraw consent, or are lost to follow-up prior to radiographic progression will be censored at that time for the analysis of DOR.

ECOG performance status will be determined by the Investigator at each assessment. A quality of life assessment as measured by the EORTC QLQ-C15-PAL and the companion symptom module EORTC QLQ-LC13 will be performed at screening, prior to consolidation chemotherapy, at 24 weeks after start of treatment, every 8 weeks until one year after beginning therapy and at the final visit.

Pharmacokinetic:

Blood samples for veliparib assay will be collected for the determination of pharmacokinetic parameters of veliparib such as apparent oral clearance (CL/F) and volume of distribution (V/F).

Pharmacodynamic:

Research to find biomarkers that may serve as surrogates for clinical endpoints in future veliparib studies or that may be predictive of veliparib activity will be conducted. Serum, plasma, blood and archived tissue samples will be collected at designated time points throughout the study. Study-specific core biopsies are requested but are not required.

Safety:

Adverse events, laboratory profiles, physical examinations and vital signs will be assessed throughout the study. Results will be tabulated for each subject and summary statistics will be computed for each sampling time and each parameter.

Statistical Methods:

The following efficacy endpoint will be analyzed using data obtained from subjects in Phase 1:

Objective Response Rate (ORR)

The proportion of subjects with objective response as assessed by the investigator using RECIST version 1.1 will be calculated for all dosed subjects.

The following efficacy endpoints will be analyzed using data obtained from subjects in Phase 2:

Progression-Free survival (PFS)

Progression-Free Survival will be defined as the number of days from the date of randomization to the date of earliest radiographic disease progression or death. All radiographic disease progression will be included regardless whether the event occurred while the subject was taking study drug or had previously discontinued study drug. If the subject does not experience radiographic disease progression or death, then the data will be censored at the date of the last disease assessment.

Overall Survival (OS)

Overall survival will be defined as the number of days from the date of randomization to the date of death. For subjects who did not die, their data will be censored at the date of last study visit or the last known date to be alive, whichever is later.

Objective Response Rate (ORR)

The proportion of subjects with objective response as assessed by the investigator using RECIST version 1.1 will be evaluated for randomized subjects.

Duration of Overall Response (DOR)

Duration of overall response will be defined as the number of days from the date of first response (CR or PR) to the earliest documentation of radiographic progressive disease or death due to disease progression. If a subject is still responding, then the subject's data will be censored at the date of the subject's last available disease assessment. For subjects who never experience response, the subject's data will not be included in the analysis.

Quality of life (QoL) Measures

Changes and/or percent changes from baseline will be summarized using descriptive statistics for each scheduled post-baseline visit and for the Final Visit for quality of life measures using the EORTC QLQ-C15-PAL and EORTC QLQ-LC13 questionnaires. The QoL will be used as an exploratory endpoint and not tested against pre-specified hypothesis.

Performance Status

Changes and/or percent changes from baseline will be summarized using descriptive statistics for each scheduled post-baseline visit and for the Final Visit for ECOG performance status. Post-baseline measurements more than 30 days after the last dose of study drug will not be included. Subjects that do not have a baseline measurement or do not have any post-baseline measurements will not be included.

Efficacy Analysis:

The primary Phase 2 efficacy analysis will test if concurrent paclitaxel/carboplatin/radiotherapy/veliparib followed by consolidation paclitaxel/carboplatin/veliparib (Arm A) will improve PFS versus concurrent paclitaxel/carboplatin/radiotherapy/placebo followed by consolidation paclitaxel/carboplatin/placebo (Arm C).

Statistical Methods (Continued):

Efficacy Analysis (Continued):

The secondary Phase 2 efficacy analyses will test (in the following order):

- 1) if concurrent paclitaxel/carboplatin/radiotherapy/veliparib followed by consolidation paclitaxel/carboplatin/placebo (Arm B) results in improved Progression-Free survival (PFS) versus Arm C;
- 2a) if Arm A or
- 2b) if Arm B results in improved overall survival (OS) versus Arm C;
- 3a) if Arm A or
- 3b) if Arm B results in improved overall response rate (ORR) versus Arm C;
- 4a) if Arm A or
- 4b) if Arm B results in improved duration of overall response (DOR) versus Arm C.

Sample Size:

Assuming a hazard ratio of 0.6 for Arm A (Concurrent paclitaxel/carboplatin/radiotherapy/veliparib followed by consolidation paclitaxel/carboplatin/veliparib) versus Arm C (Concurrent paclitaxel/carboplatin/radiotherapy/placebo followed by consolidation paclitaxel/carboplatin/placebo), a total of 71 PFS events in Arm A and Arm C combined will provide an expected 95% confidence interval of 0.38 to 0.96 for the estimated hazard ratio. Assuming a hazard ratio of 0.75 for Arm B (Concurrent paclitaxel/carboplatin/radiotherapy/veliparib followed by consolidation paclitaxel/carboplatin/placebo) versus Arm C, a total of 107 PFS events will be observed across all three arms at the time when 71 PFS events are observed for Arm A and Arm C combined. A total of approximately 156 subjects (52 subjects per treatment arm) will be enrolled into the Phase 2 portion of study to obtain the 107 PFS events.

1.3 List of Abbreviations and Definition of Terms

Abbreviations

3D	Three Dimensional
ADP	Adenosine Diphosphate
AE	Adverse Event
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
aPTT	Activated Partial Thromboplastin Time
ASCO	American Society of Clinical Oncology
AST	Aspartate Aminotransferase
BID	Twice a Day
BRCA	Breast Cancer Gene
BUN	Blood Urea Nitrogen
C	Cycle
CBC	Complete Blood Count
CFR	Code of Federal Regulations
CHF	Congestive heart failure
CNS	Central Nervous System
CR	Complete Response
CRF or eCRF	Case Report Form or Electronic Case Report Form
CRT	Chemoradiotherapy
CS	Clinically Significant
CSF	Colony-Stimulating Factor
CT	Computed Tomography
CTEP	Cancer Therapy Evaluation Program
CYP	Cytochrome P450
CYP2C	Cytochrome P450 2C
CYP3A	Cytochrome P450 3A
D	Day
DDI	Drug-Drug Interaction
DLCO	Diffusing Capacity of the Lung for Carbon Monoxide
DLT	Dose Limiting Toxicity
DMC	Data monitoring committee

DNA	Deoxyribonucleic Acid
DOR	Duration of Overall Response
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
eCRF or CRF	Electronic Case Report Form or Case Report Form
EC	Ethics Committee
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic Data Capture
ERCC1	Excision Repair Cross-Complementary Group 1 Protein
EORTC	European Organization for Research and Treatment of Cancer
EORTC QLQ-C15-PAL	A questionnaire developed by EORTC to assess the quality of life of palliative cancer care patients
EORTC QLQ-C30	A questionnaire developed by EORTC to assess the quality of life of cancer patients
EORTC QLQ-LC13	A modular supplement questionnaire developed by EORTC for use in lung cancer clinical trials
EMA	European Medicines Agency
EMEA	Europe, Middle East and Africa
ESMO	European Society for Medical Oncology
EU	European Union
FDA	US Food and Drug Administration
FEV1	Forced Expiratory Volume in 1 Second (lung airflow measure)
FFPE	Formalin fixed, paraffin embedded
GCP	Good Clinical Practice
G-CSF	Granulocyte Colony-Stimulating Factor
GFR/eGFR	Glomerular Filtration Rate/estimated Glomerular Filtration Rate
Gy	Gray (derived unit of ionizing radiation dose in Radiotherapy)
hCG	Human Chorionic Gonadotropin
ICH	International Conference on Harmonization
ICRU	International Commission on Radiation Units and Measurements
IEC	Independent Ethics Committee
IIA	Investigator Information and Agreement
IIS	Investigator Initiated Studies
IMP	Investigational Medicinal Product
IMRT	Intensity Modulated Radiotherapy

INR	International Normalized Ratio
IRB	Institutional Review Board
IUD	Intra-Uterine Device
IV, i.v.	Intravenous
IRT	Interactive Response Technology
LD	Longest Diameter
LDH	Lactate Dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
mL	Milliliter
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NCS	Not Clinically Significant
NCI CTCAE	National Cancer Institute Common Terminology Criteria For Adverse Events
NSCLC	Non-small Cell Lung Cancer
ORR	Objective Response Rate
OS	Overall Survival
PAR	Poly-(ADP-ribose)
PARP	Poly-(ADP-ribose)-Polymerase
PBO	Placebo
PD	Pharmacodynamic or Progressive Disease
PET	Positron Emission Tomography
PET CT	Positron Emission Tomography – Computed Tomography
PFS	Progression-Free Survival
PFTs	Pulmonary Function Tests
PG	Pharmacogenetic
pH	Potential Hydrogen (The pH scale measures how acidic or basic a substance is)
PK	Pharmacokinetic
PMID	PubMed identifier or PubMed unique identifier
PO	Oral Route of Administration
POR	Proof of Receipt
PR	Partial Response

QA	Quality Assurance
QARC	Quality Assurance Review Center
QC	Quality Control
QLQ	Quality of Life Questionnaire
QTc	QT interval corrected for heart rate
QoL	Quality of Life
RBC	Red Blood Cell
RECIST	Response Evaluation Criteria in Solid Tumors
RPTD	Recommended Phase 2 Dose
RT	Radiotherapy
SAE	Serious Adverse Event
SCLC	Small Cell Lung Cancer
SD	Stable Disease
SGOT	Serum glutamic-oxaloacetic transaminase
SGPT	Serum glutamic-pyruvic transaminase
SmPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMZ	Temozolomide
TPN	Total Parenteral Nutrition
TNM	Tumor size, Nodes and Metastasis presence
ULN	Upper Limit of Normal
US	Ultrasound or United States
VATS	Video-assisted Thoracoscopic Surgery
W, Wk	Week
WBC	White Blood Cell
WBRT	Whole Brain Radiation Therapy
WJTOG	West Japan Thoracic Oncology Group
XPF	Xeroderma Pigmentosum Group F

Definition of Terms

ABT-888	Veliparib
AUC	Area under the plasma concentration-time curve
C_{max}	Maximum observed plasma concentration
GDSM	Global Drug Supply Management
T_{max}	Time to maximum observed plasma concentration

2.0	Table of Contents	
1.0	Title Page	1
1.1	Protocol Amendment: Summary of Changes	2
1.2	Synopsis	4
1.3	List of Abbreviations and Definition of Terms	13
2.0	Table of Contents	18
3.0	Introduction	24
3.1	Non-Small Cell Lung Cancer	24
3.2	Combined Modality Chemoradiotherapy Therapy	24
3.3	Paclitaxel/Carboplatin	25
3.4	PARP Inhibition for Cancer Treatment	26
3.5	Veliparib	27
3.5.1	Rationale for Combining Veliparib with Concurrent Chemoradiotherapy and Consolidation Chemotherapy	27
3.5.2	Veliparib Preclinical Toxicology	27
3.5.3	Pharmacokinetics and Pharmacodynamics	28
3.5.4	Clinical Experience	29
3.6	Study Rationale	32
3.7	Differences Statement	32
3.8	Benefits and Risks	32
4.0	Study Objective	33
5.0	Investigational Plan	34
5.1	Overall Study Design and Plan: Description	34
5.2	Selection of Study Population	34
5.2.1	Inclusion Criteria	42
5.2.2	Exclusion Criteria	44
5.2.3	Prior and Concomitant Therapy	45
5.2.3.1	Prior Therapy	45
5.2.3.2	Concomitant Therapy	46
5.3	Efficacy Pharmacokinetic, Pharmacodynamic, Pharmacogenetic and Safety Assessments/Variables	48
5.3.1	Efficacy and Safety Measurements Assessed and Flow Chart	48

5.3.1.1	Study Procedures.....	53
5.3.1.2	Blood Samples for Pharmacogenetic Analysis	59
5.3.1.3	Collection and Handling of Pharmacodynamic Variables	60
5.3.2	Drug Concentration Measurements.....	61
5.3.2.1	Blood Samples for Pharmacokinetic Analysis.....	61
5.3.2.2	Measurement Methods	61
5.3.3	Efficacy Variables	61
5.3.4	Safety Variables	61
5.3.5	Pharmacokinetic Variables	62
5.3.6	Pharmacogenetic Variables.....	62
5.3.7	Pharmacodynamic Variables	63
5.4	Removal of Subjects from Therapy or Assessment	64
5.4.1	Discontinuation of Individual Subjects	64
5.4.1.1	Discontinuation of Veliparib/Placebo and Paclitaxel/Carboplatin	65
5.4.2	Discontinuation of Entire Study.....	66
5.5	Treatments	66
5.5.1	Treatments Administered.....	66
5.5.1.1	Administration of Veliparib/Placebo (All Subjects)	68
5.5.1.2	Administration of Paclitaxel, and Carboplatin (All Subjects)	69
5.5.1.3	Thoracic Radiotherapy	70
5.5.2	Identity of Investigational Products	76
5.5.2.1	Standard of Care Medicinal Products for Study Treatment.....	76
5.5.2.2	Packaging and Labeling.....	76
5.5.2.3	Storage and Disposition of Study Drugs	77
5.5.3	Method of Assigning Subjects to Treatment Groups	78
5.5.4	Selection and Timing of Dose for Each Subject	79
5.5.5	Blinding	79
5.5.5.1	Blinding of Investigational Product	79
5.5.5.2	Blinding of Data for Data Monitoring Committee (DMC)	80
5.5.6	Treatment Compliance	80
5.5.7	Drug Accountability	81
5.6	Discussion and Justification of Study Design.....	82
5.6.1	Discussion of Study Design and Choice of Control Groups	82

5.6.2	Appropriateness of Measurements	83
5.6.3	Suitability of Subject Population	83
5.6.4	Selection of Doses in the Study	83
6.0	Adverse Events	84
6.1	Definitions	85
6.1.1	Adverse Event	85
6.1.2	Serious Adverse Events	86
6.2	Adverse Events Expected Due to NSCLC or Progression of NSCLC	87
6.3	Adverse Event Severity	87
6.4	Relationship to Study Drug	88
6.5	Adverse Event Collection Period	89
6.6	Adverse Event Reporting	89
6.6.1	Deaths	89
6.6.2	Lack of Efficacy or Worsening of Disease	90
6.6.3	Reporting Serious Adverse Events	90
6.7	Pregnancy	92
6.8	Toxicity Management	93
6.8.1	Dose Limiting Toxicities	93
6.8.2	Determination of the MTD	94
6.8.3	Determination of the RPTD	94
6.8.4	Dose Modifications During Concurrent Therapy	95
6.8.4.1	Dose Modifications for Hematologic Toxicity	95
6.8.4.2	Dose Modifications for Non-hematologic Toxicity	96
6.8.4.3	Dose Modifications for In-Field, Non-Hematologic Toxicity During Concurrent Therapy	96
6.8.5	Dose Modifications During Consolidation Therapy	97
6.8.5.1	Veliparib Dose Reductions and Delays	97
6.8.5.2	Paclitaxel/Carboplatin Dose Reductions and Delays	98
7.0	Protocol Deviations	100
8.0	Statistical Methods and Determination of Sample Size	100
8.1	Statistical and Analytical Plans	100

8.1.1	Baseline Characteristics	101
8.1.1.1	Demographics	101
8.1.1.2	Medical History.....	101
8.1.2	Efficacy Endpoints	102
8.1.2.1	Primary Efficacy Endpoint	102
8.1.2.2	Secondary Efficacy Endpoints	102
8.1.2.3	Tertiary Efficacy Endpoints.....	103
8.1.3	Primary Analysis of Efficacy	103
8.1.4	Secondary Analysis of Efficacy	104
8.1.5	Tertiary Analysis of Efficacy	104
8.1.6	Safety Assessments	105
8.1.6.1	Duration of Study Drug	105
8.1.6.2	Adverse Event	105
8.1.6.3	Serious Adverse Event.....	106
8.1.6.4	Death.....	106
8.1.6.5	Longitudinal Analyses of Laboratory and Vital Signs Data.....	106
8.1.6.6	Analyses of Laboratory Data Using NCI CTCAE	107
8.1.6.7	Analyses of Vital Signs Using Criteria for Potentially Clinically Significant Vital Sign Values.....	107
8.1.7	Timing of Efficacy Analyses and Safety Evaluations	108
8.1.8	Interim Analysis	108
8.2	Determination of Sample Size	108
8.3	Randomization Methods.....	109
9.0	Ethics.....	109
9.1	Independent Ethics Committee (IEC) or Institutional Review Board (IRB)	109
9.2	Ethical Conduct of the Study	110
9.3	Subject Information and Consent.....	110
10.0	Source Documents and Case Report Form Completion	111
10.1	Source Documents.....	111
10.2	Case Report Forms	112
11.0	Data Quality Assurance	113

12.0	Use of Information	113
13.0	Completion of the Study	113
14.0	Investigator's Agreement.....	115
15.0	Reference List.....	116

List of Tables

Table 1.	Dose Escalation.....	35
Table 2.	Study Activities (Phase 1 and 2).....	49
Table 3.	Schedule of Pharmacogenetic and Pharmacodynamic Assessments	52
Table 4.	Pharmacokinetic Assessments (Phase 1).....	52
Table 5.	Schedule of Pharmacokinetic Assessments (Phase 2).....	53
Table 6.	Clinical Laboratory Tests	57
Table 7.	Identity of Investigational Product.....	76
Table 8.	Standard of Care Medicinal Products for Study Treatment.....	76
Table 9.	Study Drug Storage Conditions	77
Table 10.	Suggested Guidelines for Veliparib + Paclitaxel/Carboplatin Independent Dose Reduction	97

List of Figures

Figure 1.	Phase 1 Study Schematic	38
Figure 2.	Phase 2 Study Schematic	40
Figure 3.	Adverse Event Collection	89

List of Appendices

Appendix A.	Responsibilities of the Clinical Investigator.....	119
Appendix B.	List of Protocol Signatories	121
Appendix C.	Adverse Events Expected Due to NSCLC or Progression of NSCLC	122
Appendix D.	Suggested Guidelines for Paclitaxel/Carboplatin Dose Delay or Reduction During Consolidation Chemotherapy	124
Appendix E.	RECIST Version 1.1 for Tumor Response (PFS).....	125

Appendix F. Protocol Amendment: List of Changes132

3.0 Introduction

3.1 Non-Small Cell Lung Cancer

Lung cancer is the most common cancer with an estimated 1.8 million new cases globally in 2012, accounting for approximately 13% of the global cancer burden. It is also the most common cause of cancer-related death worldwide with an estimated 1.6 million annual deaths and mortality to incidence rate of 0.87. Most lung carcinomas are diagnosed at an advanced stage, conferring poor prognosis.¹

Non-small cell lung cancer (NSCLC) accounts for more than 85% of all lung cancer cases, and it includes two major types: 1) non-squamous (including adenocarcinoma, large-cell carcinoma, and other cell types); and 2) squamous cell (epidermoid) carcinoma. The incidence of NSCLC increases with age; 60% occur in patients aged 60 years and older, and 30% to 40% in patients aged 70 years and older. Surgery, radiotherapy, and chemotherapy, either alone or in combination, are the modalities commonly used to treat NSCLC patients. Thirty-Five to 40 percent of NSCLC patients have locally advanced and inoperable disease, for which concurrent chemoradiotherapy is commonly utilized.² Despite improvements in the treatment of locally advanced NSCLC, long-term survival is achieved in less than 25% of patients. Thus, there is a major need to identify therapies with improved outcome in this clinical setting.^{2,3}

3.2 Combined Modality Chemoradiotherapy Therapy

Combined modality chemoradiotherapy is standard of care for the treatment of patients with inoperable or locally advanced NSCLC. In 1980, radiotherapy for subjects with locally advanced NSCLC was shown to confer a median survival of 10 months and 5-year survival of 5%.⁴ The survival benefit of adding chemotherapy to radiation was subsequently established in multiple Phase 3 trials. Beginning in 1996, trials showed that cisplatin-based induction chemotherapy followed by conventional RT (60 Gy/approximately 30 fractions) resulted in better survival than conventional RT alone.⁵⁻⁸ Later randomized trials established concurrent chemotherapy and radiation to be

superior to sequential administration. In RTOG 9410, concurrent administration of cisplatin/vinblastine and RT was superior to the same regimen given sequentially (median survival of 17.0 versus 14.6 months). The LAMP (Locally Advanced Multi-modality Protocol) Phase 2 study, compared i) induction paclitaxel/carboplatin/ followed by RT, versus ii) induction paclitaxel/carboplatin followed by concurrent RT + weekly paclitaxel/carboplatin, versus iii) concurrent RT + weekly paclitaxel/carboplatin followed by consolidation paclitaxel/carboplatin.⁹ Median overall survival was 13, 12.7, and 16.3 months in the three arms respectively. In a more recent study, RTOG 0617, concurrent RT + paclitaxel/carboplatin followed by consolidation paclitaxel/carboplatin were administered with high (74 Gy) versus low (60 Gy) dose RT. Median overall survival was 23.5 months in the 60 Gy arm, while no benefit of higher dose radiation was seen.¹⁰ Principle toxicities associated with concurrent therapy in these trials were esophagitis and pneumonitis. In a multi-arm conducted by the West Japan Thoracic Oncology Group (WJTOG), concurrent RT + weekly paclitaxel/carboplatin followed by consolidation paclitaxel/carboplatin resulted in similar survival and less toxicity versus concurrent RT + MVP (mitomycin, vendesine, cisplatin) followed by MVP consolidation (PMID# 20625120).¹¹

3.3 Paclitaxel/Carboplatin

Carboplatin is a commonly used platinum compound that acts by producing interstrand deoxyribonucleic acid (DNA) cross-links and, thus, interrupting cell division. It is approved by the Food Drug Administration (FDA) for the treatment of ovarian cancer and by the European Medicines Agency (EMA) for ovarian cancer of epithelial origin and small cell lung carcinoma. It is also used for the treatment of non-small cell lung cancer (NSCLC), head and neck cancer, endometrial cancer, metastatic seminoma, and more recently in breast cancer. Carboplatin is eliminated by renal excretion and the clearance is related to the glomerular filtration rate (GFR). Therefore, it is dosed on the basis of GFR and the target area under the concentration versus time curve (AUC). Myelosuppression is the dose limiting toxicity of carboplatin and is dose dependent. Anemia may be cumulative and require transfusion support with prolonged therapy. Anaphylactic-like

reactions to carboplatin have been reported and may occur within minutes of carboplatin administration. The risk of allergic reactions is increased in patients previously exposed to platinum therapy. Other toxicities include nausea, vomiting, renal toxicity, and neurotoxicity.

Paclitaxel promotes the assembly of microtubule formation and stabilizes them by preventing depolymerization. It is insoluble in water and, therefore, is formulated in cremophor. Paclitaxel is approved by the FDA for the treatment of breast cancer, non-small cell lung cancer, ovarian cancer, and Kaposi's sarcoma. It is also in use for the treatment of several other solid tumor malignancies. It is administered as an intravenous (IV) infusion and can be used either on an every 3-week schedule or a weekly schedule. Main toxicities associated with the use of paclitaxel are myelosuppression, myalgias/arthralgias, and sensory neuropathy. Hypersensitivity reactions requiring treatment have occurred in 2% to 4% of patients receiving paclitaxel in clinical trials; thus, patients should be pretreated with corticosteroids, diphenhydramine, and H2 antagonists.

Paclitaxel/Carboplatin is one of several common chemotherapy backbones recommended for use in chemoradiotherapy regimens for Stage III NSCLC.^{12,13}

3.4 PARP Inhibition for Cancer Treatment

Poly(ADP-ribose)-polymerase (PARP) 1 and 2 are nuclear enzymes that recognize deoxyribonucleic acid (DNA) damage and facilitate DNA repair.¹⁴ Inactive PARPs 1 and 2 bind to damaged DNA, which leads to their auto-activation. The resulting activated PARP enzymes then poly(ADP-ribosyl)ate many nuclear target proteins, including those that facilitate DNA repair of both single-stranded or double-stranded DNA breaks. Thus PARP inhibition will result in less efficient DNA repair following a cytotoxic insult.

DNA damaging agents including cytotoxic chemotherapy and radiotherapy, remain a mainstay of treatment for many patients with cancer. Since cancer cells are genetically unstable, often exhibiting complex karyotypes that include large deletions, insertions, and

unbalanced translocations of chromosomal material, these cells are more susceptible than normal tissues to cytotoxicity induced by DNA-damaging agents.¹⁵ Of these, deficiencies in mismatch repair or homologous recombination are associated with the largest number of malignancies. These deficiencies render cells more dependent on PARP for DNA repair, and hence more sensitive to PARP inhibition.¹⁶

PARP enabled DNA repair may also compensate for the loss of other repair pathways. Higher expression of PARP in cancer cells compared to normal cells has been linked to drug resistance and the overall ability of cancer cells to sustain genotoxic stress.¹⁷

3.5 Veliparib

A detailed discussion of the preclinical toxicology, metabolism, and pharmacology can be found in the veliparib Investigator's Brochure.¹⁷

3.5.1 Rationale for Combining Veliparib with Concurrent Chemoradiotherapy and Consolidation Chemotherapy

Administration of veliparib in vitro or in vivo inhibits the formation of poly (ADP-ribose) (PAR) polymers. When veliparib and DNA-damaging cytotoxic agents or DNA-damaging radiation are co-administered, veliparib inhibits the repair of DNA. In a variety of nonclinical tumor models, including lung, melanoma, breast, prostate, colon, and glioma, veliparib significantly enhanced the antitumor activity when dosed on a schedule that overlapped the administration of a DNA-damaging therapy.

3.5.2 Veliparib Preclinical Toxicology

The toxicological profile of veliparib has been evaluated in nonclinical general toxicity studies that included single-dose (rats and mice), repeat-dose (duration of up to 6 months in rats and up to 9 months in dog), reproductive (embryofetal development in rat and rabbit), genetic (Ames, in vitro cytogenetics, in vivo micronucleus), phototoxicity (in vitro photosensitivity) and juvenile rat toxicity studies. Primary nonclinical findings included effects on the central nervous system (CNS) (convulsions, tremors), hematopoietic system (bone marrow depletion and resultant decreased circulating white

and red blood cells), reproductive system (male germ cell depletion, female reproductive tract tissues degeneration), and lymphoid tissues (lymphocyte depletion), with lesser effects on the gastrointestinal tract (single-cell necrosis) and cardiovascular system (10% QTc interval prolongation). Convulsions and other CNS-related signs were considered exposure-dependent, and were generally self-limiting, ameliorated by dose reduction or cessation of dosing, or responsive to treatment. All other findings were dose dependent and reversible upon discontinuation of veliparib administration. Veliparib was also genotoxic (induced chromosomal aberrations in vitro and increased micronuclei formation in vivo) and was toxic to the developing fetus (increases in the incidence of fetal external/visceral/skeletal malformations/variations) in rats and rabbits. Veliparib demonstrated no phototoxic potential in the photosensitivity assay. With the exception of CNS and cardiovascular effects, the toxicity of veliparib is generally consistent with the pharmacology of the compound.

3.5.3 Pharmacokinetics and Pharmacodynamics

The pharmacokinetic exposure of veliparib is approximately dose-proportional over 10 through 500 mg BID dose range. The absorption of veliparib after oral dosing is relatively fast where veliparib plasma concentrations peak at approximately 1 to 2 hours after dosing across dose levels. The terminal half-life ($t_{1/2}$) of veliparib is about 6 hours, with minimal accumulation following multiple BID dosing. Food does not have a significant effect on veliparib bioavailability. The administration of a high-fat meal had no significant effect on AUC and only caused a slight decrease in veliparib C_{max} (17%) and a delay of approximately 1 hour in T_{max} . The mean urinary recovery of unchanged veliparib was 73% and the total urinary recovery of veliparib (as parent compound and M8 metabolite) was 90%, which indicates that renal excretion is a major pathway in veliparib elimination. Veliparib is not a potent inhibitor, nor an inducer, of the major human cytochrome P450s (CYPs), suggesting a minimal potential for DDIs at the anticipated therapeutic concentrations. Potential drug-drug interactions (DDI) of veliparib are being evaluated in veliparib combination studies. There was no significant pharmacokinetic interaction between veliparib and temozolomide (TMZ), between

veliparib and carboplatin/paclitaxel (C/P), between veliparib and folinic acid, fluorouracil, and irinotecan (FOLFIRI), and between veliparib and capecitabine/5-fluorouracil (5-FU). Preliminary results also indicate the absence of a DDI between veliparib and carboplatin/gemcitabine and between veliparib and carboplatin/etoposide.

3.5.4 Clinical Experience

Veliparib is investigated in AbbVie-sponsored studies, in Investigator initiated studies (IIS), and in CTEP-sponsored studies. In these studies, veliparib is administered as monotherapy, combined with a variety of chemotherapeutic agents, or combined with radiotherapy.

Summary preliminary or final efficacy data from AbbVie sponsored studies show that veliparib has activity in combination with TMZ, with radiotherapy, and with carboplatin + paclitaxel.¹⁸ Data from non-AbbVie sponsored studies show veliparib has activity as monotherapy for treatment of ovarian cancer¹⁹ and activity in combination with carboplatin + paclitaxel for treatment of early breast cancer.²⁰ Veliparib is currently in Phase 2 clinical development in combination with several DNA-damaging agents across a variety of cancer indications and Phase 3 clinical development in combination with carboplatin and paclitaxel for early breast cancer and for advanced/metastatic squamous NSCLC. At present, AbbVie's safety database for veliparib is based on the exposure of approximately 2000 cancer patients to veliparib in clinical studies. Veliparib's known and potential safety risks were identified based on clinical safety analyses, as well as evaluation of pharmacological mechanism, preclinical studies, and literature. Identified risks associated with veliparib administration are hematological cytopenias when veliparib is added to backbone chemotherapy regimens. Most observed toxicities in patients exposed to veliparib have been as expected with DNA-damaging agents and are manageable with routine oncology supportive care. Potential risks of veliparib administration, identified mostly in preclinical studies or based on pharmacological mechanism, but not confirmed in clinical studies, are seizures, changes in testes/ovaries, and toxicity to the developing fetus. A potential risk of secondary malignancies is theoretical based on veliparib's mechanism of action.

Veliparib and Radiotherapy

Study M10-128 was a Phase 1, open-label dose escalation study evaluating the safety, tolerability and pharmacokinetics of veliparib in combination with whole brain radiation therapy (WBRT) in subjects with brain metastases. Doses of 200 mg or less were tolerated and were not associated with toxicity above that attributable to WBRT alone. G3/4 adverse events in 5% or more of treated subjects (N = 81) included fatigue (7.4%) and hyponatremia (6.2%). The median survival of subjects with brain metastases from NSCLC was 10.0 months. Based on these results, AbbVie is conducting a randomized Phase 2 study investigating veliparib in combination with whole brain radiation therapy for subjects with brain metastases from NSCLC.

Study M12-950²¹ was a Phase 1b study investigating veliparib in combination with capecitabine and radiation in subjects with locally advanced rectal cancer. In this study, veliparib was dose-escalated and well-tolerated in 32 subjects including 16 at the maximum administered dose of 400 mg BID. The MTD was not reached based on the study design. Dose-limiting toxicities occurred in 2 subjects: grade 2 radiation skin injury in a 70 mg BID subject and grade 2 nausea and vomiting in a 400 mg BID subject. None of these events were serious adverse events. Overall, treatment-emergent adverse events reported for $\geq 25.0\%$ of the 32 subjects were nausea (53.1%), diarrhea (50.0%), fatigue (50.0%), radiation skin injury (28.1%), constipation (25.0%), and vomiting (25.0%). Similar results were observed for treatment emergent adverse events considered possibly or probably related to study drug. These events are consistent with the known adverse event profile of capecitabine and/or radiation treatment.

Overall, 8 subjects experienced at least 1 grade 3 treatment-emergent adverse event. The only grade 3 adverse event experienced by more than 1 subject was diarrhea (1 [14.3%] of 7 subjects in the $> 70 - < 400$ mg BID group, 2 [12.5%] of 16 subjects in the 400 mg BID group). There were no grade 4 treatment-emergent adverse events in this study.

Veliparib in combination with capecitabine and radiation showed promising preliminary antitumor activity. Complete response was achieved in 4 of 16 subjects (25.0%) who

received < 400 mg BID of veliparib and 5 of 15 subjects (33.3%) who received veliparib 400 mg BID and had a postsurgery assessment. The majority of subjects in each dose group achieved tumor downstaging (12 of 16 subjects [75.0%] for < 400 mg BID, 12 of 15 subjects [80.0%] for 400 mg BID) and had a reduction of $\geq 50\%$ in their CEA value relative to baseline (12 of 16 subjects [75.0%] for < 400 mg BID, 9 of 15 subjects [60.0%] for 400 mg BID). The majority of subjects underwent sphincter-sparing surgery (11 of 16 subjects [68.8%] for < 400 mg BID, 12 of 15 subjects [80.0%] for 400 mg BID).

Veliparib and Paclitaxel/Carboplatin for NSCLC

Phase 1 data from patients treated with veliparib, carboplatin, and paclitaxel for advanced NSCLC are available from CTEP Study 7967.²¹ Subjects had advanced solid tumors, received ≤ 3 prior chemotherapy regimens for advanced disease, and had ECOG performance status 0 to 2. Veliparib was given on Days 1 to 7 of each 21-day cycle, and paclitaxel and carboplatin were administered on Day 3. Two DLTs (febrile neutropenia and hyponatremia) were observed in 2 of 7 evaluable subjects treated at the maximum tolerated dose of veliparib 120 mg BID, paclitaxel 200 mg/m², and carboplatin AUC 6. The most common AEs reported in this study were neutropenia and fatigue (reported in > 50% of subjects); nausea, thrombocytopenia, and peripheral sensory neuropathy (> 40% of subjects); and anemia, constipation, alopecia, diarrhea, decreased appetite, lymphopenia, and myalgia (> 20% of subjects). Among 68 initial patients, partial responses were seen in 11 patients and complete response in 2 patients. Among 11 subjects with NSCLC (8 evaluable), 4 subjects had responses and 3 additional subjects had stable disease at first tumor evaluation. A double-blind, randomized Phase 2 study of carboplatin and paclitaxel with veliparib or placebo for subjects with advanced NSCLC is ongoing. Therapy is delivered for up to 6 cycles with carboplatin AUC 6 (IV) and paclitaxel 200 mg/m² (IV) every 3 weeks plus veliparib/placebo 120 mg BID (PO) on seven days around chemotherapy administration. All subjects have completed therapy, and final data are pending. Preliminary data showed an improvement in median progression-free survival of approximately 1.6 months and an improvement in overall survival of approximately 2 months among NSCLC subjects treated with veliparib

(differences not statistically significant; unpublished data on file at AbbVie). Leukopenia was increased in frequency by < 15% for veliparib versus placebo-treated subjects, and neutropenia was increased in frequency by < 10% for veliparib versus placebo-treated subjects. No other AE was increased by > 5%. AEs led to reduction or discontinuation of backbone therapies at similar rates (\pm 4%) with or without veliparib. Based on these data, AbbVie is conducting additional studies of veliparib in combination with paclitaxel/carboplatin for patients with advanced/metastatic NSCLC.

3.6 Study Rationale

A moderate proportion of NSCLC patients are diagnosed with Stage III disease, for which multi-modality therapy is recommended and prognosis is poor. Current standard therapy for Stage III NSCLC provides time-to-progression of 1 – 1.5 years.⁵⁻¹⁰ Phase 1 data and preliminary Phase 2 data described above suggest the addition of veliparib to radiotherapy, paclitaxel and carboplatin may improve outcome of patients with NSCLC. This study will investigate concurrent radiotherapy and consolidation chemotherapy with veliparib for Stage III NSCLC.

3.7 Differences Statement

The current study (Study M14-360) is the first AbbVie-sponsored study investigating the efficacy and tolerability of veliparib in combination with paclitaxel/carboplatin-based chemoradiotherapy followed by consolidation paclitaxel/carboplatin in subjects with locally advanced Stage III non-small cell lung cancer.

3.8 Benefits and Risks

This study proposes to establish improved clinical outcomes for patients with Stage III NSCLC through the addition of veliparib to standard treatment with radiotherapy, carboplatin and paclitaxel. Preclinical data demonstrate that veliparib potentiates the anti-tumor activity of radiation and platinum, and data from early-phase studies (completed or preliminary) is consistent with these observations. As described below, subjects with advanced or metastatic NSCLC receiving veliparib with carboplatin and

paclitaxel have shown favorable, though not statistically significant, results for the endpoints of overall survival; and subjects with brain metastases from NSCLC receiving veliparib with radiotherapy (single arm study) had longer than expected survival.

Risks in this study include toxicity from the addition of veliparib to standard therapy. Preliminary safety data from a blinded, randomized Phase 2 study of carboplatin, paclitaxel, and veliparib in subjects with advanced NSCLC suggest low rates of additional toxicities and no compromise to the delivery of carboplatin and paclitaxel. Safety data from a single arm Phase 1 study of radiotherapy and veliparib in subjects with NSCLC brain metastases show minimal additional toxicities and no compromise to the delivery of radiation. Standard clinical practices to manage the toxicity of chemoradiotherapy and consolidation chemotherapy are well established. Other potential risks of veliparib administration, identified in preclinical studies or based on pharmacological mechanism, but not confirmed in clinical studies must also be considered. These risks include seizures, changes in testes/ovaries, toxicity to the developing fetus and secondary malignancies.

4.0 Study Objective

The primary objectives of the study are to establish the recommended Phase 2 dose (RPTD) of veliparib in combination with concurrent paclitaxel/carboplatin-based chemoradiotherapy (CRT) and paclitaxel/carboplatin-based consolidation chemoradiotherapy and to assess whether the addition of oral veliparib versus placebo to paclitaxel/carboplatin-based chemoradiotherapy with consolidation paclitaxel/carboplatin will improve progression-free survival (PFS) in patients with Stage III non-small cell lung cancer (NSCLC).

The secondary objectives of the study are to assess overall survival (OS), objective response rate (ORR), duration of overall response (DOR), safety and tolerability of veliparib versus placebo added to standard therapy.

The tertiary objectives are to assess Quality of Life (QoL) and ECOG performance status. In addition, biomarkers including, but not limited to, defects in DNA-repair genes will be assessed in correlation with safety and efficacy data.

5.0 Investigational Plan

5.1 Overall Study Design and Plan: Description

This two-phase study consists of 1) dose-escalation of veliparib to determine an RPTD for combination with concurrent paclitaxel/carboplatin-based CRT and paclitaxel/carboplatin-based consolidation chemoradiotherapy; and 2) a randomized, double-blinded study to determine whether veliparib improves outcome relative to placebo when added to paclitaxel/carboplatin based CRT followed by consolidation paclitaxel/carboplatin in subjects with previously untreated Stage III NSCLC.

5.2 Selection of Study Population

The study was designed to enroll approximately 206 subjects with Stage III NSCLC (approximately 50 in the dose escalation portion and approximately 156 in the randomized portion) at approximately 50 – 75 study centers to meet scientific and regulatory objectives without enrolling an undue number of subjects in alignment with ethical considerations. Therefore, if the target number of subjects has been enrolled, there is a possibility that additional subjects in Screening will not be enrolled.

Dose Escalation Portion (Phase 1)

In the dose escalation phase (Phase 1) of the study, subjects will receive veliparib in combination with carboplatin AUC 2+ paclitaxel 45 mg/m² + thoracic radiotherapy. Radiation delivery will be over no more than 9 weeks by 3-dimensional conformal radiotherapy or intensity modulated radiotherapy (IMRT), and the total dose will be 60 – 63 Gy. Dose escalation of veliparib during chemoradiotherapy will occur in cohorts derived from the 3 + 3 design described in Section 5.5.1. The first cohort of at least 3 – 6 subjects will receive veliparib 60 mg BID throughout CRT. Additional eligible subjects

may be enrolled at the current dose level at the discretion of the Investigators and the AbbVie Medical Monitor. Based on tolerability, subsequent cohorts will receive doses of veliparib as shown in [Table 1](#).

Table 1. Dose Escalation

Dose Escalation in the Concurrent Chemoradiotherapy

Cohort	Dose Level	Number of Subjects	Veliparib (mg)
1	1	3 – 6	60
2	2	3 – 6	80
3	3	3 – 6	120
4	4	3 – 6	200
5	5	3 – 6	240
	-1	0 – 6	40

Dose Escalation in the Consolidation Chemotherapy

Cohort	Dose Level	Number of Subjects	Veliparib (mg)
1 – 5		3 – 6	120
6		3 – 6	240

To insure subject safety during the Phase 1 portion of the study, other doses may be selected for investigation based on cumulative safety data with agreement between the investigators and medical monitor. Veliparib doses will be escalated or reduced by multiples of 20 mg (the tablet size) based on review of the cumulative experience in prior cohorts with the Phase 1 Investigators. Also, no dose level will exceed the prior dose by > 67%, and no dose above 240 mg will be given.

Dose limiting toxicity (DLT) events will be collected for each dosing cohort until a new dosing cohort is opened or until the RPTD is identified. During CRT dose escalation, the DLT period for each subject will be from the start of veliparib dosing through 28 days following completion of RT or until consolidation chemotherapy is initiated, and the DLT period for all subjects at each dose level will end upon initiation of the next dose level.

CRT dose escalation will occur with a consolidation dose of veliparib of 120 mg BID + carboplatin (AUC 6 mg/mL/min) + paclitaxel (200 mg/m²) for up to two 21-day cycles. Once the concurrent CRT RPTD is identified, an additional cohort will be enrolled to explore the tolerability of a consolidation dose of veliparib at 240 mg BID + carboplatin (AUC 6 mg/mL/min) + paclitaxel (200 mg/m²) for up to two 21-day cycles.

Subjects overenrolled in Cohort 5 will be allowed to roll over into Cohort 6 as long as they have not started the consolidation phase, and at the discretion of the Investigators and the AbbVie Medical Monitor.

For Cohort 6, the DLT period will be 21 days from start of consolidation chemotherapy or until the start of Cycle 2 consolidation therapy.

For this cohort, if 3 or less subjects were able to take Cycle 2 of consolidation chemotherapy, the reason of dose reduction and treatment discontinuation will be reviewed as part of consideration to determine MTD/RPTD of veliparib for the consolidation phase.

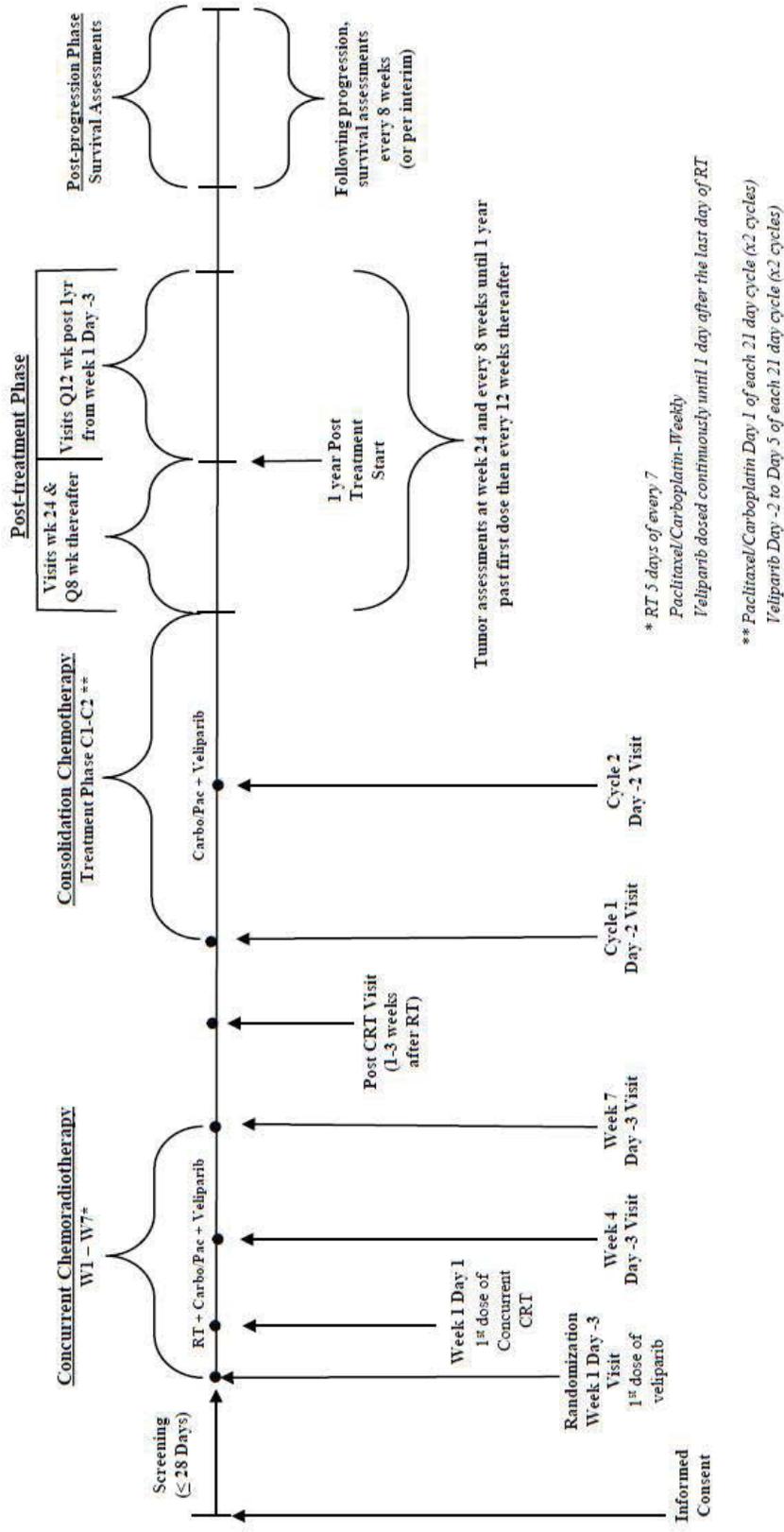
DLTs are defined as the following events that are considered by the investigator group to be related to treatment:

1. Radiation induced Grade 3 or greater cardiac toxicity (e.g., myocarditis, pericarditis, heart failure, ventricular dysfunction, myocardial infarction).
2. Radiation induced myelopathy/myelitis (does not include L'Hermitte's syndrome).
3. Radiation-related pneumonitis resulting in delay in radiotherapy, chemotherapy (CRT or consolidation) or veliparib of more than 3 weeks or early discontinuation of RT (total dose < 50 Gy).
4. G4 or greater esophagitis or esophagitis, dysphagia, and odynophagia requiring treatment interruption of > 7 days despite medical management.
5. G2 or greater seizure.

6. Grade 4 or greater neutropenia for > 7 days or neutropenic fever (defined as ANC < 500 and a temperature of 38.5°C or above).
7. Grade 4 or greater thrombocytopenia.
8. Grade 4 diarrhea or nausea/vomiting despite appropriate antiemetic therapy lasting > 48 hours.
9. Any other toxicity resulting in delay in radiotherapy, chemotherapy, or veliparib of more than 14 days or early discontinuation of RT (total dose < 50 Gy).
10. All other non-hematologic toxicities of Grade 3 or greater, with the following exceptions:
 - a. Anorexia
 - b. Fatigue
 - c. Grade 3 infection
 - d. Grade 3 AST/ALT elevations \leq 7 days
 - e. Infusion reactions. Patients with Grade 3 or worse infusion reactions will be removed from study and replaced and will not be considered evaluable for DLT
 - f. Grade 3 or 4 lymphopenia
 - g. Grade 3 or 4 electrolyte abnormalities that are corrected to Grade 2 or less in less than 48 hours

A schematic of the Phase 1 treatment is shown in [Figure 1](#).

Figure 1. Phase 1 Study Schematic



Randomized Phase 2 Portion

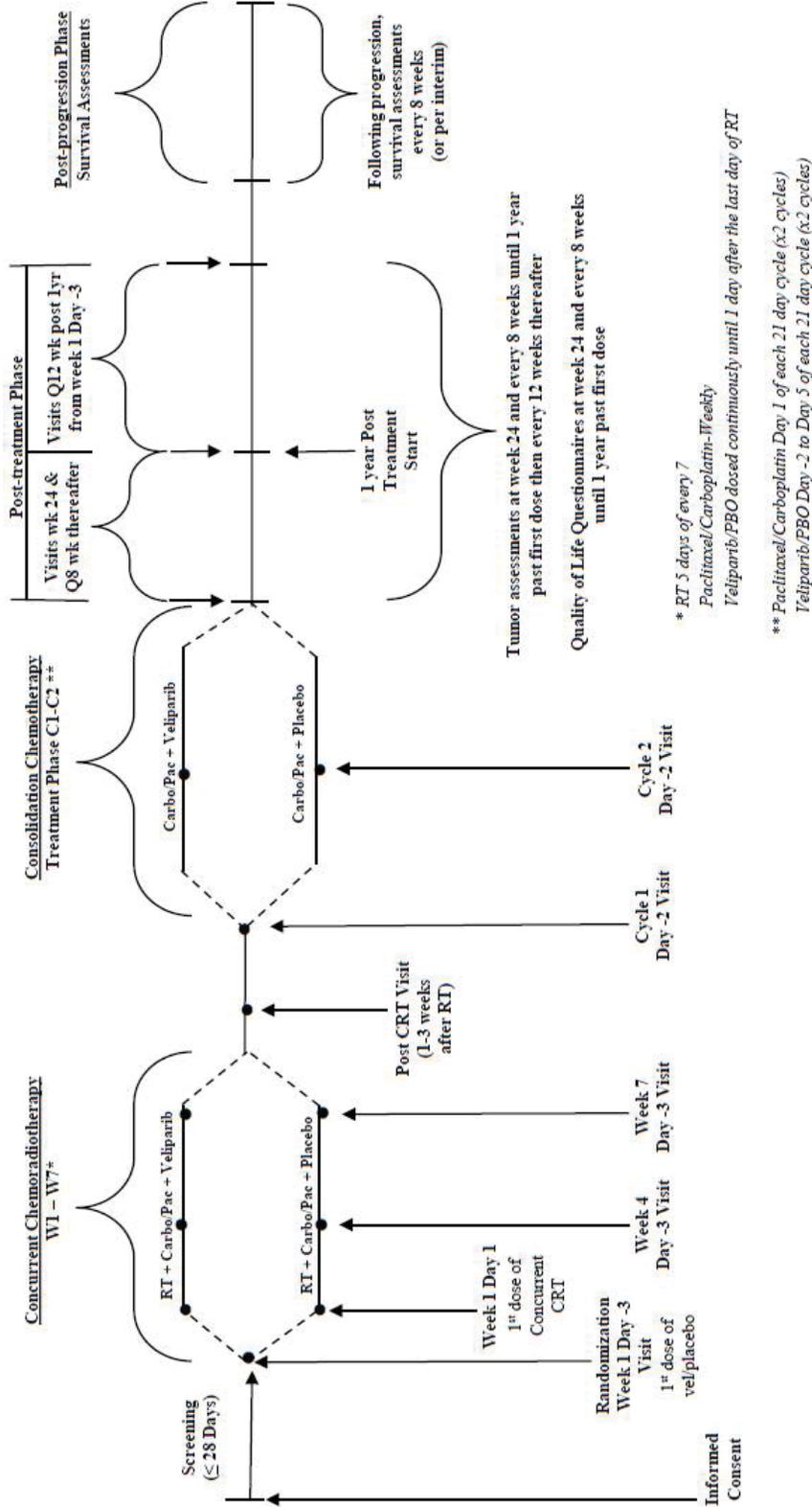
Following the dose escalation portion of the study, the RPTD will be determined by the sponsor and at the discretion of the sponsor, the Phase 2 portion of the study will begin with patient randomization in a 1:1:1 ratio to the treatment arms as follows:

- A. Concurrent paclitaxel/carboplatin/radiotherapy/veliparib followed by consolidation paclitaxel/carboplatin/veliparib
- B. Concurrent paclitaxel/carboplatin/radiotherapy/veliparib followed by consolidation paclitaxel/carboplatin/placebo
- C. Concurrent paclitaxel/carboplatin/radiotherapy/placebo followed by consolidation paclitaxel/carboplatin/placebo

Subject randomization will be stratified by tumor volume (≤ 90 versus > 90 cm³) and smoking history (current smoker versus former smoker versus never smoked).

A schematic of the Phase 2 treatment arms is shown in [Figure 2](#).

Figure 2. Phase 2 Study Schematic



Screening procedures, QoL assessments, and baseline radiographic tumor assessments will be performed within 28 days prior to randomization.

Subjects who experience toxicities due to carboplatin, paclitaxel, radiotherapy, or veliparib/placebo may require a delay in the dosing schedule or a dose modification as described in [Appendix D](#). Subjects without clinical progression of disease and with tolerable side effects should continue to receive treatment until completion of all prescribed cycles (chemoradiotherapy plus 2 cycles of consolidation chemotherapy).

Radiographic tumor assessments will be conducted at baseline, prior to consolidation chemotherapy, at 24 weeks after start of treatment, every 8 weeks until one year after beginning therapy, then every 12 weeks. Radiographic progression will be determined using the Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 beginning with the second scan after completion of CRT). RECIST criteria can be found in [Appendix E](#). Clinical progression prior to that time will be determined by the investigator. In Phase 2 portion of the study, a QoL assessment as measured by the EORTC QLQ-C15-PAL and the companion symptom module EORTC QLQ-LC13 will be performed at screening, prior to consolidation chemotherapy, at 24 weeks after start of treatment, every 8 weeks until one year after beginning therapy and at the final visit.

After completion of protocol therapy, subjects will be observed without further therapy until progression. The visit at which an investigator identifies disease progression or at which a subject meets other criteria for study discontinuation will be considered the final visit. Criteria for discontinuation can be found in [Section 5.4](#).

All subjects with a final visit < 30 days after the last dose of drug will have one Follow-Up Visit approximately 30 days after the Final Visit. If a subject is discontinued from the study with an ongoing adverse event or an unresolved clinically significant laboratory result, the site will attempt to provide follow-up until a satisfactory clinical resolution of the laboratory results or adverse event is achieved.

Overall survival (OS) will be determined by the Investigator until radiographic progression. After radiographic progression, survival information will be collected via the electronic CRF at 8 week intervals (or as requested by sponsor to support data analysis).

Details regarding study visits and study procedures mentioned above can be found in Section 5.3.1.1 and in Table 2.

5.2.1 Inclusion Criteria

1. Subject must be ≥ 18 years of age;
2. Subject must have histologically or cytologically confirmed Stage III NSCLC. When pleural fluid is visible on the CT scan or on a chest x-ray, a thoracentesis is required to confirm that the pleural fluid is serous AND cytologically negative. Effusions that are minimal (i.e., not visible on chest x-ray) or that are too small to safely tap are exempted from the requirement for thoracentesis.
3. Subjects in the randomized portion of the study must have measurable disease as per the RECIST version 1.1 criteria;
4. Subject must consent to provide archived tissue or cytology sample of NSCLC lesion for analysis;
5. Subjects must have V20 (volume of lung to receive 20 Gy radiotherapy according to simulation) $< 35\%$;
6. Subject must have an Eastern Cooperative Oncology Group (ECOG) performance score of 0 – 1;
7. Subject must have adequate hematologic, renal, hepatic, and lung function as follows:
 - Bone marrow: Absolute Neutrophil count (ANC) $\geq 1,500/\mu\text{L}$; Platelets $\geq 100,000/\text{mm}^3$; Hemoglobin ≥ 9.0 g/dL (without transfusion);
 - Renal function: Calculated creatinine clearance ≥ 50 mL/min by the Cockcroft-Gault formula;

- Hepatic function and enzymes: aspartate aminotransferase (AST) and alanine aminotransferase (ALT) $\leq 2.5 \times$ the upper limit of normal (ULN) of institution's normal range; Bilirubin $\leq 1.5 \times$ ULN; subjects with Gilbert's syndrome may have a bilirubin $\geq 1.5 \times$ ULN of central laboratory normal range;
 - Pulmonary function tests (PFTs) including FEV1 within 12 weeks prior to randomization; for FEV1, the best value obtained pre- or post-bronchodilator must be ≥ 1.2 liters/second and/or $\geq 50\%$ predicted.
8. Female subjects of childbearing potential (i.e., those who are not postmenopausal for at least 1 year or surgically sterile by bilateral tubal ligation, bilateral oophorectomy or hysterectomy) and their male partner should practice at least one of the methods of birth control listed below for at least 6 months after treatment with chemotherapy. Male subjects and their female partners of childbearing potential should practice at least one of the methods of birth control listed below for at least 6 months after treatment with chemotherapy.
- Total abstinence from sexual intercourse (if it is the subject's preferred and usual lifestyle; beginning a minimum one complete menstrual cycle prior to study drug administration and to extend 6 months after treatment);
 - Vasectomized subject or partner(s); vasectomy (males);
 - Intrauterine device (females)
 - Double-barrier method (condoms, contraceptive sponge, diaphragm or vaginal ring with spermicidal jellies or creams; both males and females)
 - Hormonal contraceptives (oral, parenteral or transdermal) for at least 90 days prior to study drug administration (females). If hormonal contraceptives are used, the subject and her partner should also use a single barrier method.
9. Subject must voluntarily sign and date an informed consent, approved by an Independent Ethics Committee (IEC)/Institutional Review Board (IRB), prior to the initiation of and Screening for study-specific procedures.

Rationale for Inclusion Criteria

- 1 – 7 To select the appropriate subject population with sufficient disease severity for evaluation
- 8 The impact of veliparib plus paclitaxel/carboplatin-based chemoradiotherapy followed by paclitaxel/carboplatin consolidation on the unborn fetus is unknown; therefore, these criteria ensure that adequate precautions are taken to avoid pregnancy
- 9 In accordance with harmonized Good Clinical Practice (GCP)

5.2.2 Exclusion Criteria

- 1. Subject with prior chemotherapy or radiotherapy for current NSCLC. Subjects curatively treated for past early stage NSCLC greater than 3 years ago may be included;
- 2. Subject with prior exposure to PARP inhibitors;
- 3. Subjects with known hypersensitivity to carboplatin, paclitaxel, or formulations containing polyethoxylated castor oil (Cremophor);
- 4. Subject with prior mediastinal or thoracic radiotherapy. Prior tangential RT to prior breast cancer is acceptable;
- 5. Subject with major surgery in the 4 weeks prior to randomization (VATS and/or mediastinoscopy is not considered major surgery);
- 6. Subject with a previous or concurrent malignancy except for treated basal cell or squamous cell skin cancer, in situ cervical cancer, or other cancer for which the patient received potentially curative treatment and has been disease-free for 3 years or is considered cured by the investigator if has been disease-free for less than 3 years;
- 7. Any medical condition, which in the opinion of the study investigator, places the subject at an unacceptably high risk for toxicities, or any subject circumstance that prohibits trial participation according to local law;

8. Subject is pregnant or lactating;
9. Subject with sensory peripheral neuropathy of \geq Grade 2 at baseline;
10. Subject is unable to swallow medication;
11. Subjects with prior history of seizure within the prior 12 months.

Rationale for Exclusion Criteria

1 – 11 For the safety of the subjects

5.2.3 Prior and Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins and/or herbal supplements) that the subject is receiving at the time of enrollment, or receives during the study, must be recorded along with the reason for use, date(s) of administration including start and end dates, and dosage information including dose, route and frequency.

The AbbVie study designated physician should be contacted if there are any questions regarding concomitant or prior therapy(ies).

5.2.3.1 Prior Therapy

Subjects who have received anti-cancer therapy for NSCLC prior to entry into the study are not eligible. For the purposes of this protocol, prior anti-cancer therapy for NSCLC is defined as anti-cancer agents (e.g., cytotoxic chemotherapy, immunotherapy, biologic therapy, and herbal anti-cancer medicine), radiotherapy and investigational agents. An investigational agent is any drug or therapy not currently approved for use in humans.

5.2.3.2 Concomitant Therapy

The locally approved product label or applicable Summary of Product Characteristics (SmPC) for carboplatin and paclitaxel should be referenced for any concomitant therapy guidelines.

- Premedication:** To reduce the severity of hypersensitivity reactions due to treatment with paclitaxel, manage according to institutional guidelines, the locally approved product label, local practice, or applicable SmPC (i.e., premedication with corticosteroids, diphenhydramine, and H2 antagonists).
- Anti-Cancer Agents:** No anti-cancer agents or investigational agents may be taken concurrently with veliparib. The locally approved carboplatin and paclitaxel product labels or SmPCs should be referenced to determine if there are any contraindications associated with concomitant medications (e.g., yellow fever vaccine, phenytoin, etc.). Hormonal contraceptives, hormonal replacement therapy, etc. are allowed.

- Supportive Care:** Best supportive care and treatment will be given as appropriate to each subject (antiemetics, antibiotics, transfusions, nutritional support, palliative treatment for pain, etc.) according to institutional guidelines, NCCN guidelines³ or ASCO guidelines.²² For anti-emetic therapy, ASCO guidelines recommend for consolidation chemotherapy a two drug combination of palonosetron and dexamethasone. If palonosetron is not available, any of the first generation 5-HT₃ receptor antagonists may be used, preferably ondansetron or granisetron. ASCO dosing guidelines are as follows:
Palonosetron: 0.25 g IV OR 0.50 mg oral, Day 1 only
Dexamethasone: 8 mg (IV or oral), Days 1 to 3
Aprepitant is not recommended, though clinicians may consider its use. If clinicians opt to use aprepitant, dosing guidelines are as follows:
Aprepitant: 125 mg Day 1, 80 mg Days 2 and 3
5-HT₃ receptor antagonist dosing
Dexamethasone: 12 mg on Day 1 only
- Growth Factors:** Biologic response modifiers administered for erythropoiesis (e.g., erythropoietin, darbepoetin alpha) may be administered during consolidation chemotherapy, but are not permitted during chemoradiotherapy. Granulocyte growth factors (e.g., G-CSF, GM-CSF, etc.) are to be administered according to the Investigator's standard practice and/or ASCO guidelines. Growth factors may be given with the intent to prevent dose reductions or delays.
- Surgery:** If the subject requires surgery during the study, the AbbVie medical monitor must be contacted.
- Alternative Therapy:** No herbal remedies or non-prescription anti-cancer supplements may be taken for cancer treatment concurrently with veliparib.

**Therapies to Take
Caution with when
Administered with
Paclitaxel or
Carboplatin:**

Caution should be taken when administering paclitaxel with known substrates (e.g., midazolam, buspirone, felodipine, lovastatin, eletriptan, sildenafil, simvastatin, and triazolam), inhibitors (e.g., atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, and telithromycin), and inducers (e.g., rifampicin and carbamazepine) of CYP3A4 or known substrates (e.g., repaglinide and rosiglitazone), inhibitors (e.g., gemfibrozil), and inducers (e.g., rifampicin) of CYP2C8. Caution should also be taken when administering carboplatin with aminoglycosides and diuretics. Recommendations per the local label should be observed.

**5.3 Efficacy Pharmacokinetic, Pharmacodynamic,
Pharmacogenetic and Safety Assessments/Variables**

**5.3.1 Efficacy and Safety Measurements Assessed and Flow
Chart**

A schedule of study activities is presented in [Table 2](#). Pharmacodynamic (PD) and Pharmacogenetic (PG) assessments will be performed as summarized in [Table 3](#). Pharmacokinetic (PK) assessments will be performed as summarized in [Table 4](#) and [Table 5](#).

Table 2. Study Activities (Phase 1 and 2)

Activity	Screening ^a	Concurrent (Chemoradiotherapy)					Post CRT Visit ^c	Consolidation ^d			Post-Treatment Visit ^e	Final Visit ^f	30-Day FU Visit ^g	Survival Period
		Wk 1 Day -3	Wk 1-3 Day 1	Wk 4 Day -3	Wk 4-9 ^b Day 1	Wk 7 Day -3 ^b		Cycle 1 Day -2	Cycle 1 Day 1	Cycle 2 Day 1				
Informed Consent ^{h,i}	X													
Medical and Oncology History	X													
PET Scan ^j	X													
MRI of Brain ^{j,k}	X													
Physical Exam (including weight)	X ^l	X ^l		X		X	X	X			X	X		
Vital Signs	X	X		X		X	X	X			X	X		
12-Lead ECG	X										X ⁿ	X		
PFT ^m	X										X			
Performance Status (ECOG)	X	X		X		X	X	X			X	X		
Documentation of Non Childbearing Status or Pregnancy Test	X	X ^o												
Chemistry/Hematology ^p	X	X		X		X	X	X		X	X			
Urinalysis ^p	X											X		
aPTT, INR	X													
Tumor Assessment (CT Scan) ^{q,r}	X ^q						X ^{q,r}				X ^{q,r}	X ^r		
QoL Questionnaires ^{s,t}	X						X				X	X		
Adverse Event/Concomitant Medication Assessment	X	X	X	X	X	X	X	X	X	X	X ^u	X	X	
Randomization ^s		X												
Dispense Veliparib/placebo ^v		X		X		X		X		X				
Administer Veliparib/placebo ^v		X ^w		X ^w		X ^w		X ^x		X ^x				
Administer Paclitaxel/Carboplatin			X		X				X	X				

Table 2. Study Activities (Phase 1 and 2) (Continued)

Activity	Screening ^a	Concurrent (Chemoradiotherapy)					Post CRT Visit ^c	Consolidation ^d			Post-Treatment Visit ^e	Final Visit ^f	30-Day FU Visit ^g	Survival Period
		Wk 1 Day -3	Wk 1-3 Day 1	Wk 4 Day -3	Wk 4-9 ^b Day 1	Wk 7 Day -3 ^b		Cycle 1 Day -2	Cycle 1 Day 1	Cycle 2 Day 1				
Administer Radiotherapy			X ^y		X ^y									
Survival Assessment ^z										X				X

- a. The Screening Visit must be performed within 28 days of Week 1 Day -3 and is considered baseline.
- b. Week 7 - 9 if necessary due to radiotherapy continuing > 6 weeks.
- c. Post CRT visit can be 1 - 3 weeks after completing CRT.
- d. Subjects who discontinue therapy prior to Week 12, should have an unscheduled visit at Week 12 and at Week 18 to assess AE, physical exam, vital signs and ECOG performance status. Subjects who discontinue therapy after Week 12 and prior to Week 18, should have an unscheduled visit at Week 18 with the same assessments as above.
- e. Begin post-treatment follow-up at Week 24. Continue every 8 weeks until 1 year after randomization, then every 12 weeks.
- f. The Final Visit will be defined as the visit at which disease progression is identified or at the time at which the Investigator determines that the subject should discontinue the study or the subject discontinues for other reasons (i.e., withdraw consent, etc.).
- g. A 30-day Follow-Up Visit is required if the Final Visit is < 30 days from the last administration of drug.
- h. Study consent must be performed prior to initiation of any screening or study-specific procedures.
- i. Pharmacogenomic sample: If the sample is not collected at Week 1 Day -3, it may be collected at any time throughout the study after the sub-study consent is signed.
- j. A PET scan and Brain MRI are required for staging, following diagnosis.
- k. MRI with contrast is required to rule out brain metastases. CT with contrast may be performed instead if subject is unable to undergo MRI scanning.
- l. Physical exam not required, if done within 7 days prior to Week 1 Day -3. Height only measured at Screening.
- m. A Pulmonary Function Test does not need to be repeated at screening, if one was performed within 12 weeks prior to Week 1 Day -3. PFT will be performed at 12 months post start of radiation therapy. If subject is no longer coming in for Post-Treatment Visits, every effort should be made to still collect the PFT at this 12 month timepoint.
- n. 12-Lead ECG only at first post-treatment visit.
- o. Serum pregnancy test will be done at Screening. Urine pregnancy test will be done prior to dosing at Week 1 Day -3 unless the serum pregnancy test was collected within 7 days of Week 1 Day -3.
- p. Study samples for central laboratory analysis may be performed within 72 hours of the scheduled day. A certified local laboratory may be used to perform laboratory analyses for treatment decisions. Blood Draw (hemoglobin only) to be collected in the Post Treatment visit at 12 months post start of radiation therapy.

Table 2. Study Activities (Phase 1 and 2) (Continued)

- q. Baseline tumor assessments must be conducted within 28 days of Week 1 Day -3. Post-baseline tumor assessment will be conducted prior to consolidation chemotherapy, at 24 weeks after start of treatment, and every 8 weeks (± 7 days) until 1 year after beginning of treatment, and then every 12 weeks (± 7 days).
- r. Tumor assessment is to be performed at the Final Visit for subjects who discontinue the study for reasons other than radiographic progression and if no assessment has been performed within the last 4 weeks.
- s. For subjects in the Phase 2 portion only.
- t. Questionnaires for the assessment of quality of life will be collected at screening, post concurrent chemoradiotherapy, at 24 weeks after start of treatment, every 8 weeks until 1 year on study and at the final visit for Phase 2 portion.
- u. AE assessment only at first post-treatment visit.
- v. Veliparib in phase 1 and veliparib/placebo in Phase 2.
- w. Veliparib is to be dosed continuously until 1 day following the last day of CRT.
- x. Veliparib is to be dosed continuously for 7 days (Day -2 – Day 5) in each consolidation cycle. It is recommended the site contact the subject on consolidation Cycle 1/Cycle 2 Day 5 to instruct subject about ceasing dosing.
- y. Radiotherapy is given 5 of 7 days of each week during the CRT.
- z. Following progression, survival assessments performed every 8 weeks.

Note: Subjects who complete protocol therapy or who discontinue treatment prior to reaching an event of disease progression are to continue visits and radiographic assessments until progression as per RECIST version 1.1 criteria ([Appendix E](#)).

Table 3. Schedule of Pharmacogenetic and Pharmacodynamic Assessments

Procedure	Visit Schedule	Before Drug Administration	After Drug Administration	Sampling Plan
				Specimen Matrix
PG Blood Sampling Genetic (DNA)* ^a (optional)	Chemoradiotherapy: Week 1 Day -3 Visit	N/A	N/A	Whole Blood Frozen -20°C or colder
Plasma Markers	Chemoradiotherapy: Week 1 Day -3, Week 4 Day -3, Post CRT and Final Visit ^b	Prior to dose	N/A	Blood → Plasma Frozen -70°C or colder
Serum Markers	Chemoradiotherapy: Week 1 Day -3, Post CRT and Final Visit ^b	Prior to dose	N/A	Blood → Serum Frozen -70°C or colder
Archived Tissue Sample Collection	Screening	N/A	N/A	FFPE ^c

* (Optional) only to be collected after additional informed consent is obtained.

- Every effort should be made to obtain sample at Week 1 Day -3, however sample may be collected at any point (with consent).
- The Final Visit will be defined as the visit at which the Investigator determines that the subject should discontinue the study or the subject discontinues for other reasons (i.e., withdraw consent, etc.).
- Formalin fixed, paraffin embedded (FFPE) – Sample collection should be prior to treatment start. Subjects must consent to provide available archival tissue for analysis. It is preferred to send FFPE blocks, however slides prepared by the local pathology laboratory are acceptable and should be prepared as described in the study specific laboratory manual. If there is not enough tissue to provide the number of slides specified in the laboratory manual, sites should provide as many slides as possible with the available tissue.

Table 4. Pharmacokinetic Assessments (Phase 1)

Procedure	Visit Schedule	Before Drug Administration	After Drug Administration (hours)	Sampling Plan
				Specimen Matrix
PK Blood Sampling for Veliparib (ABT-888)	Chemoradiotherapy: Week 4 Day -3	Pre-dose	1, 2, 3, 6	Blood → Plasma Frozen -20°C or colder

The date and time of the morning dose of veliparib on PK sampling day will be recorded.

The date and time of the two doses of veliparib prior to PK sampling on Week 4 Day -3 will be recorded.

Table 5. Schedule of Pharmacokinetic Assessments (Phase 2)

Procedure	Visit Schedule	Before Drug Administration	After Drug Administration (hours)	Sampling Plan
				Specimen Matrix
PK Blood Sampling for Veliparib (ABT-888)	Chemoradiotherapy: Week 4 Day -3	Pre-dose	1, 2, 3	Blood → Plasma Frozen -20°C or colder
PK Blood Sampling for Veliparib (ABT-888)	Consolidation C1D1, C2D1	Pre-dose	--	Blood → Plasma Frozen -20°C or colder

The date and time of the morning dose of veliparib on PK sampling day will be recorded.

In Phase 2 Chemoradiotherapy portion, the date and time of the two doses of veliparib prior to PK sampling on Week 4 Day -3 will be recorded.

In Phase 2 Consolidation portion, the date and time of the two doses of veliparib prior to PK sampling on C1D1 and C2D1 will be recorded.

5.3.1.1 Study Procedures

The study procedures outlined in [Table 2](#) are discussed in detail in this section, with the exception of dispensing dosing cards (Section 5.5.1.1), treatments administered (Section 5.5), timing of dosing (Section 5.5.4), monitoring of treatment compliance (Section 5.5.6), and adverse events (Section 6.0). All study data will be recorded on electronic case report forms (eCRFs), with supporting source documentation. Screening procedures must be performed within 28 days prior to chemoradiotherapy Week 1 Day -3. For procedures performed at Screening then repeated on Week 1 Day -3 prior to dosing, the later procedure(s) will serve as baseline for clinical assessment. Subsequent study procedures should be performed within 4 days surrounding the scheduled visit date. Clinical laboratory tests can be performed up to 72 hours prior to dosing.

Informed Consent

Signed informed consent will be obtained from the subject before any study procedures are undertaken or before any prohibited medications are withheld from the subject in order to participate in this study. A separate optional informed consent will be required

for pharmacogenetic testing. Archived tissue collection is optional for all subjects participating in Cohort 1 – 5. Subjects participating in Cohort 6 must consent to provide archived tissue or cytology sample for analysis.

Subjects will be considered screen failures if the informed consent has been signed and a study-specific procedure has been performed (e.g., central laboratories drawn), but subject does not randomize into the study. The reason for screen failure will be documented in the source and will be captured in the eCRF.

Medical and Oncology History

The medical history includes complete medical history, including documentation of any clinically significant medical condition; history of tobacco and alcohol use; presence and severity of any symptoms/conditions associated with NSCLC; and detailed NSCLC oncology history (histology, TNM staging, date of diagnosis).

On chemoradiotherapy Week 1 Day –3 any changes observed from the screening assessments, prior to dosing, will be recorded in the subject's medical history. At each subsequent visit, the subject's medical history will be reviewed and any clinically significant changes from baseline will be recorded in the source documents and on the adverse event eCRF.

PET Scan/Brain MRI

To evaluate eligibility, a full body PET Scan must be performed to assess the subject for distant metastases, and a MRI of the brain must be performed to assess the subject for brain metastases.

Physical Examination

A physical examination, including body weight, will be performed per [Table 2](#). Clinically significant changes from baseline will be documented in the source documentation and eCRFs as adverse events. Height will be measured at the Screening Visit only. For height and weight assessments, the subject should not wear shoes. Physical exam will

include neurological (sensory, motor, cranial nerves), head and neck, lymphatic, cardiac, pulmonary, hepatobiliary, gastrointestinal, genitourinary, and skin evaluation per local standard of care and in line with local label requirements.

Vital Signs

Vital signs will be performed per [Table 2](#). Vital sign determinations include sitting blood pressure, heart rate and body temperature. If possible, blood pressure and heart rate measurements should not immediately follow scheduled blood collections.

12-Lead Electrocardiogram (ECG)

A resting 12-lead ECG will be performed per [Table 2](#). A qualified physician will determine whether any findings outside of normal physiological variation are clinically significant (in consultation with a cardiologist if necessary). The physician will document whether findings are clinically significant (CS) or not clinically significant (NCS) on the tracing and sign and date the tracing. The original annotated ECG tracing along with a photocopy of the tracing containing the physician's assessment will be retained in the subject's records at the study site.

Pulmonary Function Test procedure (PFT)

The PFT procedure will be performed per [Table 2](#). The Pulmonary function test should include spirometry with FEV1 and DLCO documentation. Hemoglobin lab assessment will be needed to generate a DLCO (Hb).

ECOG Performance Status

The ECOG performance status will be assessed per [Table 2](#) as follows:

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

Documentation of Non-Childbearing Status or Pregnancy Test

For each female subject, the Investigator will document non-childbearing status (surgically sterile or postmenopausal for at least 1 year) or potential childbearing status. Subjects with non-childbearing status do not require pregnancy tests. For subjects of childbearing potential, a serum pregnancy test will be performed at Screening and the results must be available prior to the administration of the first dose of study drug on Day -3. A urine pregnancy test should also be performed prior to dosing on Day -3 if > 7 days since obtaining Screening serum test results. The test results must be reviewed and determined to be negative prior to dosing. A positive urine pregnancy test will be confirmed with a serum pregnancy test. Pregnancy tests may also be repeated at the discretion of the Investigator at any time during the study.

Should a female study subject become pregnant or suspect she is pregnant while participating in this study, she should inform the treating Investigator immediately (Section 6.7).

Clinical Laboratory Tests

Samples for chemistry, hematology and urinalysis will be collected per [Table 2](#). Specific laboratory assessments are outlined in [Table 6](#).

A certified local laboratory may be used to perform laboratory analyses for treatment decisions. All study samples indicated in [Table 2](#) are to be shipped to the central laboratory, and central laboratory results will be used for data analysis. The central laboratory will provide instructions regarding the collection, processing and shipping of samples.

Qualified medical staff at the site will review, initial and date all local and central laboratory results. Any laboratory value outside the reference range that is considered clinically significant by the Investigator will be followed as appropriate. Clinically significant laboratory values will be recorded as adverse events if they meet the criteria as specified in [Section 6.0](#).

Table 6. Clinical Laboratory Tests

Hematology	Clinical Chemistry	Urinalysis
Hematocrit	Blood urea nitrogen (BUN)	Specific gravity
Hemoglobin	Serum creatinine	Ketones
Red blood cell (RBC) count	Total bilirubin	pH
White blood cell (WBC) count	Serum glutamic-pyruvic transaminase (SGPT/ALT)	Protein
Neutrophils	Serum glutamic-oxaloacetic transaminase (SGOT/AST)	Blood
Bands (if indicated)	Alkaline phosphatase	Glucose
Lymphocytes	Sodium	Urobilinogen
Monocytes	Potassium	Bilirubin
Basophils (if indicated)	Calcium	Serum Pregnancy Test
Eosinophils (if indicated)	Inorganic phosphorus	Human Chorionic Gonadotropin (hCG)**
Platelet count (estimate not acceptable)	Uric acid	
Coagulation	Cholesterol	
Activated Partial Thromboplastin Time (aPTT)*	Total protein	
International Normalized Ratio (INR)*	Glucose	
	Triglycerides	
	Albumin	
	Lactate dehydrogenase (LDH)	
	Magnesium	
	Chloride	
	Bicarbonate/CO ₂	

* Collected at Screening only.

** At Screening and at any time point in which pregnancy is suspected or following a positive urine pregnancy test.

Tumor Assessments (Radiologic)

A CT scan of the full chest and abdomen (with image of liver and adrenal glands) must be performed during screening to assess locoregional disease. If the subject is unable to undergo a CT scan with IV contrast due to allergy or renal insufficiency, a non-contrast CT may be performed. Magnetic resonance imaging (MRI) may be conducted in cases where local laws/requirements mandate, but should have Sponsor approval prior to performing the MRI.

Post-baseline tumor assessments will be conducted per [Table 2](#) using RECIST version 1.1 in the evaluation of tumor responses, as appropriate. Tumor assessment is to be performed at the Final Visit for subjects who discontinue the study for reasons other than radiographic progression and if no assessment has been performed within the last 4 weeks.

Quality of Life Assessment

To assess the subject's health-related quality of life and symptoms, the EORTC QLQ C15-PAL and the companion symptom module EORTC QLQ-LC13 will be administered (Phase 2 only). All subjects in Phase 2 portion of the study must complete this questionnaire on paper forms, which is then entered into EDC by the Investigator or designee. The Investigator or a designee will need to check the form returned by the subject for completeness before the subject leaves the clinic.

The EORTC QLQ-C15-PAL is an abbreviated 15-item version of the EORTC QLQ-C30 and consists of a global health status/QoL scale, two functional scales (physical functioning and emotional functioning), and seven symptom scales/items (fatigue, nausea and vomiting, pain, dyspnea, insomnia, appetite loss, constipation).

The EORTC QLQ-LC13 is a 13-item instrument meant for assessment of patients with lung cancer of various stages. It was created according to the EORTC guidelines and is designed to be used in conjunction with a "core" measure such as the QLQC15-Pal. Along with functional scales assessed by the core instrument, the QLQ-LC13 allows for

assessment of dyspnea (through a three-item scale) and pain (three total: chest, arm/shoulder, other), coughing, sore mouth, dysphagia, peripheral neuropathy, alopecia and hemoptysis, via single-item scales. All scores are rated in reference to the past week on a scale of 1 "not at all" to 4 "very much" and are converted to a 0 – 100 scale, with higher scores representing greater severity for symptom scales or better functioning in functional scales.

Randomization and Subject Number Assignment

Subject number assignment for the Phase 1 dose escalation portion and randomization into the Phase 2 portion will be performed as described in Section 5.5.3 and Section 5.5.4.

Dispensing Study Drug

Study drug will be dispensed as per Section 5.5.3 and Section 5.5.4. The Interactive Response Technology (IRT) will assign every bottle of study drug to be dispensed to a subject. AbbVie or designee will provide specific instructions on the use of IRT.

Chemotherapy and Radiotherapy Administration

Trained site personnel will administer radiotherapy, paclitaxel, and carboplatin as per Table 2. Subjects will be supervised during treatment.

Survival Assessment

Survival information (the date and cause of death or last known alive date if not deceased; including post-treatment cancer therapy) will be collected per Table 2. If the subject withdraws from study follow-up, the study staff may use a public information source (such as county records) to obtain information about survival status only, as appropriate per local regulations.

5.3.1.2 Blood Samples for Pharmacogenetic Analysis

One 4 mL whole blood sample for DNA isolation will be collected per Table 3 from each subject who consents to provide samples for pharmacogenetic analysis. The procedure for

obtaining and documenting informed consent is discussed in Section 9.3. If the sample is not collected at Chemoradiotherapy Week 1 Day –3, it may be collected at any time throughout the study (with consent).

The sample collection tubes will minimally be labeled with "PG-DNA," protocol number, and subject number. Samples will be shipped frozen to AbbVie or a designated laboratory for DNA extraction and long-term storage. Instructions for the preparation and shipment of pharmacogenetic samples will be provided in the lab manual.

AbbVie will store the DNA samples in a secure storage space with adequate measures to protect confidentiality. The samples will be retained while research on veliparib (or drugs of this class) continues but no longer than 20 years.

5.3.1.3 Collection and Handling of Pharmacodynamic Variables

Pharmacodynamic correlative studies are exploratory in nature. Serum, plasma and tissue specimens may be utilized to evaluate known and novel markers (nucleic acids, peptides/proteins and/or metabolites) of disease status. PD variables will be further discussed in Section 5.3.7.

Blood Collection for Plasma and Serum Markers

Blood will be collected pre-dose by venipuncture at timepoints outlined in Table 3 in conjunction with PK samples, if possible. The collection, processing and storage should be performed as described in the study-specific laboratory manual. The complete process of centrifugation, transfer to cryovial and freezing should be accomplished in less than 1 hour from the time of blood draw. Refer to the study-specific laboratory manual for detailed instructions on sample collection, processing and shipment.

Archived Tissue Collection

If available, fixed samples from most recent biopsy should be collected from subjects participating in Cohort 1 – 5 who have consented, while subject is active on study. While sending FFPE blocks is preferred, slides prepared by the local pathology laboratory are

acceptable and should be prepared as described in the study-specific laboratory manual. Subjects participating in Cohort 6 must consent to provide available archived tumor for analysis. It is recognized that the availability of the samples suitable for analysis may not be known at the time of consent for all subjects. Study-specific biopsies are not required for subject participation.

5.3.2 Drug Concentration Measurements

5.3.2.1 Blood Samples for Pharmacokinetic Analysis

Veliparib Pharmacokinetic Specimen Collection

Samples will be collected per [Table 4](#) and [Table 5](#). Refer to the study-specific laboratory manual for detailed instructions on sample collection, processing and shipment.

5.3.2.2 Measurement Methods

Plasma concentrations of veliparib will be determined using a validated method under the supervision of the Drug Analysis Department at AbbVie. Additionally, veliparib metabolite(s) concentrations in plasma samples may be determined using a non-validated or a validated assay.

5.3.3 Efficacy Variables

The primary efficacy endpoint is Progression Free Survival (PFS). The secondary efficacy endpoints are Overall Survival (OS), Objective Response Rate (ORR), and Duration of Overall Response (DOR). The tertiary efficacy endpoints are Quality of Life and ECOG performance status.

5.3.4 Safety Variables

AbbVie will assess adverse events, laboratory data, ECGs and vital signs during the study. Adverse events will be assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events NCI CTCAE version 4.0.²³ During the conduct of the study, the AbbVie medical and safety team will be monitoring subject laboratory

results and serious adverse event data as it is reported. AbbVie will review blinded aggregate safety data on a regular basis and may enlist the assistance of the DMC at any time to evaluate any trends in the safety data that are identified.

5.3.5 Pharmacokinetic Variables

For Phase 1 portion, values for the pharmacokinetic parameters of veliparib and its possible metabolite(s), including the maximum observed plasma concentration (C_{\max}), the time to C_{\max} (peak time, T_{\max}), and the area under the plasma concentration-time curve (AUC) will be determined using non-compartmental methods.

In addition, a nonlinear mixed effect modeling (NONMEM) analysis may be conducted using veliparib concentration data collected in both Phase 1 and Phase 2 portions to estimate the population pharmacokinetic parameters of veliparib, including apparent oral clearance (CL/F) and volume of distribution (V/F). Results of the NONMEM analysis may be reported in a separate pharmacokinetic report.

Additional parameters may be estimated if useful in the interpretation of the data.

AbbVie or a designated laboratory will store the pharmacokinetic samples in a secure storage space with adequate measures to protect confidentiality. To increase confidence in trends, remaining sample aliquots may be used to perform replicate tests, or sample analysis at additional time points for tests currently identified in the protocol. Upon completion of this research AbbVie or a designated laboratory will destroy the samples.

5.3.6 Pharmacogenetic Variables

DNA samples may be sequenced and data analyzed for genetic factors contributing to the disease or to the subject's response to veliparib (or other study treatment) in terms of pharmacokinetics, efficacy, tolerability, and safety. Such genetic factors may include genes for drug metabolizing enzymes, drug transport proteins, genes within the target pathway, genes believed to be related to the disease or to drug response. Some genes currently insufficiently characterized or unknown may be understood to be important at

the time of analysis. The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to veliparib, drugs of this class, or the disease state. The samples may also be used for the development of diagnostic tests related to veliparib, drugs of this class, or the disease state. The results of pharmacogenetic analyses may not be reported with the study summary.

5.3.7 Pharmacodynamic Variables

Several putative biomarkers of efficacy and response may be evaluated in this protocol with the goal of exploring the relationship between tumor response and/or disease status.

Biospecimens collected may be evaluated for genetic lesions whether they occur by amplification, chromosomal loss and/or mutational/methylation with the intent of identifying potential associations with subject outcome or to better characterize the disease. These characterizations may be included, but are not limited, characterization of gene expression, methylation/mutational status or copy number changes of genes, particularly those involved in DNA repair pathways. Additional analysis aimed at identifying underlying defects in the homologous recombination pathway, regardless of etiology, may be performed and associated with response.

Biospecimens may be evaluated for levels of biomarkers including nucleic acids, proteins/peptides and metabolites. For example, protein analysis of relevant proteins, including but not limited to, DNA repair proteins, such as ERCC1 and XPF, may be performed on tumor tissue obtained from each consented subject.

Samples collected during the course of this study may be used to investigate new scientific questions related to this study. Additionally, the samples may be anonymized and used for diagnostic test development. AbbVie (or a designated laboratory) will store the samples in a secure storage space with adequate measures to protect confidentiality. The samples will be retained while research on veliparib (or drugs of this class) continues for up to but no longer than 20 years.

5.4 Removal of Subjects from Therapy or Assessment

Each subject has the right to withdraw from study treatment at any time. In addition, the Investigator may discontinue a subject from the study treatment at any time for any reason if the Investigator considers it necessary, including the occurrence of an adverse event or noncompliance with the protocol. Each subject will be withdrawn from the study or study treatment (as applicable) per Section 5.4.1 if any of the following occur:

- The subject has radiographic progression according to RECIST version 1.1.
- The subject requires alternate anti-cancer agents during the study period.
- The subject experiences unacceptable treatment toxicity or the Investigator believes it is otherwise in the best interest of the subject.
- Subject is suspected to be pregnant; pregnancy is confirmed or begins breastfeeding during the treatment portion of the study.
- The subject or subject's legally acceptable representative decides to withdraw consent for any reason.
- Any other medical reason that AbbVie or the study Investigator deems appropriate.

5.4.1 Discontinuation of Individual Subjects

Subjects who discontinue treatment with veliparib/placebo + paclitaxel/carboplatin prior to reaching an event of disease progression are to continue assessments until disease progression. Refer to Section 5.4.1.1 for more details.

When subject discontinuation from the study (without reaching a protocol-defined endpoint) is planned, the Investigator is to notify the AbbVie medical monitor or the clinical team representative (Section 7.0) via telephone as soon as possible (provided, in each case, subject care and safety are not compromised). If not notified prior to discontinuation, the AbbVie medical monitor may contact the site to discuss the reason for withdrawal from the study.

The visit at which the subject discontinues the study will be considered the final visit. At the Final Visit, the reason(s) for the discontinuation from the study will be recorded and assessments will be performed per [Table 2](#). For the randomized portion of the study, the investigator must report the withdrawal in the IRT system within three days of the subject's discontinuation visit.

Subjects who have a Final Visit within 30 days of therapy will have one Follow-Up Visit approximately 30 days after the Final Visit. If a subject is discontinued from the study with an ongoing adverse event or an unresolved clinically significant laboratory result, the site will attempt to provide follow-up until a satisfactory clinical resolution of the laboratory results or adverse event is achieved.

In the event that a positive result is obtained on a pregnancy test for a subject during the study, the administration of study drug to that subject must be discontinued immediately. The site must report the positive pregnancy test result by telephone within 24 hours to one of the AbbVie representatives listed in [Section 6.6](#).

5.4.1.1 Discontinuation of Veliparib/Placebo and Paclitaxel/Carboplatin

Subjects will receive veliparib/placebo, thoracic radiotherapy, paclitaxel and carboplatin per [Table 2](#) or until reaching a protocol defined event of disease progression or experiencing unmanageable toxicity. Dose reductions of carboplatin and paclitaxel will occur on the basis of the toxicity observed and may result in discontinuation of either agent. The subject may continue veliparib/placebo while any other component of therapy is ongoing. If toxicities have resulted in discontinuation of radiotherapy and paclitaxel and carboplatin, veliparib/placebo will also be discontinued. At the Investigator's discretion, radiotherapy or paclitaxel or carboplatin administration may continue after veliparib/placebo has been discontinued.

5.4.2 Discontinuation of Entire Study

AbbVie may terminate this study prematurely, either in its entirety or at any study site, for reasonable cause provided that written notice is submitted in advance of the intended termination. The investigator may also terminate the study at his/her site for reasonable cause, after providing written notice to AbbVie in advance of the intended termination. Advance notice is not required by either party if the study is stopped due to safety concerns.

The following procedures for discontinuation will be followed:

- If the Sponsor has decided to prematurely discontinue the study, the Sponsor will promptly notify in writing each Investigator as well as regulatory authorities of the decision and give detailed reasons for the discontinuation.
- Each Investigator must promptly notify the IRB/IEC and give detailed reasons for the discontinuation.
- Each Investigator must promptly notify the enrolled subjects of the premature discontinuation and administer appropriate treatments such as replacement of protocol therapy, if applicable, by other appropriate regimens.

5.5 Treatments

5.5.1 Treatments Administered

All subjects will receive the following:

Concurrent Chemoradiotherapy

Veliparib will be administered BID beginning 3 days prior to beginning chemoradiotherapy. Chemotherapy will consist of Carboplatin AUC 2 mg/mL/min and Paclitaxel 45 mg/m² administered intravenously on Day 1 of each week during radiotherapy. Radiotherapy will be delivered using 3D conformal RT or IMRT and subjects will receive a total of 60 – 63 Gy. Chemoradiotherapy may be extended up to 9 weeks in duration due to treatment delays. Subjects who have not completed

chemoradiotherapy after 9 weeks should proceed to consolidation therapy or observation at the discretion of the Investigator.

The first cohort of subjects in the dose escalation portion of the study will receive veliparib 60 mg BID during the chemoradiotherapy portion of treatment. Additional cohorts of subjects will be treated at the dose levels indicated in [Table 1](#), with cohort size and dose change determined according to tolerability. AbbVie and the Phase 1 investigator group will review available safety data through the completion of radiotherapy for each cohort and for all prior patient cohorts prior to making a decision to expand a dose level cohort, escalate to a higher dose level, or proceed to a lower dose level in a new cohort. The following rules for enrollment of an additional 3 patients per cohort, dose escalation, and determination of the maximum tolerated dose (MTD) will be applied:

1. If no subject (0/3) experiences a dose limiting toxicity (DLT), then dose escalation may occur.
2. If one subject (1/3) experiences a DLT, then 3 additional subjects will be enrolled at the same dose level. If none of the additional subjects (0/3) experience a DLT (i.e., 5/6 patients did not experience a DLT at the current dose level), then dose escalation may occur. If $\geq 2/6$ patients experience the same DLT at the current dose level, then no further patients will be enrolled in the cohort and the MTD will be considered to have been exceeded.
3. If ≥ 2 patients ($\geq 2/3$) experience the same DLT, then no further patients will be enrolled in the cohort and the MTD will be considered to have been exceeded. If ≥ 2 patients experience different DLT's, either the MTD will be considered to have been exceeded OR 3 additional subjects will be enrolled at the same dose level. Dose escalation may occur provided $\geq 2/6$ patients do not experience the same DLT at the current dose level. If $\geq 2/6$ patients experience the same DLT, the MTD will be considered to have been exceeded.

Consolidation Chemotherapy

No more than 8 weeks after completion of concurrent chemoradiotherapy, veliparib/placebo 120 mg or 240 mg BID will be administered beginning 2 days prior to the start of paclitaxel/carboplatin infusion and will continue through Day 5 of each 21-day cycle. Carboplatin AUC 6 mg/mL/min and Paclitaxel 200 mg/m² will be administered intravenously on Day 1 of each 21-day cycle. Subjects will receive a maximum of 2 cycles of consolidation chemotherapy. Subjects who require > 8 weeks to recover from toxicities resulting from chemoradiotherapy should not receive consolidation.

Phase 2 Treatment Regimen: RPTD or Placebo

AbbVie will review available safety data from all subjects in the dose escalation portion of the study and determine the CRT and consolidation RPTDs. Subjects in the randomized portion of the study will receive the veliparib RPTD or placebo during CRT and consolidation.

5.5.1.1 Administration of Veliparib/Placebo (All Subjects)

Subjects will self-administer the morning dose of veliparib/placebo and the evening doses of veliparib/placebo approximately 12 hours apart with or without food in the same calendar day.

It is recommended that if a subject misses a scheduled dose of veliparib/placebo and less than 6 hours have passed since the scheduled dosing time, the dose should be immediately taken. It is recommended that if more than 6 hours have passed since the scheduled dosing time, the subject should not take the missed dose but should wait for the next regularly scheduled dose.

If the subject vomits within 15 minutes of taking veliparib/placebo, another dose is to be taken. The dose may only be repeated once. If more than 15 minutes has passed from the time of oral dosing then no additional doses will be taken. The subject is to contact the Investigator if additional veliparib/placebo is needed to complete BID dosing through Day 5 of the cycle.

Subjects will be provided self-administration instructions and subject dosing cards to record the date and time the veliparib/placebo was administered. Subjects will be instructed to store veliparib/placebo according to specific directions included in Section 5.5.2.3. Subjects should return bottles of veliparib/placebo (empty, partially filled or full) to the study site as indicated in Section 5.5.7.

5.5.1.2 Administration of Paclitaxel, and Carboplatin (All Subjects)

Paclitaxel and Carboplatin During Concurrent Chemoradiotherapy

Carboplatin and paclitaxel will be administered intravenously, on Day 1 of every week during radiotherapy. Paclitaxel will be infused prior to carboplatin. Investigators should evaluate subjects for carboplatin and paclitaxel treatment per the locally approved product label,^{1,2} local practice, or applicable SmPC. Paclitaxel will be administered intravenously over approximately 60 minutes at a dose of 45 mg/m². Carboplatin will be administered intravenously over approximately 30 minutes (at AUC 2 mg/mL/min) immediately following paclitaxel infusion.

Consolidation Chemotherapy

Consolidation chemotherapy will begin no more than 8 weeks following RT. Subjects who require > 8 weeks to recover from toxicities resulting from chemoradiotherapy should not receive consolidation.

Carboplatin and paclitaxel will be administered intravenously on Day 1 of every 21-day cycle. Paclitaxel will be infused prior to carboplatin. Investigators should evaluate subjects for carboplatin and paclitaxel treatment per the locally approved product label,^{24,25} local practice, or applicable SmPC. Paclitaxel will be administered intravenously over approximately 3 hours at a dose of 200 mg/m². Carboplatin will be administered intravenously over approximately 30 minutes (at AUC 6 mg/mL/min) immediately following paclitaxel infusion.

Calculation of Carboplatin Dose

Per the FDA Guidelines, the maximum dose of carboplatin (this dose should not be exceeded) may be calculated using the following formulas:²⁶

Total carboplatin dose (mg) = target AUC × (GFR + 25) [Calvert formula]

Maximum carboplatin Dose (mg) = target AUC (mg/mL/min) × (150 mL/min)

- For a target AUC = 2, the maximum dose is $2 \times 150 = 300$ mg
- For a target AUC = 6, the maximum dose is $6 \times 150 = 900$ mg

5.5.1.3 Thoracic Radiotherapy

Thoracic radiotherapy will be administered by 3-dimensional conformal RT or intensity modulated radiotherapy (IMRT), including volumetric modulated arc techniques.

Radiotherapy will be delivered in dose fractions of 1.8 – 2.0 Gy on approximately 5 of every 7 days (excluding weekends and holidays), with the total dose measuring 60 – 63 Gy. Radiotherapy will be delivered in ≤ 9 weeks.

Radiotherapy must begin on Week 1 Day 1 of CRT.

An interruption in RT of >7 days should be discussed with the AbbVie medical monitor.

Equipment

- Energy: Megavoltage quality radiation will be used with a nominal energy of 6 – 10 MV. Proton therapy is not allowed on this protocol.
- Geometry: The distance from the radiation source to the isocenter should not be less than 100 cm.
- The use of daily image-guidance is highly encouraged.

Planning Techniques:

All sites must provide details regarding their image guidance technique in EDC.

Simulation:

All patients will undergo CT based treatment planning in appropriate immobilization devices in the supine position. A custom immobilization cast is encouraged but not required. All components of immobilization must, in conjunction with the image guidance being used, ensure that both interfraction set-up uncertainty and unaccounted for intrafraction motion be minimized. The planning CT scan should be performed with IV contrast unless the patient has a known contrast allergy or renal insufficiency as IV contrast allows better distinction between tumor and adjacent normal tissue or atelectasis.

Contiguous CT slices with ≤ 3.0 mm thickness between scans in the region of the primary tumor and pathologically involved lymph nodes, and no more than 5 mm thickness in the remaining regions starting from the level of the cricoid cartilage and extending inferiorly through the entire liver volume.

Four-dimensional CT (4D-CT) is permitted and highly encouraged for the study. There are many valid approaches to defining target volumes and margins using multiple datasets representing different phases of the breathing cycle. These include but not limited to:

- a. Design of the PTV to include the excursion of the primary and nodes during free breathing (ITV approach).
- b. Limited excursion during a voluntary or automatic breath hold (e.g., Elekta ABC device).
- c. Or a gating approach (Varian RPM system).
- d. Or fiducial marker tracking.

Target Volume Definitions

The nomenclature and definitions of ICRU Reports 50 and 62,²⁷ shall be followed in this study.

GTV Definition:

The GTV will be the volume of tumor visible on CT or PET imaging or biopsy proven sites (not meeting radiographic/metabolic criteria). This will in general include lymph nodes within the mediastinum ≥ 1.0 cm in short axis diameter and/or PET positive lymph nodes (SUV max > 3). Information from PET imaging should be used to determine occult nodal areas as well as to accurately contour gross disease within areas of atelectasis. The volume(s) may be disjointed.

For areas within or near inflated lung tissue, lung window settings will be utilized for contouring. For disease within or abutting the mediastinum, soft tissue window settings will be used.

CTV Definition:

The CTV is defined to be the GTV plus a 0.5 cm to 1 cm margin as appropriate to account for microscopic tumor extension. However, the CTV should not cross natural anatomic barriers to tumor extension such as fissures or fascial planes unless these structures are directly abutted or invaded by the GTV. Elective treatment of the mediastinum and supraclavicular fossae will not be done.

PTV Definition:

PTV expansion includes two components: tumor motion and setup uncertainty. The margin for set-up uncertainty will be uniform for this study at 0.5 cm and independent of the use of IGRT. The margin for tumor motion will be dependent on type of assessment and respiratory motion management techniques used for the study and in addition to the 0.5 cm margin for set-up uncertainty.

- Free Breathing Treatment/Simulation Motion Margin: Sup-Inf: 1 cm, axial 0.5 cm
- Breathhold/gating: Sup-inf: 0.5 cm, axial 0.3 cm
- Abdominal compression: Sup-inf 0.8 cm, axial 0.5 cm
- 4DCT: Union of CTVs for Sup-inf and axial

Treatment Planning:

Techniques: 3D Conformal Planning or IMRT is required in this protocol. Both planar and non-coplanar field arrangements are acceptable. Use of IMRT/VMAT planning requires use of 4DCT imaging for full respiratory motion assessment.

Heterogeneity corrections: All radiation doses will be calculated with heterogeneity corrections to take into account the density differences within the irradiated volume. The acceptable heterogeneity dose calculation methods can be found on the QARC (Quality Assurance Review Center) website (www.QARC.org). Non-validated dose calculation algorithms (Clarkson, pencil beam) will not be allowed for this study.

Dose Specifications: The prescribed dose is 60 – 63 Gy in approximately 30 fractions (1.8 – 2.0 Gy daily). The treatment plan will be normalized such that 95% of the PTV receives the prescription dose. No more than 0.03 cc can receive more than 120% of the prescription dose. The maximum and minimum doses (0.03 cc) will be reported.

Critical Structures: Normal tissue constraints should be prioritized in the following manner for treatment planning: 1 = spinal cord, 2 = Lung, 3 = esophagus, 4 = brachial plexus, 5 = heart. Critical structures should be contoured based on the RTOG lung contouring atlas.

- Spinal Cord: The spinal cord is contoured based on the confines of the bony limits of the spinal canal. The spinal cord dose limit is the highest priority dose constraint and must be adhered to above all other dose constraints. No more than 0.03 cc of the spinal cord can receive > 50.5 Gy total dose.
- Lungs: The total lung volume is defined as the sum of the volume of both lungs minus the GTV. The dose-volume constraints to the lung is considered the second highest priority and must be met, except if it conflicts with spinal cord dose constraints. The proportion of the total lung volume that received 20 Gy or greater (V20) must be less than 35%. Additionally the mean lung dose should be less than 20 Gy.

- Esophagus: The entire esophagus from the bottom of the cricoid to the GE junction should be contoured. No more than 0.03 cc may receive > 63 Gy. The mean dose to the esophagus should be less than 34 Gy. The esophagus should not be circumferentially irradiated with > 60 Gy. The V60 should be reported for each patient.
- Brachial Plexus: The ipsilateral brachial plexus should be contoured for upper lobe tumors. No more than 0.03 cc of the brachial plexus should receive > 63 Gy.
- Heart: The heart and pericardium should be contoured from base to apex of the heart. The following limits are recommended: V60 < 33%, V45 < 66%, V40 < 100%. Every effort should be taken to minimize the dose to the heart.

Treatment Delivery:

All treatment will be administered 5 days per week, 1 treatment per day. All fields must be treated daily. The entire PTV must be treated daily.

Radiation Planning QA/Documentation Requirements

- Copies of dose calculations and daily charts will be kept with source documents. Sites participating in the Phase 2 portion of the trial will be required to submit patient treatment plans to QARC for QA. Please refer to ABT-888, Study M14-360 Radiation Therapy Quality Assurance Manual for detailed description of RT credentialing requirements and the QA process.

Definitions of Deviations in Protocol Radiation Planning/Delivery:

- Volume:
 - Minor Deviation: margins for CTV and or PTV are less than specified or excessively large as determined by radiation study chair/quality reviewer.
 - Major Deviation: GTV incorrectly identified resulting in < 100% dosing of gross disease.
- Dose Prescription:
 - Minor: The prescribed dose differs from that in the protocol by 6 – 10%.

- Major: The prescribed dose differs from that in the protocol by more than 10%.
- Dose Uniformity:
 - Minor Deviation: The protocol specified dose covers between 90 – 95% of the PTV or the minimum dose to 1 cc of the PTV is between 90 – 95% of the protocol dose or the maximum dose to 1 cc of the PTV exceeds 120% of the protocol dose.
 - Major Deviation: The protocol specified dose covers less than 90% of the PTV or the minimum dose to 1 cc of the PTV is < 90% of the protocol dose or the maximum dose to 1 cc of tissue outside the PTV exceeds 120% of the protocol dose.
- Critical Organ Radiation Dosing:
 - Minor:
 - Mean Lung Dose between 20 and 24 Gy
 - The dose to the heart, esophagus, or brachial plexus exceeds limits specified above.
 - Major:
 - Lung V20 > 35%, Mean Lung Dose > 24 Gy.
 - Spinal cord dose 0.03cc > 50.5 Gy.

Note: Deviations will be assessed by QARC at the time of final review following the completion of radiotherapy. Sites will receive a report to inform them of the results of the final review. Please see the ABT-888, Section Study M14-360 Radiation Therapy Quality Assurance Manual for further information regarding the QA process.

Radiation Therapy Adverse Events:

Esophagitis: Esophageal complaints are common with thoracic chemoradiotherapy. Esophagitis does not constitute a reason to interrupt combined therapy provided oral intake is sufficient to maintain hydration. Patients should be advised to avoid alcoholic, acidic, or spicy foods. Viscous lidocaine, sucralfate, and other medications should be used for symptom relief. The following are also commonly used to manage esophagitis:

- Ketoconazole 200 mg PO QD or Fluconazole 100 mg PO QD daily until the end of radiation.
- Proton pump inhibitor (such as omeprazole) or H2 blocker (such as Ranitidine) taken daily until the end of radiation.

5.5.2 Identity of Investigational Products

Information regarding the veliparib formulation to be used in this study is presented in [Table 7](#).

Table 7. Identity of Investigational Product

Study Drug	Dosage Form	Strength	Route of Administration	Manufacturer
Veliparib (ABT-888)	Capsule	20 mg and 40 mg active	Oral	AbbVie
Placebo	Capsule	20 mg and 40 mg placebo	Oral	AbbVie

5.5.2.1 Standard of Care Medicinal Products for Study Treatment

Information regarding carboplatin and paclitaxel to be used in this study is presented in [Table 8](#).

Table 8. Standard of Care Medicinal Products for Study Treatment

Study Treatment	Dosage Form	Route of Administration
Carboplatin (commercially available)*	Solution in a vial	Intravenously
Paclitaxel (commercially available)*	Solution in a vial	Intravenously

* Carboplatin and paclitaxel formulations may vary based on the source.

Carboplatin or paclitaxel should be obtained commercially via the site pharmacy or by a sponsor approved vendor.

5.5.2.2 Packaging and Labeling

Veliparib will be packaged in bottles containing 5, 11, or 48 doses of veliparib or placebo. This will allow for the 2, 5 or 21 days of administration with at least 1 additional dose to

cover loss, spillage or replacement due to vomiting within 15 minutes. Each bottle label will include all information as required by local regulations and must remain affixed to the bottle. All blank spaces on the label will be completed by site staff prior to dispensing to the subject.

AbbVie will provide detailed instructions and training for the handling of study supplies to the study site.

5.5.2.3 Storage and Disposition of Study Drugs

Veliparib or Placebo

Table 9. Study Drug Storage Conditions

Study Drug	Country	Storage Conditions
Veliparib or placebo	All countries, except Australia/New Zealand and Japan	Store at 15° to 25°C (59° to 77°F)
Veliparib or placebo	Australia/New Zealand	Store below 25°C
Veliparib or placebo	Japan	Store at 15° to 30°C

All clinical supplies must be stored in a secure place until they are dispensed for subject use, are destroyed at the site or are returned to AbbVie.

Investigational products are for investigational use only, and are to be used only within the context of this study. The clinical supplies for this study must be maintained under adequate security and stored under conditions specified on the label.

Storage and Disposition of Carboplatin and Paclitaxel

Paclitaxel

Vials must be stored between 15°C to 25°C (59°F to 77°F) (or per locally approved label or SmPC) in the provided cartons to protect from light.

Carboplatin

Vials must be stored between 15°C to 25°C (59°F to 77°F) (or per locally approved label or SmPC) in the provided cartons to protect from light.

5.5.3 Method of Assigning Subjects to Treatment Groups

In the Phase 1 portion, Screening number and study drug will be assigned using the IRT system. In the randomized Phase 2 portion of the study, all subjects will be randomized using an IRT system. Before the study is initiated, directions for the IRT will be provided to each site. The site will contact the IRT to obtain a Screening (subject) number once the subject has signed the informed consent and a study-specific procedure has been performed (i.e., central laboratory samples drawn). Once the screening number is assigned, if the subject is not enrolled into the study, the reason for screen failure will be documented in the source document and in the eCRF. For subjects participating in the Phase 2 portion, a unique randomization number will be provided through the IRT system.

Subjects will be permitted to re-screen for the study with permission from the AbbVie medical monitor. Subjects should keep the same subject number if re-screened.

A bottle number randomization schedule and a subject randomization schedule will be generated by the Clinical Statistics Department at AbbVie prior to the start of the study. A copy of all randomization schedules will be kept by the Clinical Statistics Department at AbbVie and a copy will be forwarded to the IRT vendor.

Each subject will be dispensed veliparib per [Table 2](#). In the event of chemotherapy and/or RT interruption and/or if vomiting occurs and additional bottles of veliparib/placebo are needed, the study site personnel must contact the IRT so that additional bottles of veliparib may be dispensed.

5.5.4 Selection and Timing of Dose for Each Subject

Subjects in the dose escalation portion of the study will receive a veliparib starting dose of 60 mg and will follow the dose escalation procedures outlined in Section 5.5.1.

All Phase 2 randomized subjects will receive the RPTD of veliparib or placebo orally BID per Table 2. No other doses or schedules of veliparib are being investigated in this study. Refer to Section 5.5.1.1, Section 5.5.1.2 and Section 5.5.1.3 for additional dosing information for veliparib/placebo, paclitaxel/carboplatin and RT.

5.5.5 Blinding

All subjects will be treated with open-label paclitaxel and carboplatin (Phase 1 and Phase 2).

Subjects in Phase 1 will be treated with open-label veliparib. In Phase 2, AbbVie, the Investigator, the study site personnel and subject will remain blinded to each randomized subject's treatment with veliparib or placebo throughout the course of the study.

5.5.5.1 Blinding of Investigational Product

AbbVie must be notified before the blind is broken unless identification of the study drug is required for medical emergency, i.e., situation in which the knowledge of the specific blinded treatment will affect the immediate management of the subject/patient's conditions (e.g., antidote is available). The IRT system will provide access to blinded subject treatment information in the case of medical emergency. AbbVie must then be notified within 24 hours of the blind being broken. The date and reason that the blind was broken must be recorded in the source documentation and eCRF, as applicable. In the event the AbbVie Clinical Project Team should break the blind, the reason will be documented in a note to study file and on the appropriate eCRF.

5.5.5.2 Blinding of Data for Data Monitoring Committee (DMC)

To ensure subject safety, an internal data monitoring committee will review un-blinded safety data when 45 subjects in the Phase 2 portion of the study have completed chemoradiotherapy, or reached an event of disease progression or death, or discontinued the study.

5.5.6 Treatment Compliance

The Investigator or his/her designated and qualified representatives will administer/dispense study drug only to subjects enrolled in the study in accordance with the protocol. The study drug must not be used for reasons other than that described in the protocol. Veliparib/placebo should be taken as directed by the Investigator. Carboplatin and paclitaxel will be administered intravenously by trained site personnel.

Subjects will be instructed to return their dosing cards and all remaining veliparib/placebo bottles (empty, partially filled or full) to the study site personnel as follows:

- On Chemoradiotherapy Week 4 Day –3 and Week 7 Day –3 (CRT)
- At the Post CRT Visit
- At the Consolidation Cycle 2 Day 1 Visit
- At the first Post-Treatment Visit

Subjects should be questioned regarding their adherence to the assigned treatment schedule at each visit. The Investigator or his/her designated and qualified representatives will also confirm that the subject took the required number of capsules per protocol.

A subject will be considered compliant with study drug, veliparib, paclitaxel/carboplatin if 80% of the assigned dose is taken during a cycle. Compliance below 80% will require counseling of the subject by study site personnel.

5.5.7 Drug Accountability

The site will record the dose of carboplatin and paclitaxel given to each subject in the source documents and on the eCRF. For sites that obtain both carboplatin and paclitaxel without sponsor assistance, site inventory and accountability of carboplatin and paclitaxel will not be performed, and drug accountability forms will not be provided. For sites that receive assistance in sourcing the commercial product, accountability must be done to the extent to manage availability and ensure all product sent has been used solely for the study.

Upon receipt of a shipment of veliparib/placebo, the representative at each site will 1) open and inspect the shipment; 2) verify that the veliparib/placebo has been received intact, in the correct amounts and at the correct address; 3) sign and date the Proof of Receipt (POR) or similar documentation accompanying the shipment; 4) register the shipment as received via the IRT. Study drug kits will not be available for dispensation to a subject until the shipment is confirmed as received in the IRT system. All study drugs must be retained in the designated secure area under proper storage conditions. This will be documented by signing and dating the Proof of Receipt (POR) or similar document or via direct recording in the IRT.

An overall accountability of the study drug will be performed and verified by the site monitor throughout the study and at the study site closeout visit. An accurate running inventory of veliparib/placebo will be maintained utilizing the IRT drug accountability module and, if required, according to your institutional policy and will include the lot number, POR number(s), the bottle/kit numbers, and the date study drug was dispensed for each subject.

In the event that the IRT is not operable, the above information will be documented on forms provided by the Sponsor.

The Investigator or designee will document the bottles of veliparib/placebo returned and the number of capsules directly in the IRT system. If the number of capsules taken and

the number of capsules returned do not add up to the total number of capsules dispensed, an explanation is required and should be documented in the IRT.

Upon completion or termination of the study, all original bottles/kits containing unused veliparib/placebo (empty containers will be defaced and discarded on site) will be returned to AbbVie according to AbbVie's instructions, or if pre-arranged between the sponsor and site, destruction of used and unused bottles will be performed at the site.

The study Investigator or his/her designated representative agrees not to supply study medication to any persons not enrolled in the study or not named as a sub-investigator listed on the FDA 1572 or Investigator Information and Agreement (IIA) form.

5.6 Discussion and Justification of Study Design

5.6.1 Discussion of Study Design and Choice of Control Groups

Phase 1 data and preliminary Phase 2 data described in Section 3.0 suggests the addition of veliparib to radiotherapy or to paclitaxel/carboplatin may improve outcome of NSCLC patients. The dose escalation portion of this trial will determine the safe dose of veliparib that can be administered with concurrent chemoradiotherapy. The randomized, double-blind, placebo controlled portion of the study will evaluate the effect of veliparib added to paclitaxel/carboplatin and radiotherapy for treatment of Stage III NSCLC.

ESMO²⁸ and National Comprehensive Cancer Network (NCCN) guidelines³ recommend chemoradiotherapy and chemotherapy for locally advanced NSCLC that is not treated by surgery. Recommendations include conformal radiotherapy with sequential chemotherapy or concurrent + sequential chemotherapy. Recommended platinum doublets for use in such regimens include carboplatin-paclitaxel, carboplatin pemetrexed, cisplatin-pemetrexed, cisplatin-etoposide, and cisplatin vinblastine. Randomized controlled studies suggest that concurrent chemoradiotherapy followed by consolidation chemotherapy may be the optimal schedule for multi-modality therapy in this setting. Thus, the backbone regimen in this study is suitable treatment for the subjects.

A randomized, double-blind, placebo controlled study such as described here is optimal for assessing the value of add-on therapy (veliparib) to a current standard treatment.

5.6.2 Appropriateness of Measurements

Standard pharmacokinetic, statistical, clinical, and laboratory procedures will be utilized in this study.

The efficacy measurements in this study are standard and validated. PFS is a commonly used surrogate for OS in non-pivotal trials of NSCLC. OS is a widely accepted endpoint of clinical importance for the evaluation of subjects with previously untreated advanced or metastatic NSCLC. Response rate and duration of response may add supporting evidence to a finding of improved PFS and OS with veliparib combination therapy. Additionally, RECIST version 1.1 is a validated guideline for the measurement of responses in subjects with advanced or metastatic solid tumors.²⁹

5.6.3 Suitability of Subject Population

Subjects with pathologically documented and previously untreated Stage III NSCLC will be selected to participate in this study. The proposed inclusion and exclusion criteria are anticipated to result in a study patient population representative of Stage III NSCLC patients who receive concurrent radiotherapy and consolidation chemotherapy according to current practice guidelines.¹⁻³

5.6.4 Selection of Doses in the Study

The doses of standard therapy (radiotherapy, carboplatin, paclitaxel) are guideline recommended or based on randomized studies of subjects with advanced NSCLC.³ The dose escalation portion of this study will determine the appropriate dose of veliparib with standard-dose concurrent chemoradiotherapy and consolidation chemotherapy by a 3 + 3 cohort design.

Both 120 mg BID veliparib and 240 mg BID (or higher) have been used in Phase 2 and Phase 3 studies in combination with platinum doublet in different patient population. In

Cohorts 1 – 5, the 120 mg BID dose of investigational agent (veliparib) in the consolidation portion was selected based on a randomized, double-blind placebo controlled Phase 2 study of carboplatin and paclitaxel ± veliparib for advanced metastatic NSCLC, and to ensure the capability to escalate veliparib dose in combination with Chemo-RT.

Once the CRT RPTD is determined, a 6th cohort will be enrolled with subjects at 240 mg BID dose in the consolidation portion as indicated in [Table 1](#). The dose selection of 240 mg BID was supported by safety data in Phase 1 studies with veliparib in combination with carboplatin/paclitaxel, an ongoing Phase 2 study of 240 mg BID of veliparib in combination of carboplatin/etoposide for extended stage of small cell lung cancer, and a Phase 3 study of 300 mg BID veliparib in combination of carboplatin/paclitaxel in front line ovarian cancer patients. As described in [Section 3.0](#), preliminary data from this study show the combination is well-tolerated, showed delivery of carboplatin and paclitaxel were not substantially compromised, and suggested improved efficacy in subjects who received veliparib.

The maximum dose of veliparib/placebo for any subject in this study is 240 mg BID continuously during chemoradiotherapy followed by 240 mg BID for 7 of 21 days over 2 cycles of consolidation chemotherapy.

6.0 Adverse Events

The investigator will monitor each subject for clinical and laboratory evidence of adverse events on a routine basis throughout the study. The investigator will assess and record any adverse event in detail including the date of onset, event diagnosis (if known) or sign/symptom, severity, time course (end date, ongoing, intermittent), relationship of the adverse event to study drug, and any action(s) taken. For serious adverse events considered as having "no reasonable possibility" of being associated with study drug or NSCLC, the investigator will provide an Other cause of the event. For adverse events to be considered intermittent, the events must be of similar nature and severity. Adverse

events, whether in response to a query, observed by site personnel, or reported spontaneously by the subject will be recorded.

All adverse events will be followed to a satisfactory conclusion.

6.1 Definitions

6.1.1 Adverse Event

An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not the event is considered causally related to the use of the product.

Such an event can result from use of the drug as stipulated in the protocol or labeling, as well as from accidental or intentional overdose, drug abuse, or drug withdrawal. Any worsening of a pre-existing condition or illness is considered an adverse event.

Worsening in severity of a reported adverse event should be reported as a new adverse event. Laboratory abnormalities and changes in vital signs are considered to be adverse events only if they result in discontinuation from the study, necessitate therapeutic medical intervention, and/or if the investigator considers them to be adverse events.

An elective surgery/procedure scheduled to occur during a study will not be considered an adverse event if the surgery/procedure is being performed for a pre-existing condition and the surgery/procedure has been pre-planned prior to study entry. However, if the pre-existing condition deteriorates unexpectedly during the study (e.g., surgery performed earlier than planned), the deterioration of the condition for which the elective surgery/procedure is being done will be considered an adverse event.

6.1.2 Serious Adverse Events

If an adverse event meets any of the following criteria, it is to be reported to AbbVie as a serious adverse event (SAE) within 24 hours of the site being made aware of the serious adverse event.

Death of Subject	An event that results in the death of a subject.
Life-Threatening	An event that, in the opinion of the investigator, would have resulted in immediate fatality if medical intervention had not been taken. This does not include an event that would have been fatal if it had occurred in a more severe form.
Hospitalization or Prolongation of Hospitalization	An event that results in an admission to the hospital for any length of time or prolongs the subject's hospital stay. This does not include an emergency room visit or admission to an outpatient facility hospitalization for respite care, or hospitalization due solely to progression of the underlying cancer.
Congenital Anomaly	An anomaly detected at or after birth, or any anomaly that results in fetal loss.
Persistent or Significant Disability/Incapacity	An event that results in a condition that substantially interferes with the activities of daily living of a study subject. Disability is not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle).

Important Medical Event Requiring Medical or Surgical Intervention to Prevent Serious Outcome

An important medical event that may not be immediately life-threatening or result in death or hospitalization, but based on medical judgment may jeopardize the subject and may require medical or surgical intervention to prevent any of the outcomes listed above (i.e., death of subject, life threatening, hospitalization, prolongation of hospitalization, congenital anomaly, or persistent or significant disability/incapacity). Additionally, any elective or spontaneous abortion or stillbirth is considered an important medical event. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

For serious adverse events with the outcome of death, the date and cause of death will be recorded on the appropriate case report form.

6.2 Adverse Events Expected Due to NSCLC or Progression of NSCLC

Adverse events that may be expected from primary NSCLC lesions or compression of adjacent thoracic structures are presented in [Appendix C](#) of the protocol.

These adverse events may occur alone or in various combinations and are considered expected adverse events in NSCLC subjects.

6.3 Adverse Event Severity

The study Investigator will rate the severity of each adverse event according to the National Cancer Institute Common Terminology Criteria for Adverse Events NCI CTCAE version 4.0.²³

For adverse events not captured by the NCI CTCAE version 4.0, the Investigator will use the following definitions to rate the severity of each adverse event:

Mild (Grade 1)	The adverse event is transient and easily tolerated by the subject.
Moderate (Grade 2)	The adverse event causes the subject discomfort and interrupts the subject's usual activities.
Severe (Grade 3 or 4)	The adverse event causes considerable interference with the subject's usual activities and may be incapacitating or life threatening.
Death (Grade 5)	The adverse event resulted in death of the subject.

If a reported adverse event **increases** in severity, the initial adverse event should be given an outcome date and a new adverse event should be reported to reflect the change in severity.

For all reported serious adverse events that increase in severity, the supplemental CRFs also need to be updated and need to include the new AE serial number.

6.4 Relationship to Study Drug

The investigator will use the following definitions to assess the relationship of the adverse event to the use of study drug:

Reasonable Possibility	An adverse event where there is evidence to suggest a causal relationship between the study drug and the adverse event.
No Reasonable Possibility	An adverse event where there is no evidence to suggest a causal relationship between the study drug and the adverse event.

The investigator will assess the relationship of each adverse event to veliparib, to carboplatin, to radiotherapy, and to NSCLC. Most events will be reasonably related to one treatment or to NSCLC, though some events may be reasonably related to more than one or to none. For causality assessments, events assessed as having a reasonable possibility of being related to veliparib will be considered "associated." Events assessed as having no reasonable possibility of being related to veliparib will be considered "not

associated." In addition, when the investigator has not reported a causality or deemed it not assessable, AbbVie will consider the event associated.

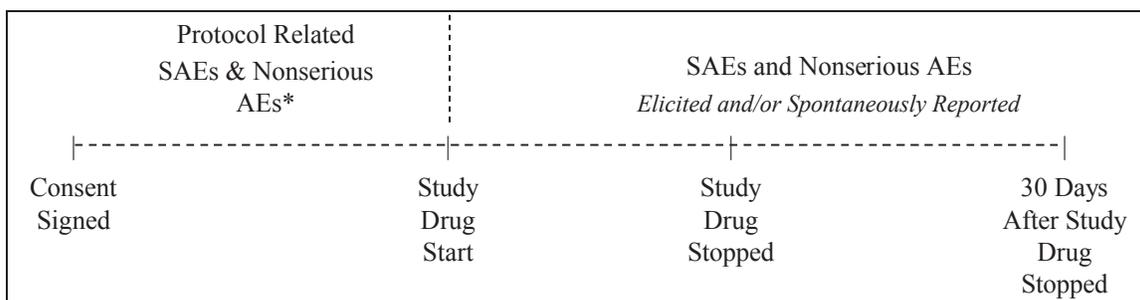
If an investigator's opinion of no reasonable possibility of being related to veliparib, to carboplatin, to paclitaxel, to radiotherapy, and to NSCLC is given, an Other cause of event must be provided by the investigator for the serious adverse event.

6.5 Adverse Event Collection Period

All protocol-related adverse events will be collected from the signing of the study-specific informed consent until 30 days following discontinuation of study drug administration have elapsed. All adverse events (regardless of whether they are protocol-related) will be collected from the time of study drug administration until 30 days following discontinuation of study drug administration have elapsed. Adverse events are to be collected whether solicited or spontaneously reported by the subject.

Adverse event information will be collected as shown in [Figure 3](#).

Figure 3. Adverse Event Collection



* Only if considered by the Investigator to be causally related to study-required procedures.

6.6 Adverse Event Reporting

6.6.1 Deaths

For this protocol, mortality is an efficacy endpoint. Deaths that occur during the protocol specified adverse event reporting period (Section 6.5) that are more likely related to

disease progression will therefore be an expected adverse event and will not be an expedited report.

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. The term "sudden death" should only be used for the occurrence of an abrupt and unexpected death due to presumed cardiac causes in a patient with or without pre-existing heart disease, within 1 hour of the onset of acute symptoms or, in the case of an unwitnessed death, within 24 hours after the patient was last seen alive and stable. If the cause of death is unknown and cannot be ascertained at the time of reporting, "unexplained death" should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death.

6.6.2 Lack of Efficacy or Worsening of Disease

Events that are clearly consistent with the expected pattern of progression of the underlying disease are also considered an expected outcome for this study and will not be subject to expedited reporting. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an adverse event.

6.6.3 Reporting Serious Adverse Events

In the event of a serious adverse event, whether associated with study drug or not, the Investigator will notify Clinical Pharmacovigilance within 24 hours of the site being made aware of the serious adverse event by entering the serious adverse event data into the electronic data capture (EDC) system. Serious adverse events that occur when the EDC system is not available should be sent on SAE Non-CRF paper forms to Clinical Pharmacovigilance within 24 hours of the site being made aware of the serious adverse event.

Serious adverse events which are considered expected due to the underlying disease of NSCLC as described in [Appendix C](#) would not be expedited as individual safety case reports to regulatory authorities.

FAX to: [REDACTED]

Email to: [REDACTED]

For safety concerns, contact the Oncology Safety Team or physician at:

Oncology Group Safety Management
AbbVie

[REDACTED]
1 North Waukegan Road
North Chicago, IL 60064

Office: [REDACTED]

Fax: [REDACTED]

Email: [REDACTED]

Primary Study Designated Physician:

[REDACTED]
AbbVie

[REDACTED]
1 North Waukegan Road
North Chicago, IL 60064

Office: [REDACTED]

Fax: [REDACTED]

Mobile: [REDACTED]

Email: [REDACTED]

In case of subject safety concerns or medical emergencies, should the Primary Study Designated Physician be unavailable, please call the following central back-up number:

Phone: [REDACTED]

The sponsor will be responsible for Suspected Unexpected Serious Adverse Reactions (SUSAR) reporting for the Investigational Medicinal Product (IMP) in accordance with Directive 2001/20/EC. The reference document used for SUSAR reporting in the EU countries will be the most current version of the Investigator's Brochure for veliparib. The reference document used for SUSAR reporting in the EU countries will be the most current version of the Summary of Product Characteristics (SmPC) for paclitaxel/carboplatin.

6.7 Pregnancy

In the event of a positive pregnancy test, subjects must immediately discontinue study drug and must be discontinued from the study. The Investigator must report the positive pregnancy test to the appropriate contact listed in protocol (Section 6.6) within 1 working day of the site becoming aware of the pregnancy.

All subjects should be informed that contraceptive measures should be taken throughout the study and for 6 months after discontinuing study drug. Information regarding a pregnancy occurrence in a study subject and the outcome of the pregnancy will be collected. The Investigator must follow the pregnancy to completion and provide an update to AbbVie after delivery.

Male subjects should be informed that contraceptive measures should be taken by their female partners. If the subject's partner should become pregnant during the study, this should also be reported and data may be collected. In the event of pregnancy occurring in the partner of an enrolled subject, written informed consent for release of medical information from the partner must be obtained prior to the collection of any pregnancy specific information and the pregnancy will be followed to outcome.

Pregnancy in a study subject is not considered an adverse event. However, the medical outcome of an elective or spontaneous abortion, stillbirth or congenital anomaly is

considered a serious adverse event and must be reported to AbbVie within 24 hours of the site becoming aware of the event.

6.8 Toxicity Management

All dose modifications (including dose delay, reduction, resumption, and discontinuation) are to be performed at the discretion of the Investigator. Guidelines suggesting dose modifications based on prior studies with veliparib, carboplatin, and paclitaxel appear in [Table 10](#) and [Appendix D](#). Study drug interruptions for events that are clearly not related to the study drug treatment, (e.g., underlying cancer, planned surgical procedures or acute viral illnesses), should not necessitate a dose reduction. The AbbVie medical monitor is to be contacted for subjects who require more than a 2-week delay in the re-initiation of chemotherapy or more than 7-day delay in the re-initiation of radiotherapy.

Management of toxicity should be performed by investigators according to standard medical practice and according to local label for toxicity due to carboplatin or paclitaxel. Following dose reductions, re escalation of paclitaxel, carboplatin, or veliparib doses is not allowed.

6.8.1 Dose Limiting Toxicities

Dose limiting toxicity (DLT) events will be collected for each dosing cohort until a new dosing cohort is opened or until the recommended Phase 2 dose is identified. A minimum of 3 subjects will be enrolled in each cohort. Additional eligible subjects may be enrolled at the current dose level at the discretion of the Investigators and the AbbVie Medical Monitor. From each cohort, subjects will be entered into the DLT assessment group of the intended cohort size in order of treatment. Subjects considered evaluable for DLTs will be those in the assessment group who receive treatment through 1 cycle or have AEs meeting DLT criteria. If a subject in the DLT assessment group becomes unevaluable, the subject will be replaced by the next-treated subject in the cohort. The DLT period for each subject in the concurrent CRT dose escalation will be from start of veliparib dosing through 28 days following completion of CRT or until consolidation chemotherapy is initiated, and the DLT period for all patients at each dose level will end upon initiation of

next dose level. The DLT period for each subject during consolidation chemotherapy dose (Cohort 6), will be 21 days from start of consolidation or until the start of Cycle 2 of the consolidation therapy or treatment discontinuation. Any of the events as described in Section 5.2 that are considered by the investigator to be related to treatment will be considered a dose limiting toxicity (DLT). At the time of dose escalation decisions, any events occurring in the DLT assessment group after the first cycle of therapy and any additional safety data available from cohort subjects not in the DLT assessment group will be taken into consideration.

Subjects experiencing DLTs will generally be discontinued from further participation in the study, but may continue at the same or a reduced dose with approval by the medical monitor if there is evidence of clinical benefit.

6.8.2 Determination of the MTD

The MTD will be determined as described in Section 5.5.1. MTD, if identified, will be defined as the highest dose level at which less than or equal to 2 of 6 subjects or $\leq 33\%$ of subjects experience the same DLT.

6.8.3 Determination of the RPTD

AbbVie will review available safety data from all subjects in the dose escalation portion of the study and determine the RPTD for veliparib during chemoradiotherapy and consolidation chemotherapy. Subjects in the randomized portion of the study will receive the veliparib CRT RPTD or placebo during chemoradiotherapy and the veliparib consolidation RPTD or placebo during consolidation. If an MTD is reached, the RPTD will not be a dose higher than the MTD and will be selected based on the types of DLTs which occur and the MTD identified. If an MTD is not reached, then the RPTD will be defined based on the safety and available PK data. The RPTD will not exceed 240 mg BID.

6.8.4 Dose Modifications During Concurrent Therapy

The following are guidelines for delay and discontinuation of CRT treatments. Doses that are missed during the weekly schedule of CRT will not be made up. Any treatment delays will be documented. If paclitaxel and/or carboplatin doses must be withheld for greater than 3 consecutive weeks, the drug(s) will be held permanently for the duration of concurrent therapy. Veliparib should be interrupted if radiotherapy, paclitaxel, and carboplatin are interrupted for > 7 days. After interruption, veliparib should be re-started 2 days prior to the resumption of radiotherapy when possible.

6.8.4.1 Dose Modifications for Hematologic Toxicity

Hematologic Toxicity: RT should be held for all Grade 4 hematologic toxicity except for Grade 4 lymphopenia, (at the discretion of the treating physician). RT should be resumed when hematologic toxicity is \leq Grade 3.

Toxicity NCI CTCAE Grade (CTCAE v. 4.0) on the Day of Due Treatment*	Paclitaxel Dose at Start of Subsequent Cycles Of Therapy	Carboplatin Dose at Start of Subsequent Cycles Of Therapy
Neutropenia 3 (500 – 999/ mm^3)	Hold therapy ^a	Hold therapy ^a
Neutropenia 4 (< 500/ mm^3)	Hold therapy ^a	Hold therapy ^a
Neutropenic fever	Hold therapy ^a	Hold therapy ^a
Thrombocytopenia 3 (25,000 – 49,999/ mm^3)	Hold therapy ^a	Hold therapy ^a
Thrombocytopenia 4 (< 24,999/ mm^3)	Hold therapy ^a	Hold therapy ^a

* RT should be held for all Grade 4 hematologic toxicity except for Grade 4 lymphopenia, (at the discretion of the treating physician). RT should be resumed when hematologic toxicity is \leq Grade 3.

a. Repeat lab work weekly and resume chemotherapy and veliparib based on this table. If paclitaxel and/or carboplatin doses must be withheld for greater than 3 consecutive weeks, the drug(s) will be held permanently for the duration of concurrent therapy.

6.8.4.2 Dose Modifications for Non-hematologic Toxicity

Non-Hematologic Toxicity: RT should be held for all Grade 4 non-hematologic toxicity in or outside the treatment field and resumed only when toxicity is \leq Grade 2.

Worst Toxicity NCI CTCAE Grade (CTCAE 4.0)	Paclitaxel Dose At Start of Subsequent Cycles Of Therapy	Carboplatin Dose at Start of Subsequent Cycles Of Therapy
Neuropathy Grade 2	Hold therapy until Grade \leq 1; restart at full dose	Maintain dose level
Neuropathy Grade 3 or 4	Discontinue therapy	Hold therapy, until \leq Grade 2
Other non-hematologic toxicities ^a Grade 3 or 4	Hold therapy, until \leq Grade 2	Hold therapy, until \leq Grade 2

- a. RT should be held for all Grade 4 non-hematologic toxicity in or outside the treatment field and resumed only when toxicity is \leq Grade 2.

Note: If there is a decline in performance status to \geq 2 for greater than 2 weeks while under treatment, radiotherapy should be held with no further chemotherapy administered. Re-evaluate patient after one week for resumption of radiotherapy.

6.8.4.3 Dose Modifications for In-Field, Non-Hematologic Toxicity During Concurrent Therapy

Treatment Modification for In-field Non-Hematologic Toxicity				
In-field	CTCAE Toxicity Grade	RT	Paclitaxel	Carboplatin
Esophagus/pharynx* (on day of RT)	4	Hold treatment Until \leq Grade 2	Hold treatment Until \leq Grade 2	Hold treatment Until \leq Grade 2
Esophagus/pharynx* (on day of chemo)	3	No change or hold \leq 5 days	Hold treatment Until \leq Grade 2	Hold treatment Until \leq Grade 2
Pulmonary	4	Discontinue	Discontinue	Discontinue
Pulmonary	3	Hold treatment Until \leq Grade 2	Hold treatment Until \leq Grade 2	Hold treatment Until \leq Grade 2
Skin	4	Hold treatment Until \leq Grade 2	Hold treatment Until \leq Grade 2	Hold treatment Until \leq Grade 2

- * Radiation esophagitis or dermatitis will use CTCAE v4.0. The grading for esophagitis as per CTCAE v. 4.0 is:
Grade 1: Asymptomatic; clinical or diagnostic observations only; intervention not indicated.
Grade 2: Symptomatic; altered eating/swallowing; oral supplements indicated.

Grade 3: Severely altered eating/swallowing; tube feeding, TPN or hospitalization indicated.

Grade 4: Life-threatening consequences; urgent operative intervention indicated.

Radiotherapy will be continued without interruption even if chemotherapy and/or veliparib/placebo are held for toxicity or any other reason. However, if radiotherapy is held for toxicity, chemotherapy and/or veliparib will be held as well.

6.8.5 Dose Modifications During Consolidation Therapy

Table 10. Suggested Guidelines for Veliparib + Paclitaxel/Carboplatin Independent Dose Reduction

Dose Level	Carboplatin	Paclitaxel	Veliparib/Placebo
Starting Dose Level (for subjects participating in Cohort 6)	AUC 6	200 mg/m ²	240 mg BID
Starting Dose Level -1			120 mg BID
Dose Level -2	AUC 5	175 mg/m ²	80 mg BID
Dose Level -3	AUC 4	150 mg/m ²	60 mg BID

6.8.5.1 Veliparib Dose Reductions and Delays

The following are guidelines for dose reduction, delay and discontinuation of Veliparib:

1. Veliparib is to be discontinued if both carboplatin and paclitaxel are discontinued.
2. For any subject who experiences Grade 3/4 toxicity which is not attributable to paclitaxel/carboplatin or the underlying disease, the Veliparib dose is to be held until the toxicity resolves to Grade 1 or lower or to baseline if Grade 2 is present at the time of study entry. Upon resuming Veliparib treatment, the dose is to be reduced one dose level. Any dose reduction beyond 40 mg BID is to result in Veliparib discontinuation.
3. If a subject begins Veliparib on Day -2 for consolidation therapy (both cycles) but subsequently experiences an event requiring delay of the paclitaxel/carboplatin dosing on Day 1, the subject is to stop Veliparib dosing immediately. Upon

resolution of the event, the subject may restart the current cycle by repeating Day -2 and Day -1. For such delays, a new Veliparib supply will be dispensed to restart the cycle at Day -2.

4. For any \geq Grade 2 event of seizure attributed to Veliparib, Veliparib is to be discontinued and the event should be discussed with the AbbVie medical monitor.

6.8.5.2 Paclitaxel/Carboplatin Dose Reductions and Delays

For carboplatin and/or paclitaxel dose modifications, the Investigator should follow procedures as defined in the locally approved product label or applicable Summary of Product Characteristics (SmPC). Suggested dose reductions for paclitaxel/carboplatin if above information is not available are outlined in [Appendix D](#). If the Investigator considers an event attributable to carboplatin and/or paclitaxel, the Investigator may consider reducing the dose of both agents.

All toxicities are to be resolved to grade 1 or less prior to initiation of a new cycle of therapy, with the exception of anemia, alopecia, neuropathy, and non-treatment related clinically insignificant laboratory abnormalities.

If chemotherapy must be withheld due to hematologic toxicity, CBC and platelet counts should be obtained weekly until the counts reach the lower limits for treatment as outlined. The treatment schedule will then proceed in the usual sequence.

For subjects who miss any one dose of veliparib/placebo in the 48 hours prior to the start of any portion of backbone therapy (Week 1 Day 1 of concurrent therapy or Day 1 of either cycle of consolidation), that therapy will be held and veliparib/placebo restarted (from Day -3 for concurrent and Day -2 for consolidation).

Hematologic Toxicity

For absolute neutrophil count (ANC) $< 1,500/\text{mm}^3$ or platelet count $< 100,000/\text{mm}^3$ on Day 1 of each cycle, treatment is to be delayed until recovery of ANC and platelet count

above these values. For febrile neutropenia or for grade 4 thrombocytopenia, carboplatin and paclitaxel doses are to be reduced by one dose level.

If the subject experiences fever with neutropenia, then neutrophil growth factors are to be given based on local standard of care guidelines or ASCO guidelines.²²

Non-Hematological Toxicity

Gastrointestinal Toxicity

For grade 3 or 4 nausea/vomiting despite maximal anti-emetic therapy or for grade 3 or 4 stomatitis, the dose of carboplatin and paclitaxel are to be reduced by 1 dose level.

Nausea, vomiting, and stomatitis are to have resolved to grade 1 before initiation of a new cycle of therapy.

If the stomatitis has not resolved to grade 1 or less within 3 weeks, the subject's study treatment is to be discontinued.

Hepatic Toxicity

For bilirubin $> 1.5 \times \text{ULN}$ with increased ALT above ULN that is attributed to protocol therapy, paclitaxel is to be held until bilirubin is $\leq 1.5 \times \text{ULN}$, and the dose is to be reduced by one level when treatment is resumed.

For ALT $> 5 \times \text{ULN}$ with bilirubin $< 1.5 \times \text{ULN}$ that is attributed to protocol therapy, paclitaxel dose is to be reduced by one level.

Neurologic Toxicity

For grade 2 neuropathy, paclitaxel dose is to be reduced to Dose Level -1. For grade 3/4 neuropathy, paclitaxel dose is to be held until neuropathy is grade 2, and the dose is to be reduced to Dose Level -2 when treatment is resumed. The dose of carboplatin will not be reduced for neurologic toxicity.

7.0 Protocol Deviations

AbbVie does not allow intentional/prospective deviations from the protocol. The principal investigator is responsible for complying with all protocol requirements, and applicable global and local laws regarding protocol deviations. If a protocol deviation occurs (or is identified) after a subject has been enrolled, the principal investigator is responsible for notifying Independent Ethics Committee (IEC)/Independent Review Board (IRB) regulatory authorities (as applicable), and the following AbbVie Clinical Monitor(s):

Clinical Team Lead:



AbbVie



1 North Waukegan Road
North Chicago, IL 60064

Office:

Fax:

Email:



Medical Monitor:



AbbVie



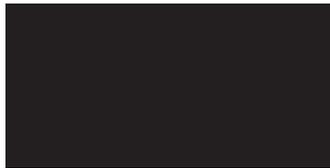
1 North Waukegan Road
North Chicago, IL 60064

Office:

Fax:

Mobile

Email:



Such contact must be made as soon as possible to permit a review by AbbVie to determine the impact of the deviation on the subject and/or the study.

8.0 Statistical Methods and Determination of Sample Size

8.1 Statistical and Analytical Plans

For subjects in the Phase 1 portion, the date of enrollment is defined as the first day of study drug administration. For subjects in the randomized Phase 2 portion, the date of

randomization (enrollment) is defined as the date that the IRT issued a randomization number.

ORR will be performed on all dosed subjects in Phase 1 portion of the study. The primary, secondary, and tertiary efficacy analyses will be performed on all subjects in the randomized Phase 2 portion of the study.

Safety analyses will be performed separately for the Phase 1 and Phase 2 portions. All subjects who receive at least one dose of the study drug will be included in the safety analysis.

Unless otherwise noted, data will be summarized for Phase 1 and Phase 2 subjects separately.

8.1.1 Baseline Characteristics

All baseline summary statistics and analyses will be based on characteristics obtained prior to the initiation of study drug (or randomization for non-treated subjects). Unless otherwise stated, baseline for a given variable will be defined as the last value for that variable obtained prior to the first dose of study drug.

8.1.1.1 Demographics

Continuous demographic data (e.g., age, height, and weight) will be summarized with means, standard deviations, medians, and minimum and maximum values. Frequencies and percentages will be computed for categorical data (e.g., sex, race, and performance status).

8.1.1.2 Medical History

Frequencies and percentages will be computed for each medical history parameter.

8.1.2 Efficacy Endpoints

8.1.2.1 Primary Efficacy Endpoint

The primary efficacy endpoint is progression-free survival (PFS). Progression-Free Survival will be defined as the number of days from the date of randomization to the date of earliest radiographic disease progression or death. All radiographic disease progression will be included regardless whether the event occurred while the subject was taking study drug or had previously discontinued study drug. If the subject does not experience radiographic disease progression or death, then the data will be censored at the date of the last disease assessment.

8.1.2.2 Secondary Efficacy Endpoints

Secondary efficacy endpoints include overall survival, objective response rate, and duration of overall response.

Overall Survival

Overall survival will be defined as the number of days from the date of randomization to the date of death. For subjects who did not die, their data will be censored at the date of last study visit or the last known date to be alive, whichever is later.

Objective Response Rate

The proportion of subjects with objective response as assessed by the investigator using RECIST version 1.1 will be evaluated for randomized subjects.

Duration of Overall Response

Duration of overall response will be defined as the number of days from the date of first response (CR or PR) to the earliest documentation of radiographic progressive disease or death due to disease progression. If a subject is still responding, then the subject's data will be censored at the date of the subject's last available disease

assessment. For subjects who never experience response, the subject's data will not be included in the analysis.

8.1.2.3 Tertiary Efficacy Endpoints

In addition to the primary and secondary efficacy analyses, tertiary efficacy analyses of performance status and quality of life will be performed.

Performance Status

Changes and/or percent changes from baseline will be summarized using descriptive statistics for each scheduled post-baseline visit and for the Final Visit for ECOG performance status (as shown in [Table 2](#)). Post-baseline measurements more than 30 days after the last dose of study drug will not be included. Subjects that do not have a baseline measurement or do not have any post-baseline measurements will not be included.

Quality of Life Measures

Changes and/or percent changes from baseline will be summarized using descriptive statistics for each scheduled post-baseline visit and for the Final Visit for quality of life measures using EORTC QLQ-C15-PAL and EORTC QLQ-LC13 questionnaire (as shown in [Table 2](#)).

8.1.3 Primary Analysis of Efficacy

PFS will be analyzed by Kaplan Meier methodology and compared between Arm A (concurrent paclitaxel/carboplatin/radiotherapy/veliparib followed by consolidation paclitaxel/carboplatin/veliparib) and Arm C (concurrent paclitaxel/carboplatin/radiotherapy/placebo followed by consolidation paclitaxel/carboplatin/placebo), using a log-rank test stratified by tumor volume. A two-sided, stratified log-rank test p-value will be provided. Median PFS time will be calculated and 95% confidence interval for median PFS time will be presented.

8.1.4 Secondary Analysis of Efficacy

Progression-Free Survival (Arm B versus Arm C)

PFS will be analyzed by Kaplan Meier methodology and compared between Arm B (concurrent paclitaxel/carboplatin/radiotherapy/veliparib followed by consolidation paclitaxel/carboplatin/placebo) and Arm C, using a log-rank test stratified by tumor volume. A two-sided, stratified log-rank test p-value will be provided. Median PFS time will be calculated and 95% confidence interval for median PFS time will be presented.

Overall Survival

OS will be analyzed by Kaplan Meier methodology and compared between Arm A and Arm C as well as between Arm B and Arm C, using a log-rank test stratified by tumor volume. A two-sided, stratified log-rank test p-value will be provided. Median OS time will be calculated and 95% confidence interval for median OS time will be presented.

Objective Response Rate

The objective response rate will be estimated and compared between Arm A and Arm C as well as between Arm B and Arm C, using a Cochran-Mantel-Haenszel test stratified by tumor volume. A two-sided, stratified CMH test p-value will be provided. In addition, a 95% confidence interval will be constructed for the estimated proportions.

Duration of Overall Response

The distribution of duration of overall response (DOR) will be estimated for each treatment arm using Kaplan-Meier methodology. Median DOR will be estimated and a 95% confidence interval will be presented for each treatment arm.

8.1.5 Tertiary Analysis of Efficacy

Quality of Life

Changes and/or percent changes from baseline will be summarized using descriptive statistics for each scheduled post-baseline visit and for the Final Visit for quality of life

measures using EORTC QLQ-C15-PAL and EORTC QLQ-LC13 questionnaire. Changes and/or percent changes from baseline to each visit will be compared between Arm A and Arm C as well as between Arm B and Arm C using an analysis of covariance with treatment arm as the factor and baseline value as a covariate.

ECOG Performance Status

Changes and/or percent changes from baseline in ECOG performance status will be summarized using descriptive statistics for each scheduled post-baseline visit and for the final visit. Post-baseline measurements more than 30 days after the last dose of study drug will not be included. Subjects that do not have a baseline measurement or do not have any post-baseline measurements will not be included. Changes and/or percent changes from baseline to each visit will be compared between Arm A and Arm C as well as between Arm B and Arm C using an analysis of covariance with treatment arm as the factor and baseline value as a covariate.

8.1.6 Safety Assessments

A safety analysis will be performed for all subjects participating in the study unless otherwise indicated. Safety analyses will be performed for Phase 1 and Phase 2 separately. The following will be included in these analyses:

8.1.6.1 Duration of Study Drug

A summary of the number of days and/or cycles subjects were exposed to study drug will be provided.

8.1.6.2 Adverse Event

Analyses of adverse events will include only "treatment-emergent" events, i.e., those that have an onset on or after the day of the first dose of study drug (veliparib or placebo).

Analyses will not include those that have an onset greater than 30 days after the last dose of study drug.

Treatment-emergent adverse events will be coded and summarized by system organ class and preferred term according to the Medical Dictionary for Regulatory Activities (MedDRA) adverse event coding dictionary. The percentage of subjects experiencing an adverse event at a given NCI CTCAE version 4.0 grade, and relationship to study drug will be provided. For Phase 1, all summaries will be done by dose level. For Phase 2, comparisons of the percentages of subjects experiencing an adverse event between Arm A and Arm C as well as between Arm B and Arm C will be performed using Fisher's exact test.

8.1.6.3 Serious Adverse Event

Serious adverse events will be summarized using the same methods as adverse events described above in Section [8.1.6.2](#).

8.1.6.4 Death

The number of subject deaths will be summarized 1) for deaths occurring while the subject was still receiving study drug in this study, 2) for deaths occurring off treatment within 30 days after the last dose of study drug, and 3) for all deaths in this study regardless of the number of days after the last dose of study drug.

8.1.6.5 Longitudinal Analyses of Laboratory and Vital Signs Data

Changes from baseline will be analyzed for each scheduled post-baseline visit and for the final visit for blood chemistry and hematology parameters, as well as urinalysis and vital sign parameters. If more than one measurement exists for a subject on a particular day, an arithmetic average will be calculated. This average will be considered to be that subject's measurement for that day. Post-baseline measurements more than 30 days after the last dose of randomized study drug will not be included. Subjects that do not have a baseline measurement or do not have any post-baseline measurements will not be included. For Phase 1, changes from baseline will be analyzed by dose level at each scheduled visit.

For Phase 2, comparisons of the differences in mean changes from baseline between Arm A and Arm C as well as between Arm B and Arm C will be made using ANCOVA with treatment group as the factor and baseline as a covariate.

8.1.6.6 Analyses of Laboratory Data Using NCI CTCAE

Where applicable, blood chemistry and hematology determinations will be categorized according to NCI CTCAE version 4.0 grades, and shifts from baseline NCI CTCAE version 4.0 grades to maximum and final post-baseline grades will be assessed. The baseline and final grades will be defined respectively as the grade of the last measurement collected prior to the first dose of study drug, and as the grade of the last post-baseline measurement collected no more than 30 days after the last dose of study drug. If multiple values are available for a post-baseline measurement, then the value with the highest NCI CTCAE grade will be used in the assessment of shift. Comparisons of the number of subjects experiencing a shift from baseline grades of 0 to 2 or no grade to maximum post-baseline grades of 3 to 4, and from baseline grades of 0 to 2 or no grade to final post-baseline grades of 3 to 4 between Arm A and Arm C as well as between Arm B and Arm C will be performed using Fisher's exact tests. Additional analyses including all measurements collected, regardless of the number of days after the last dose of study drug, will be performed.

Detailed listings of data for subjects experiencing NCI CTCAE Grade 3 to 4 blood chemistry and hematology values will be provided. All measurements collected, regardless of the number of days after the last dose of study drug, will be included in these listings.

8.1.6.7 Analyses of Vital Signs Using Criteria for Potentially Clinically Significant Vital Sign Values

Detailed listings of data for subjects experiencing potentially clinically significant vital sign values according to the AbbVie-defined criteria for vital sign values will be provided. All measurements collected, regardless of the number of days after the last dose of study drug, will be included in these listings.

8.1.7 Timing of Efficacy Analyses and Safety Evaluations

At the time when the 107th PFS events are observed, all efficacy and safety data as of this time will be retrieved and entered into the clinical database prior to breaking the study blind. When the data collection is completed and reviewed for completeness and all data management quality assurance (QA) and quality control (QC) procedures are performed, the study blind will be broken and clinical database data will be extracted for documentation and statistical analyses of the efficacy and safety data.

Overall survival (OS) will be collected on all subjects after they discontinue from the study until the study is concluded by AbbVie. After all survival data have been collected and entered into the clinical database, the clinical database will be extracted once again for documentation and a "Final OS Analysis" will be performed on this dataset.

8.1.8 Interim Analysis

To ensure subject safety, an internal data monitoring committee (DMC) will review un-blinded safety data when 45 subjects in Phase 2 portion of the study have completed chemoradiotherapy, reached an event of disease progression or death, or discontinued the study.

Only safety will be evaluated at interim analysis. AbbVie clinical and statistical personnel directly responsible for the conduct of the study will not have access to either the treatment codes or the interim analyses prepared for the DMC.

8.2 Determination of Sample Size

Approximately 50 subjects will be enrolled in the dose escalation portion of the study.

Assuming a hazard ratio of 0.6 for Arm A (Concurrent paclitaxel/carboplatin/radiotherapy/veliparib followed by consolidation paclitaxel/carboplatin/veliparib) versus Arm C (Concurrent paclitaxel/carboplatin/radiotherapy/placebo followed by consolidation paclitaxel/carboplatin/placebo), a total of 71 PFS events in Arm A and Arm C combined

will provide an expected 95% confidence interval of 0.38 to 0.96 for the estimated hazard ratio. Assuming a hazard ratio of 0.75 for Arm B (Concurrent paclitaxel/carboplatin/radiotherapy/veliparib followed by consolidation paclitaxel/carboplatin/veliparib) versus Arm C, a total of 107 PFS events will be observed across all three arms at the time when 71 PFS events are observed for Arm A and Arm C combined. A total of approximately 156 subjects (52 subjects per treatment arm) will be enrolled into Phase 2 portion of the study to obtain the 107 PFS events.

8.3 Randomization Methods

In Phase 2, the IRT will randomize subjects in a 1:1:1 ratio to one of the treatment arms as follows:

- A. Concurrent paclitaxel/carboplatin/radiotherapy/veliparib followed by consolidation paclitaxel/carboplatin/veliparib
- B. Concurrent paclitaxel/carboplatin/radiotherapy/veliparib followed by consolidation paclitaxel/carboplatin/placebo
- C. Concurrent paclitaxel/carboplatin/radiotherapy/placebo followed by consolidation paclitaxel/carboplatin/placebo

Subject randomization will be stratified by tumor volume (≤ 90 versus > 90 cm³) and smoking history (current smoker versus former smoker versus never smoked). The stratification factors used for the randomization should be the last values on or prior to the date of randomization and should be consistent with those on the eCRF.

9.0 Ethics

9.1 Independent Ethics Committee (IEC) or Institutional Review Board (IRB)

Good Clinical Practice (GCP) requires that the clinical protocol, any protocol amendments, the Investigator's Brochure, the informed consent and all other forms of subject information related to the study (e.g., advertisements used to recruit subjects) and

any other necessary documents be reviewed by an IEC/IRB. The IEC/IRB will review the ethical, scientific and medical appropriateness of the study before it is conducted. IEC/IRB approval of the protocol, informed consent and subject information and/or advertising, as relevant, will be obtained prior to the authorization of drug shipment to a study site.

Any amendments to the protocol will require IEC/IRB approval prior to implementation of any changes made to the study design. The investigator will be required to submit, maintain and archive study essential documents according to ICH GCP.

Any serious adverse events that meet the reporting criteria, as dictated by local regulations, will be reported to both responsible Ethics Committees and Regulatory Agencies, as required by local regulations. During the conduct of the study, the investigator should promptly provide written reports (e.g., ICH Expedited Reports, and any additional reports required by local regulations) to the IEC/IRB of any changes that affect the conduct of the study and/or increase the risk to subjects. Written documentation of the submission to the IEC/IRB should also be provided to AbbVie.

9.2 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, International Conference on Harmonization (ICH) guidelines, applicable regulations and guidelines governing clinical study conduct and the ethical principles that have their origin in the Declaration of Helsinki. Responsibilities of the clinical investigator are specified in Appendix A.

9.3 Subject Information and Consent

The investigator or his/her representative will explain the nature of the study to the subject, and answer all questions regarding this study. Prior to any study-related screening procedures being performed on the subject, the informed consent statement will be reviewed and signed and dated by the subject, the person who administered the informed consent, and any other signatories according to local requirements. A copy of the informed consent form will be given to the subject and the original will be placed in

the subject's medical record. An entry must also be made in the subject's dated source documents to confirm that informed consent was obtained prior to any study-related procedures and that the subject received a signed copy.

Pharmacogenetic analysis will only be performed if the subject has voluntarily signed and dated a separate pharmacogenetic informed consent, approved by an IRB/IEC, after the nature of the testing has been explained and the subject has had an opportunity to ask questions. The separate pharmacogenetic informed consent must be signed before the pharmacogenetic testing is performed. If the subject does not consent to the pharmacogenetic testing, it will not impact the subject's participation in the study.

For subjects participating in Cohort 1 – 5, archived tissue analysis will only be performed if the subject has voluntarily consented for tissue sampling on the informed consent, approved by an IRB/IEC, after the nature of the testing has been explained and the subject has had an opportunity to ask questions. If the subject does not consent to the archived tissue analysis, it will not impact the subject's participation in the study. Subjects in Cohort 6 must consent to provide available archival tumor for analysis. It is recognized that the availability of the samples suitable for analysis may not be known at the time of consent for all subjects.

10.0 Source Documents and Case Report Form Completion

10.1 Source Documents

Source documents are defined as original documents, data and records. This may include hospital records, clinical and office charts, laboratory data/information, subjects' diaries or evaluation checklists, pharmacy dispensing and other records, recorded data from automated instruments, microfiches, photographic negatives, microfilm or magnetic media, and/or x-rays. Data collected during this study must be recorded on the appropriate source documents.

The investigator(s)/institution(s) will permit study-related monitoring, audits, IEC/IRB review, and regulatory inspection(s), providing direct access to source data documents.

10.2 Case Report Forms

Case report forms (CRF) must be completed for each subject screened/enrolled in this study. These forms will be used to transmit information collected during the study to AbbVie and regulatory authorities, as applicable. The CRF data for this study are being collected with an electronic data capture (EDC) system called Rave[®] provided by the technology vendor Medidata Solutions Incorporated, NY, USA. The EDC system and the study-specific electronic case report forms (eCRFs) will comply with Title 21 CFR Part 11. The documentation related to the validation of the EDC system is available through the vendor, Medidata, while the validation of the study-specific eCRFs will be conducted by AbbVie and will be maintained in the Trial Master File at AbbVie.

The investigator will document subject data in his/her own subject files. These subject files will serve as source data for the study. All eCRF data required by this protocol will be recorded by investigative site personnel in the EDC system. All data entered into the eCRF will be supported by source documentation.

The investigator or an authorized member of the investigator's staff will make any necessary corrections to the eCRF. All change information, including the date and person performing the corrections, will be available via the audit trail, which is part of the EDC system. For any correction, a reason for the alteration will be provided. The eCRFs will be reviewed periodically for completeness, legibility, and acceptability by AbbVie personnel (or their representatives). AbbVie (or their representatives) will also be allowed access to all source documents pertinent to the study in order to verify eCRF entries. The principal investigator will review the eCRFs for completeness and accuracy and provide his or her electronic signature and date to eCRFs as evidence thereof.

Medidata will provide access to the EDC system for the duration of the study through a password-protected method of internet access. Such access will be removed from

investigator sites at the end of the site's participation in the study. Data from the EDC system will be archived on appropriate data media (CD-ROM, etc.) and provided to the investigator at that time as a durable record of the site's eCRF data. It will be possible for the investigator to make paper printouts from that media.

11.0 Data Quality Assurance

Computer logic and manual checks will be created to identify items such as inconsistent study dates. Any necessary corrections will be made to the eCRF.

12.0 Use of Information

Any pharmacogenetic research that may be done using DNA samples from this study will be experimental in nature and the results will not be suitable for clinical decision making or patient management. Hence, neither the investigator, the subject, nor the subject's physician (if different from the investigator) will be informed of individual subject pharmacogenetic results, should analyses be performed, nor will anyone not directly involved in this research. Correspondingly, genetic researchers will have no access to subject identifiers. Individual results will not be reported to anyone not directly involved in this research other than for regulatory purposes. Aggregate pharmacogenetic information from this study may be used in scientific publications or presented at medical conventions. Pharmacogenetic information will be published or presented only in a way that does not identify any individual subject.

13.0 Completion of the Study

The investigator will conduct the study in compliance with the protocol and complete the study within the timeframe specified in the contract between the investigator and AbbVie. Continuation of this study beyond this date must be mutually agreed upon in writing by both the investigator and AbbVie. The investigator will provide a final report to the IEC/IRB following conclusion of the study, and will forward a copy of this report to AbbVie or their representative.

The investigator must retain any records related to the study according to local requirements. If the investigator is not able to retain the records, he/she must notify AbbVie to arrange alternative archiving options.

AbbVie will select the signatory investigator from the investigators who participate in the study. Selection criteria for this investigator will include level of participation as well as significant knowledge of the clinical research, investigational drug and study protocol. The signatory investigator for the study will review and sign the final study report in accordance with the European Agency for the Evaluation of Medicinal Products (EMA) Guidance on Investigator's Signature for Study Reports.

The end-of-study is defined as the date of the last subject's last visit.

14.0 Investigator's Agreement

1. I have received and reviewed the Investigator's Brochure for veliparib and the product labeling for carboplatin and paclitaxel.
2. I have read this protocol and agree that the study is ethical.
3. I agree to conduct the study as outlined and in accordance with all applicable regulations and guidelines.
4. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.
5. I agree that all electronic signatures will be considered the equivalent of a handwritten signature and will be legally binding.

Protocol Title: A Phase 1 Dose Escalation and Phase 2 Randomized, Placebo-Controlled Study of the Efficacy and Tolerability of Veliparib in Combination with Paclitaxel/Carboplatin-Based Chemoradiotherapy Followed by Veliparib and Paclitaxel/Carboplatin Consolidation in Subjects with Stage III Non-Small Cell Lung Cancer (NSCLC)

Protocol Date: 15 August 2017

Signature of Principal Investigator

Date

Name of Principal Investigator (printed or typed)

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Appendix A. Responsibilities of the Clinical Investigator

Clinical research studies sponsored by AbbVie are subject to the Good Clinical Practices (GCP) and local regulations and guidelines governing the study at the site location. In signing the Investigator Agreement in Section 14.0 of this protocol, the investigator is agreeing to the following:

1. Conducting the study in accordance with the relevant, current protocol, making changes in a protocol only after notifying AbbVie, except when necessary to protect the safety, rights or welfare of subjects.
2. Personally conducting or supervising the described investigation(s).
3. Informing all subjects, or persons used as controls, that the drugs are being used for investigational purposes and complying with the requirements relating to informed consent and ethics committees [e.g., independent ethics committee (IEC) or institutional review board (IRB)] review and approval of the protocol and amendments.
4. Reporting adverse experiences that occur in the course of the investigation(s) to AbbVie and the site director.
5. Reading the information in the Investigator's Brochure/safety material provided, including the instructions for use and the potential risks and side effects of the investigational product(s).
6. Informing all associates, colleagues, and employees assisting in the conduct of the study about their obligations in meeting the above commitments.
7. Maintaining adequate and accurate records of the conduct of the study, making those records available for inspection by representatives of AbbVie and/or the appropriate regulatory agency, and retaining all study-related documents until notification from AbbVie.
8. Maintaining records demonstrating that an ethics committee reviewed and approved the initial clinical investigation and all amendments.

9. Reporting promptly, all changes in the research activity and all unanticipated problems involving risks to human subjects or others, to the appropriate individuals (e.g., coordinating investigator, institution director) and/or directly to the ethics committees and AbbVie.
10. Following the protocol and not make any changes in the research without ethics committee approval, except where necessary to eliminate apparent immediate hazards to human subjects.

Appendix B. List of Protocol Signatories

Name	Title	Functional Area
		Clinical
		GDSM
		Clinical
		Clinical
		Statistics
		Clinical Pharmacology & Pharmacometrics
		Bioanalysis
		Biometrics

Appendix C. Adverse Events Expected Due to NSCLC or Progression of NSCLC

Preferred Term (MedDRA Version 13.1)
Pleural effusion
Malignant pleural effusion
Metastases to pleura
Dyspnoea
Cough
Non-cardiac chest pain
Haemoptysis*
Oesophageal obstruction
Pneumonia*
Vocal cord paralysis
Dysphonia
Dysphagia
Superior vena cava syndrome
Horner's syndrome
Metastases to bone
Metastases to lymph nodes
Metastases to liver
Metastases to spine
Metastases to the mediastinum
Metastases to pleura
Metastases to adrenals
Metastases to meninges
Metastases to central nervous system
Metastatic pain
Cancer pain
Tumour pain
Fatigue
Asthenia
Pulmonary embolism*
Blood Antidiuretic Hormonal Abnormal (SIADH)
Cushing's syndrome

Preferred Term (MedDRA Version 13.1)
Cachexia
Shock*
Septic shock*
Deep vein thrombosis*
Lower respiratory tract infection*
Respiratory tract infection*
Upper respiratory tract infection*
Opportunistic infection*
Viral infection*
Fungal infection*
Bacterial infection*
Pulmonary haemorrhage*
Lung abscess*
Empyema*
Sepsis*
Lymphadenopathy
Decreased appetite
Malaise
Weight decreased
Headache
Pain excluding chest pain
Pyrexia

* Includes life threatening or fatal events.

Appendix D. Suggested Guidelines for Paclitaxel/Carboplatin Dose Delay or Reduction During Consolidation Chemotherapy

Adverse Event	Carboplatin Dose	Paclitaxel Dose
Grade 3/4 Neutropenia without fever	Wait until ANC $\geq 1,500/\text{mm}^3$.	Wait until ANC $\geq 1,500/\text{mm}^3$.
Grade 3/4 Febrile Neutropenia	Reduce to Dose Level -1 for 1 st episode and Dose Level -2 for 2 nd episode. Consider Prophylactic G-CSF after 1 st episode	Reduce to Dose Level -1 for 1 st episode and Dose Level -2 for 2 nd episode. Consider Prophylactic G-CSF after 1 st episode.
Grade 3/4 nausea, vomiting despite standard supportive care, or grade 3/4 Stomatitis	Dose Level -1 for 1 st episode and Dose Level -2 for 2 nd episode.	Dose Level -1 for 1 st episode and Dose Level -2 for 2 nd episode.
Grade 4 Thombocytopenia	Dose Level -1 for 1 st episode and Dose Level -2 for 2 nd episode.	Dose Level -1 for 1 st episode and Dose Level -2 for 2 nd episode.
Bilirubin $> 1.5 \times \text{ULN}$ with increased ALT above ULN	No Change	Hold until recovery; then reduce to Dose Level -1 for 1 st episode and Dose Level -2 for 2 nd episode.
ALT $> 5 \times \text{ULN}$ with Bilirubin $< 1.5 \times \text{ULN}$	No Change	Reduce to Dose Level -1 for 1 st episode and Dose Level -2 for 2 nd episode.
Grade 2 Neuropathy	No Change	Reduce to Dose Level -1.
Grade 3/4 Neuropathy	No Change	Hold until recovery to Grade 2. Reduce to Dose Level -2.
Any other Grade 3/4 toxicity	Discuss with AbbVie medical monitor	Discuss with AbbVie medical monitor

Appendix E. RECIST Version 1.1 for Tumor Response (PFS)

Response criteria will be assessed using RECIST version 1.1. Changes in the measurable lesions over the course of therapy must be evaluated using the criteria listed below.

Eligibility

Subjects with measurable disease at baseline can have objective tumor response evaluated by RECIST version 1.1. Measurable disease is defined by the presence of at least one measurable lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology if possible.

Measurability

Measurable Lesions	Lesions accurately measured in at least one dimension with a minimum size of: <ul style="list-style-type: none">• Longest diameter \geq 10 mm (CT scan slice thickness no greater than 5 mm)• 10 mm caliper measurement by clinical exam
Non-Measurable Lesions	All other lesions, including small lesions (longest diameter < 10 mm) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung and also abdominal masses that are not confirmed and followed by imaging techniques.
Measurable Malignant Lymph Nodes	To be considered pathologically enlarged and measurable, a lymph node must be \geq 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.
Non-Measurable Malignant Lymph Nodes	Pathological lymph nodes with \geq 10 to < 15 mm short axis.

**Special Considerations
Regarding Lesion
Measurability**

Bone lesions

Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as MRI/CT can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.

Blastic bone lesions are non-measurable.

Cystic lesions

Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non measurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above.

However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with prior local treatment

Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion.

All measurements should be taken and recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as closely as possible to the beginning of treatment and not more than 28 days before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.

Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥ 10 mm diameter as assessed using calipers. For

the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is recommended.

Methods of Measurement

Conventional CT should be performed with cuts of 5 mm or less in slice thickness contiguously. This applies to tumors of the chest and abdomen. A scale should be incorporated into all radiographic measurements. MRI can be performed if required by local law, but should have sponsor approval.

If prior to enrollment, it is known a subject is not able to undergo CT scans with IV contrast due to allergy or renal insufficiency, the decision as to whether a non-contrast CT or MRI should be used to evaluate the subject at baseline and follow-up should be guided by the tumor type under investigation and the anatomic location of the disease. For subjects who develop contraindications to contrast after baseline contrast CT is done, the decision as to whether non-contrast CT or MRI should be made based upon discussion with the AbbVie medical monitor.

For accurate objective response evaluation, ultrasound (US) should not be used to measure tumor lesions.

The utilization of endoscopy and laparoscopy for objective tumor evaluation is not advised. However, such techniques can be useful in confirming complete pathological response when biopsies are obtained.

Cytology and histology can be used to differentiate between partial response (PR) and complete response (CR) in rare cases.

Baseline Documentation of "Target" and "Non-Target" Lesions

All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in

addition should be those that lend themselves to reproducible repeated measurements. Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion.

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm \times 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥ 10 mm but < 15 mm) should be considered non-target lesions. Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed.

A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum LD will be used as reference by which to characterize the objective tumor response.

All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence (stable, increasing or decreasing) or absence of each should be noted throughout follow-up.

Evaluation of Target Lesions

Complete Response (CR):

The disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.

Partial Response (PR):

At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD):

At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started (baseline or after) or the appearance of one or more new lesions. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.

Stable Disease (SD):

Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started (baseline or after).

Assessment of Target Lesions:

Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the 'sum' of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm. For PR, SD and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

All lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (< 5 mm). However, sometimes target lesions or lymph nodes become too small to measure. If it is in the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present, but too small to measure, a default value of 5 mm should be assigned (as derived from the 5 mm CT slice thickness). The measurement of these lesions is potentially non-reproducible; therefore providing this default value will prevent false responses or progression based upon measurement error.

Evaluation of Non-Target Lesions

Complete Response (CR):

The disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (< 10 mm short axis).

Non-CR/Non-PD:

Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD):

Unequivocal progression of existing non-target lesions.

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

New Lesions

The appearance of new malignant lesions denotes disease progression. While there are no specific criteria for the identification of new radiographic lesions, the findings of a new lesion should be unequivocal; i.e., not attributable to differences in scanning technique, timing of scanning, phase of contrast administration, change in imaging modality or finding thought to represent something other than tumor (e.g., some 'new' bone lesions may be simply healing or flare of pre-existing lesions). A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is the patient who has visceral disease at baseline and while on study has a CT or MRI brain ordered which reveals metastases. The patient's brain metastases are considered evidence of progressive disease even if he/she did not have brain imaging at baseline.

If a new lesion is equivocal (e.g., too small to measure), continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is a new lesion, then progression should be declared using the date of the initial scan.

Appendix F. Protocol Amendment: List of Changes

The summary of changes is listed in Section 1.1.

Specific Protocol Changes:

Section 1.0 Title Page

"Sponsor/Emergency Contact:" previously read:

Sponsor/Emergency
Contact:

[REDACTED]

Phone:
Fax:

[REDACTED]

1 North Waukegan Road
North Chicago, IL 60064

Has been changed to read:

Sponsor/Emergency
Contact:

[REDACTED]

Phone:
Fax:

[REDACTED]

AbbVie
1 North Waukegan Road
North Chicago, IL 60064

Section 1.2 Synopsis

Previously read:

AbbVie Inc.	Protocol Number: M14-360
Name of Study Drug: Veliparib/ABT-888	Phase of Development: 1/2
Name of Active Ingredient: Not Applicable	Date of Protocol Synopsis: 29 September 2016
Protocol Title: A Phase 1 Dose Escalation and Phase 2 Randomized, Placebo-Controlled Study of the Efficacy and Tolerability of Veliparib in Combination with Paclitaxel/Carboplatin-Based Chemoradiotherapy Followed by Veliparib and Paclitaxel/Carboplatin Consolidation in Subjects with Stage III Non-Small Cell Lung Cancer (NSCLC)	

Objective(s):

The primary objectives of the study are to establish the recommended Phase 2 dose (RPTD) of veliparib in combination with concurrent Paclitaxel/Carboplatin-based chemoradiotherapy (Phase 1 portion) and to assess whether the addition of oral veliparib versus placebo to Paclitaxel/Carboplatin-based chemoradiotherapy with Paclitaxel/Carboplatin consolidation will improve progression-free survival (PFS) in patients with Stage III non-small cell lung cancer (Phase 2 portion).

The secondary objectives of the study are to assess overall survival (OS), objective response rate (ORR), duration of overall response (DOR), safety and tolerability of veliparib versus placebo added to standard therapy (Phase 2 portion).

The tertiary objectives are to assess Quality of Life (QoL) (Phase 2 portion) and ECOG performance status. In addition, biomarkers including, but not limited to, defects in DNA-repair genes will be assessed in correlation with safety and efficacy data.

Investigator(s): Multicenter

Study Site(s): Approximately 50 – 75

Study Population: Subjects with Stage III NSCLC suitable for definitive chemoradiotherapy (CRT) who have not received prior therapy for NSCLC

Number of Subjects to be Enrolled: Approximately 30 in the dose escalation portion and approximately 156 in the randomized portion of the study

Methodology:

This two-phase study consists of 1) dose-escalation of veliparib to determine an RPTD for combination with concurrent paclitaxel/carboplatin-based CRT; and followed by 2) a randomized, double-blinded study to determine whether veliparib improves outcome relative to placebo when added to Paclitaxel/Carboplatin-based CRT followed by consolidation Paclitaxel/Carboplatin in subjects with previously untreated Stage III NSCLC.

In the dose escalation phase of the study, subjects will receive veliparib in combination with carboplatin AUC 2+ paclitaxel 45 mg/m² + thoracic radiotherapy. Radiation delivery will be over no more than 9 weeks by 3-dimensional conformal radiotherapy or intensity modulated radiotherapy (IMRT), and the total dose will be 60 – 63 Gy. The first cohort of at least 3 – 6 subjects will receive veliparib 60 mg BID throughout CRT. Based on tolerability, subsequent cohorts will receive doses of veliparib from 40 mg BID to 240 mg BID. The consolidation dose of veliparib will be 120 mg BID + carboplatin AUC 6 + paclitaxel 200 mg/m² for up to two 21-day cycles.

Methodology (Continued):

Dose limiting toxicity (DLT) events will be collected for each dosing cohort until a new dosing cohort is opened or until the recommended Phase 2 dose is identified. A minimum of 3 subjects will be enrolled in each cohort. Additional eligible subjects may be enrolled at the current dose level at the discretion of the Investigators and the AbbVie Medical Monitor. From each cohort, subjects will be entered into the DLT assessment group of the intended cohort size in order of treatment. Subjects considered evaluable for DLTs will be those that receive treatment through 1 cycle or have AEs meeting DLT criteria. If a subject in the DLT assessment group becomes unevaluable, the subject will be replaced by the next-treated subject in the cohort. The DLT period for each subject will be from start of veliparib dosing through 28 days following completion of CRT or until consolidation chemotherapy is initiated, and the DLT period for all patients at each dose level will end upon initiation of next dose level.

Dose limiting toxicities are the following events that are considered by the investigator group to be related to treatment:

1. Radiation induced Grade 3 or greater cardiac toxicity (e.g., myocarditis, pericarditis, heart failure, ventricular dysfunction, myocardial infarction).
2. Radiation induced myelopathy/myelitis (does not include L'Hermitte's syndrome).
3. Radiation-related pneumonitis resulting in delay in radiotherapy, chemotherapy (CRT or consolidation) or veliparib of more than 3 weeks or early discontinuation of RT (total dose < 50 Gy).
4. G4 or greater esophagitis or esophagitis, dysphagia, and odynophagia requiring treatment interruption of > 7 days despite medical management.
5. G2 or greater seizure.
6. Grade 4 or greater neutropenia for > 7 days or neutropenic fever (defined as ANC < 500 and a temperature of 38.5°C or above).
7. Grade 4 or greater thrombocytopenia.
8. Grade 4 diarrhea or nausea/vomiting despite appropriate antiemetic therapy lasting > 48 hours.
9. Any other toxicity resulting in delay in radiotherapy, chemotherapy, or veliparib of more than 14 days or early discontinuation of RT (total dose < 50 Gy).
10. All other non-hematologic toxicities of Grade 3 or greater, with the following exceptions:
 - a. Anorexia
 - b. Fatigue
 - c. Grade 3 infection
 - d. Grade 3 AST/ALT elevations \leq 7 days
 - e. Infusion reactions. Patients with Grade 3 or worse infusion reactions will be removed from study and replaced and will not be considered evaluable for DLT
 - f. Grade 3 or 4 lymphopenia
 - g. Grade 3 or 4 electrolyte abnormalities that are corrected to Grade 2 or less in less than 48 hours

Following the dose escalation portion of the trial, the RPTD will be determined by the sponsor, and at the discretion of the sponsor, the Phase 2 portion of the study will begin with patient randomization in a 1:1:1 ratio to the treatment arms as follows:

- A. Concurrent paclitaxel/carboplatin/radiotherapy/veliparib followed by consolidation paclitaxel/carboplatin/veliparib

Methodology (Continued):

- B. Concurrent paclitaxel/carboplatin/radiotherapy/veliparib followed by consolidation paclitaxel/carboplatin/placebo
- C. Concurrent paclitaxel/carboplatin/radiotherapy/placebo followed by consolidation paclitaxel/carboplatin/placebo

Subject randomization will be stratified by tumor volume (≤ 90 versus > 90 cm³) and smoking history (current smoker versus former smoker versus never smoked). Screening procedures, QoL assessment, and baseline radiographic tumor assessments will be performed within 28 days prior to randomization.

Concurrent chemoradiotherapy (CRT) will consist of radiotherapy (RT) using either 3D conformal RT or IMRT plus paclitaxel, (45 mg/m² as a 60 minute infusion), immediately followed by carboplatin, (AUC 2 mg/mL/min as a 30 minute infusion) weekly beginning on Day 1 of radiotherapy. Veliparib (or placebo), will be administered continuously beginning 3 days prior to RT through one day after RT completion.

Consolidation chemotherapy will begin no more than 8 weeks following RT. Subjects who require > 8 weeks to recover from toxicities resulting from CRT should not receive consolidation chemotherapy. Consolidation chemotherapy will consist of paclitaxel, (200 mg/m² as a 3 hour infusion, immediately followed by carboplatin, AUC 6 mg/mL/min as a 30 minute infusion) on Day 1 of each 21-day cycle for up to 2 cycles. Veliparib (or Placebo), 120 mg BID, will begin on Day -2 (2 days prior to the start of paclitaxel/carboplatin infusion) and will continue through Day 5 of each 21-day cycle.

Subjects who experience toxicities due to carboplatin, paclitaxel, RT, or veliparib/placebo may require a delay in the dosing schedule or a dose modification.

Radiographic tumor assessments will be conducted at baseline, prior to consolidation chemotherapy, at 24 weeks after start of treatment, every 8 weeks until one year after beginning therapy, then every 12 weeks. Beginning 12 weeks after randomization, progression will be determined based on Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1. Progression prior to that time will be determined by the Investigator. A QoL assessment as measured by the EORTC QLQ-C15-PAL and the companion symptom module EORTC QLQ-LC13 will be performed at Screening, prior to consolidation chemotherapy, at 24 weeks after start of treatment, every 8 weeks until one year after beginning therapy and at the final visit.

After completion of protocol therapy, subjects will be observed without further therapy until progression. The visit at which an investigator identifies disease progression or at which a subject meets other criteria for study discontinuation will be considered the final visit. All subjects with a final visit < 30 days after the last dose of drug will have one Follow-Up Visit approximately 30 days after the Final Visit.

If a subject is discontinued from the study with an ongoing adverse event or an unresolved clinically significant laboratory result, the site will attempt to provide follow-up until a satisfactory clinical resolution of the laboratory results or adverse event is achieved.

To ensure subject safety, an internal data monitoring committee (DMC) will review un-blinded safety data when approximately 45 subjects in the Phase 2 portion of the study have completed CRT, reached an event of disease progression or death, or discontinued the study.

Diagnosis: Stage III NSCLC

Diagnosis and Main Criteria for Inclusion/Exclusion:

Main Inclusion (Phase 1 and Randomized Phase 2):

- Subject must be ≥ 18 years of age;
- Subject must have histologically or cytologically confirmed Stage III NSCLC. When pleural fluid is visible on the CT scan or on a chest x-ray, a thoracentesis is required to confirm that the pleural fluid is serous AND cytologically negative. Effusions that are minimal (i.e., not visible on chest x-ray) or that are too small to safely tap are exempted from the requirement for thoracentesis.
- Subjects in the randomized portion of the study must have measurable disease per RECIST version 1.1 criteria;
- Subjects must have V20 (volume of lung to receive 20 Gy radiotherapy according to simulation) $< 35\%$;
- Subject must have an Eastern Cooperative Oncology Group (ECOG) performance score of 0 – 1;
- Subject must have adequate hematologic, renal, hepatic, and lung function as follows:
 - Bone marrow: Absolute Neutrophil count (ANC) $\geq 1,500/\mu\text{L}$; Platelets $\geq 100,000/\text{mm}^3$; Hemoglobin ≥ 9.0 g/dL (without transfusion);
 - Renal function: calculated creatinine clearance ≥ 50 mL/min by the Cockcroft-Gault formula;
 - Hepatic function and enzymes: aspartate aminotransferase (AST) and alanine aminotransferase (ALT) $\leq 2.5 \times$ the upper limit of normal (ULN) of institution's normal range; Bilirubin $\leq 1.5 \times$ ULN; subjects with Gilbert's syndrome may have a bilirubin $\geq 1.5 \times$ ULN of central laboratory normal range;
 - Pulmonary function tests (PFTs) including FEV1 within 12 weeks prior to randomization; for FEV1, the best value obtained pre- or post-bronchodilator must be ≥ 1.2 liters/second and/or $\geq 50\%$ predicted.
- Female subjects of childbearing potential (i.e., those who are not postmenopausal for at least 1 year or surgically sterile by bilateral tubal ligation, bilateral oophorectomy or hysterectomy) and their male partner should practice at least one of the methods of birth control listed below for at least 6 months after treatment with chemotherapy. Male subjects and their female partners of childbearing potential should practice at least one of the methods of birth control listed below for at least 6 months after treatment with chemotherapy:
 - Total abstinence from sexual intercourse (if it is the subject's preferred and usual lifestyle; beginning a minimum one complete menstrual cycle prior to study drug administration and to extend 6 months after treatment);
 - Vasectomized subject or partner(s), vasectomy (males);
 - Intrauterine device (females);
 - Double-barrier method (condoms, contraceptive sponge, diaphragm or vaginal ring with spermicidal jellies or creams; both males and females);
 - Hormonal contraceptives (oral, parenteral or transdermal) for at least 90 days prior to study drug administration (females). If hormonal contraceptives are used, the subject and her partner should also use a single barrier method.
- Subject must voluntarily sign and date an informed consent, approved by an Independent Ethics Committee (IEC)/Institutional Review Board (IRB), prior to the initiation of and Screening for study-specific procedures.

Diagnosis and Main Criteria for Inclusion/Exclusion (Continued):

Main Exclusion:

- Subject with prior chemotherapy or radiotherapy for current NSCLC; subjects curatively treated for past early stage NSCLC greater than 3 years ago may be included;
- Subject with prior exposure to PARP inhibitors;
- Subjects with known hypersensitivity to carboplatin, paclitaxel, or formulations containing polyethoxylated castor oil (Cremophor);
- Subject with prior mediastinal or thoracic radiotherapy. Prior tangential RT to prior breast cancer is acceptable;
- Subject with major surgery in the 4 weeks prior to randomization (VATS and/or mediastinoscopy is not considered major surgery);
- Subject with a previous or concurrent malignancy except for treated basal cell or squamous cell skin cancer, in situ cervical cancer, or other cancer for which the patient received potentially curative treatment and has been disease-free for 3 years or is considered cured by the investigator if has been disease-free for less than 3 years;
- Any medical condition, which in the opinion of the study investigator, places the subject at an unacceptably high risk for toxicities, or any subject circumstance that prohibits trial participation according to local law;
- Subject is pregnant or lactating;
- Subject with sensory peripheral neuropathy of \geq Grade 2 at baseline;
- Subject is unable to swallow medication;
- Subjects with prior history of seizure within the prior 12 months.

Investigational Product: Veliparib (ABT-888) or Placebo

Dose(s): 60 – 240 mg BID (concurrent chemoradiotherapy); 120 mg BID (consolidation)

Mode of Administration: Oral

Reference Therapy: Carboplatin

Dose(s): AUC 2 mg/mL/min (concurrent chemoradiotherapy);
AUC 6 mg/mL/min (consolidation)

Mode of Administration: Intravenous

Duration of Treatment:

Subjects without clinical progression of disease and with tolerable side effects should continue to receive treatment until completion of all prescribed cycles (chemoradiotherapy plus 2 cycles of consolidation chemotherapy).

Criteria for Evaluation:

Efficacy:

Progression-free survival (PFS) will be derived according to radiographic progression per RECIST version 1.1 (beginning with the second scan after completion of CRT) or death. Radiographic tumor assessments for response will be conducted at baseline, prior to consolidation chemotherapy, at 24 weeks after start of treatment, every 8 weeks until one year after beginning therapy, then every 12 weeks until radiographic progression or death. Subjects who require additional therapy, withdraw consent, or are lost to follow-up prior to radiographic progression will be censored at that time for the analysis of PFS.

Overall survival (OS) will be determined by the Investigator until radiographic progression. After radiographic progression, survival information will be collected via the electronic CRF at 8-week intervals (or as requested by sponsor to support data analysis).

Objective response rate (ORR), and duration of overall response (DOR) will be derived per RECIST version 1.1. Radiographic tumor assessments for response will be conducted at baseline, prior to consolidation chemotherapy, at 24 weeks after start of treatment, every 8 weeks until one year after beginning therapy, then every 12 weeks until radiographic progression or death. Subjects who require additional therapy, withdraw consent, or are lost to follow-up prior to radiographic progression will be censored at that time for the analysis of DOR.

ECOG performance status will be determined by the Investigator at each assessment. A quality of life assessment as measured by the EORTC QLQ-C15-PAL and the companion symptom module EORTC QLQ-LC13 will be performed at screening, prior to consolidation chemotherapy, at 24 weeks after start of treatment, every 8 weeks until one year after beginning therapy and at the final visit.

Pharmacokinetic:

Blood samples for veliparib assay will be collected for the determination of pharmacokinetic parameters of veliparib such as apparent oral clearance (CL/F) and volume of distribution (V/F).

Pharmacodynamic:

Research to find biomarkers that may serve as surrogates for clinical endpoints in future veliparib studies or that may be predictive of veliparib activity will be conducted. Serum, plasma, blood and archived tissue samples (optional) will be collected at designated time points throughout the study. Study-specific core biopsies are requested but are not required.

Safety:

Adverse events, laboratory profiles, physical examinations and vital signs will be assessed throughout the study. Results will be tabulated for each subject and summary statistics will be computed for each sampling time and each parameter.

Statistical Methods:

The following efficacy endpoint will be analyzed using data obtained from subjects in Phase 1:

Objective Response Rate (ORR)

The proportion of subjects with objective response as assessed by the investigator using RECIST version 1.1 will be calculated for all dosed subjects.

The following efficacy endpoints will be analyzed using data obtained from subjects in Phase 2:

Progression-Free survival (PFS)

Progression-Free Survival will be defined as the number of days from the date of randomization to the date of earliest radiographic disease progression or death. All radiographic disease progression will be included regardless whether the event occurred while the subject was taking study drug or had previously discontinued study drug. If the subject does not experience radiographic disease progression or death, then the data will be censored at the date of the last disease assessment.

Overall Survival (OS)

Overall survival will be defined as the number of days from the date of randomization to the date of death. For subjects who did not die, their data will be censored at the date of last study visit or the last known date to be alive, whichever is later.

Objective Response Rate (ORR)

The proportion of subjects with objective response as assessed by the investigator using RECIST version 1.1 will be evaluated for randomized subjects.

Duration of Overall Response (DOR)

Duration of overall response will be defined as the number of days from the date of first response (CR or PR) to the earliest documentation of radiographic progressive disease or death due to disease progression. If a subject is still responding, then the subject's data will be censored at the date of the subject's last available disease assessment. For subjects who never experience response, the subject's data will not be included in the analysis.

Quality of life (QoL) Measures

Changes and/or percent changes from baseline will be summarized using descriptive statistics for each scheduled post-baseline visit and for the Final Visit for quality of life measures using the EORTC QLQ-C15-PAL and EORTC QLQ-LC13 questionnaires. The QoL will be used as an exploratory endpoint and not tested against pre-specified hypothesis.

Performance Status

Changes and/or percent changes from baseline will be summarized using descriptive statistics for each scheduled post-baseline visit and for the Final Visit for ECOG performance status. Post-baseline measurements more than 30 days after the last dose of study drug will not be included. Subjects that do not have a baseline measurement or do not have any post-baseline measurements will not be included.

Efficacy Analysis:

The primary Phase 2 efficacy analysis will test if concurrent paclitaxel/carboplatin/radiotherapy/veliparib followed by consolidation paclitaxel/carboplatin/veliparib (Arm A) will improve PFS versus concurrent paclitaxel/carboplatin/radiotherapy/placebo followed by consolidation paclitaxel/carboplatin/placebo (Arm C).

Statistical Methods (Continued):

Efficacy Analysis (Continued):

The secondary Phase 2 efficacy analyses will test (in the following order):

- 1) if concurrent paclitaxel/carboplatin/radiotherapy/veliparib followed by consolidation paclitaxel/carboplatin/placebo (Arm B) results in improved Progression-Free survival (PFS) versus Arm C;
- 2a) if Arm A or
- 2b) if Arm B results in improved overall survival (OS) versus Arm C;
- 3a) if Arm A or
- 3b) if Arm B results in improved overall response rate (ORR) versus Arm C;
- 4a) if Arm A or
- 4b) if Arm B results in improved duration of overall response (DOR) versus Arm C.

Sample Size:

Assuming a hazard ratio of 0.6 for Arm A (Concurrent paclitaxel/carboplatin/radiotherapy/veliparib followed by consolidation paclitaxel/carboplatin/veliparib) versus Arm C (Concurrent paclitaxel/carboplatin/radiotherapy/placebo followed by consolidation paclitaxel/carboplatin/placebo), a total of 71 PFS events in Arm A and Arm C combined will provide an expected 95% confidence interval of 0.38 to 0.96 for the estimated hazard ratio. Assuming a hazard ratio of 0.75 for Arm B (Concurrent paclitaxel/carboplatin/radiotherapy/veliparib followed by consolidation paclitaxel/carboplatin/placebo) versus Arm C, a total of 107 PFS events will be observed across all three arms at the time when 71 PFS events are observed for Arm A and Arm C combined. A total of approximately 156 subjects (52 subjects per treatment arm) will be enrolled into the Phase 2 portion of study to obtain the 107 PFS events.

Has been changed to read:

AbbVie Inc.	Protocol Number: M14-360
Name of Study Drug: Veliparib/ABT-888	Phase of Development: 1/2
Name of Active Ingredient: Not Applicable	Date of Protocol Synopsis: 15 August 2017
Protocol Title: A Phase 1 Dose Escalation and Phase 2 Randomized, Placebo-Controlled Study of the Efficacy and Tolerability of Veliparib in Combination with Paclitaxel/Carboplatin-Based Chemoradiotherapy Followed by Veliparib and Paclitaxel/Carboplatin Consolidation in Subjects with Stage III Non-Small Cell Lung Cancer (NSCLC)	
Objective(s): The primary objectives of the study are to establish the recommended Phase 2 dose (RPTD) of veliparib in combination with concurrent Paclitaxel/Carboplatin-based chemoradiotherapy and consolidation with Paclitaxel/Carboplatin-based chemotherapy (Phase 1 portion) and to assess whether the addition of oral veliparib versus placebo to Paclitaxel/Carboplatin-based chemoradiotherapy with Paclitaxel/Carboplatin consolidation will improve progression-free survival (PFS) in patients with Stage III non-small cell lung cancer (Phase 2 portion). The secondary objectives of the study are to assess overall survival (OS), objective response rate (ORR), duration of overall response (DOR), safety and tolerability of veliparib versus placebo added to standard therapy (Phase 2 portion). The tertiary objectives are to assess Quality of Life (QoL) (Phase 2 portion) and ECOG performance status. In addition, biomarkers including, but not limited to, defects in DNA-repair genes will be assessed in correlation with safety and efficacy data.	
Investigator(s): Multicenter	
Study Site(s): Approximately 50 – 75	
Study Population: Subjects with Stage III NSCLC suitable for definitive chemoradiotherapy (CRT) who have not received prior therapy for NSCLC	
Number of Subjects to be Enrolled: Approximately 50 in the dose escalation portion and approximately 156 in the randomized portion of the study.	
Methodology: This two-phase study consists of 1) dose-escalation of veliparib to determine an RPTD for combination with concurrent paclitaxel/carboplatin-based CRT; and followed by 2) a randomized, double-blinded study to determine whether veliparib improves outcome relative to placebo when added to Paclitaxel/Carboplatin-based CRT followed by consolidation Paclitaxel/Carboplatin in subjects with previously untreated Stage III NSCLC.	

Methodology (Continued):

In the dose escalation phase of the study, subjects will receive veliparib in combination with carboplatin AUC 2+ paclitaxel 45 mg/m² + thoracic radiotherapy. Radiation delivery will be over no more than 9 weeks by 3-dimensional conformal radiotherapy or intensity modulated radiotherapy (IMRT), and the total dose will be 60 – 63 Gy. The first cohort of at least 3 – 6 subjects will receive veliparib 60 mg BID throughout CRT. Based on tolerability, subsequent cohorts will receive doses of veliparib from 40 mg BID to 240 mg BID. As the CRT RPTD dose is explored (Cohorts 1 – 5), the consolidation RPTD of veliparib will be 120 mg BID + carboplatin AUC 6 + paclitaxel 200 mg/m² for up to two 21-day cycles. The consolidation dose of veliparib in Cohort 6 will be 240 mg BID + carboplatin AUC 6 + paclitaxel 200 mg/m² for up to two 21-day cycles.

Dose limiting toxicity (DLT) events will be collected for each dosing cohort until a new dosing cohort is opened or until the recommended Phase 2 dose is identified. A minimum of 3 subjects will be enrolled in each cohort. Additional eligible subjects may be enrolled at the current dose level at the discretion of the Investigators and the AbbVie Medical Monitor. From each cohort, subjects will be entered into the DLT assessment group of the intended cohort size in order of treatment. For Cohorts 1 – 5, subjects considered evaluable for DLTs will be those that receive treatment through 1 cycle of CRT or have AEs meeting DLT criteria. For Cohort 6, subjects considered evaluable for DLTs will be those that receive treatment through 1 cycle of consolidation chemotherapy. If a subject in the DLT assessment group becomes unevaluable, the subject will be replaced by the next-treated subject in the cohort. The DLT period for each subject participating in Cohorts 1 – 5 will be from start of veliparib dosing through 28 days following completion of CRT or until consolidation chemotherapy is initiated. The DLT period for each subject participating in Cohort 6, will be from the start of Cycle 1 of the consolidation chemotherapy through the start of the Cycle 2 of the consolidation therapy or treatment discontinuation. The DLT period for all subjects at each dose level will end upon initiation of next dose level.

Dose limiting toxicities are the following events that are considered by the investigator group to be related to treatment:

1. Radiation induced Grade 3 or greater cardiac toxicity (e.g., myocarditis, pericarditis, heart failure, ventricular dysfunction, myocardial infarction).
2. Radiation induced myelopathy/myelitis (does not include L'Hermitte's syndrome).
3. Radiation-related pneumonitis resulting in delay in radiotherapy, chemotherapy (CRT or consolidation) or veliparib of more than 3 weeks or early discontinuation of RT (total dose < 50 Gy).
4. G4 or greater esophagitis or esophagitis, dysphagia, and odynophagia requiring treatment interruption of > 7 days despite medical management.
5. G2 or greater seizure.
6. Grade 4 or greater neutropenia for > 7 days or neutropenic fever (defined as ANC < 500 and a temperature of 38.5°C or above).
7. Grade 4 or greater thrombocytopenia.
8. Grade 4 diarrhea or nausea/vomiting despite appropriate antiemetic therapy lasting > 48 hours.
9. Any other toxicity resulting in delay in radiotherapy, chemotherapy, or veliparib of more than 14 days or early discontinuation of RT (total dose < 50 Gy).

Methodology (Continued):

10. All other non-hematologic toxicities of Grade 3 or greater, with the following exceptions:

- a. Anorexia
- b. Fatigue
- c. Grade 3 infection
- d. Grade 3 AST/ALT elevations ≤ 7 days
- e. Infusion reactions. Patients with Grade 3 or worse infusion reactions will be removed from study and replaced and will not be considered evaluable for DLT
- f. Grade 3 or 4 lymphopenia
- g. Grade 3 or 4 electrolyte abnormalities that are corrected to Grade 2 or less in less than 48 hours

For Cohort 6, if 3 or fewer subjects were able to take Cycle 2 of consolidation chemotherapy, the reason of dose reduction and treatment discontinuation will be reviewed as part of consideration to determine MTD/RPTD of veliparib for the consolidation phase.

Following the dose escalation portion of the trial, the RPTD will be determined by the sponsor, and at the discretion of the sponsor, the Phase 2 portion of the study will begin with patient randomization in a 1:1:1 ratio to the treatment arms as follows:

- A. Concurrent paclitaxel/carboplatin/radiotherapy/veliparib followed by consolidation paclitaxel/carboplatin/veliparib
- B. Concurrent paclitaxel/carboplatin/radiotherapy/veliparib followed by consolidation paclitaxel/carboplatin/placebo
- C. Concurrent paclitaxel/carboplatin/radiotherapy/placebo followed by consolidation paclitaxel/carboplatin/placebo

Subject randomization will be stratified by tumor volume (≤ 90 versus > 90 cm³) and smoking history (current smoker versus former smoker versus never smoked). Screening procedures, QoL assessment, and baseline radiographic tumor assessments will be performed within 28 days prior to randomization.

Concurrent chemoradiotherapy (CRT) will consist of radiotherapy (RT) using either 3D conformal RT or IMRT plus paclitaxel, (45 mg/m² as a 60 minute infusion), immediately followed by carboplatin, (AUC 2 mg/mL/min as a 30 minute infusion) weekly beginning on Day 1 of radiotherapy. Veliparib (or placebo), will be administered continuously beginning 3 days prior to RT through one day after RT completion.

Consolidation chemotherapy will begin no more than 8 weeks following RT. Subjects who require > 8 weeks to recover from toxicities resulting from CRT should not receive consolidation chemotherapy. Consolidation chemotherapy will consist of paclitaxel, (200 mg/m² as a 3 hour infusion, immediately followed by carboplatin, AUC 6 mg/mL/min as a 30 minute infusion) on Day 1 of each 21-day cycle for up to 2 cycles. Veliparib (or Placebo in the Phase 2 portion), 120 mg (Cohorts 1 – 5) or 240 mg (Cohort 6) BID, will begin on Day -2 (2 days prior to the start of paclitaxel/carboplatin infusion) and will continue through Day 5 of each 21-day cycle.

Subjects who experience toxicities due to carboplatin, paclitaxel, RT, or veliparib/placebo may require a delay in the dosing schedule or a dose modification.

Methodology (Continued):

Radiographic tumor assessments will be conducted at baseline, prior to consolidation chemotherapy, at 24 weeks after start of treatment, every 8 weeks until one year after beginning therapy, then every 12 weeks. Beginning 12 weeks after randomization, progression will be determined based on Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1. Progression prior to that time will be determined by the Investigator. A QoL assessment as measured by the EORTC QLQ-C15-PAL and the companion symptom module EORTC QLQ-LC13 will be performed at Screening, prior to consolidation chemotherapy, at 24 weeks after start of treatment, every 8 weeks until one year after beginning therapy and at the final visit.

After completion of protocol therapy, subjects will be observed without further therapy until progression. The visit at which an investigator identifies disease progression or at which a subject meets other criteria for study discontinuation will be considered the final visit. All subjects with a final visit < 30 days after the last dose of drug will have one Follow-Up Visit approximately 30 days after the Final Visit.

If a subject is discontinued from the study with an ongoing adverse event or an unresolved clinically significant laboratory result, the site will attempt to provide follow-up until a satisfactory clinical resolution of the laboratory results or adverse event is achieved.

To ensure subject safety, an internal data monitoring committee (DMC) will review un-blinded safety data when approximately 45 subjects in the Phase 2 portion of the study have completed CRT, reached an event of disease progression or death, or discontinued the study.

Diagnosis: Stage III NSCLC

Diagnosis and Main Criteria for Inclusion/Exclusion:

Main Inclusion (Phase 1 and Randomized Phase 2):

- Subject must be \geq 18 years of age;
- Subject must have histologically or cytologically confirmed Stage III NSCLC. When pleural fluid is visible on the CT scan or on a chest x-ray, a thoracentesis is required to confirm that the pleural fluid is serous AND cytologically negative. Effusions that are minimal (i.e., not visible on chest x-ray) or that are too small to safely tap are exempted from the requirement for thoracentesis.
- Subjects in the randomized portion of the study must have measurable disease per RECIST version 1.1 criteria;
- Subject must consent to provide archived tissue or cytology sample of NSCLC lesion for analysis;
- Subjects must have V20 (volume of lung to receive 20 Gy radiotherapy according to simulation) < 35%;
- Subject must have an Eastern Cooperative Oncology Group (ECOG) performance score of 0 – 1;

Diagnosis and Main Criteria for Inclusion/Exclusion (Continued):

Main Inclusion (Continued):

- Subject must have adequate hematologic, renal, hepatic, and lung function as follows:
 - Bone marrow: Absolute Neutrophil count (ANC) $\geq 1,500/\mu\text{L}$; Platelets $\geq 100,000/\text{mm}^3$; Hemoglobin ≥ 9.0 g/dL (without transfusion);
 - Renal function: calculated creatinine clearance ≥ 50 mL/min by the Cockcroft-Gault formula;
 - Hepatic function and enzymes: aspartate aminotransferase (AST) and alanine aminotransferase (ALT) $\leq 2.5 \times$ the upper limit of normal (ULN) of institution's normal range; Bilirubin $\leq 1.5 \times$ ULN; subjects with Gilbert's syndrome may have a bilirubin $\geq 1.5 \times$ ULN of central laboratory normal range;
 - Pulmonary function tests (PFTs) including FEV1 within 12 weeks prior to randomization; for FEV1, the best value obtained pre- or post-bronchodilator must be ≥ 1.2 liters/second and/or $\geq 50\%$ predicted.
- Female subjects of childbearing potential (i.e., those who are not postmenopausal for at least 1 year or surgically sterile by bilateral tubal ligation, bilateral oophorectomy or hysterectomy) and their male partner should practice at least one of the methods of birth control listed below for at least 6 months after treatment with chemotherapy. Male subjects and their female partners of childbearing potential should practice at least one of the methods of birth control listed below for at least 6 months after treatment with chemotherapy:
 - Total abstinence from sexual intercourse (if it is the subject's preferred and usual lifestyle; beginning a minimum one complete menstrual cycle prior to study drug administration and to extend 6 months after treatment);
 - Vasectomized subject or partner(s), vasectomy (males);
 - Intrauterine device (females);
 - Double-barrier method (condoms, contraceptive sponge, diaphragm or vaginal ring with spermicidal jellies or creams; both males and females);
 - Hormonal contraceptives (oral, parenteral or transdermal) for at least 90 days prior to study drug administration (females). If hormonal contraceptives are used, the subject and her partner should also use a single barrier method.
 - Subject must voluntarily sign and date an informed consent, approved by an Independent Ethics Committee (IEC)/Institutional Review Board (IRB), prior to the initiation of and Screening for study-specific procedures.

Diagnosis and Main Criteria for Inclusion/Exclusion (Continued):

Main Exclusion:

- Subject with prior chemotherapy or radiotherapy for current NSCLC; subjects curatively treated for past early stage NSCLC greater than 3 years ago may be included;
- Subject with prior exposure to PARP inhibitors;
- Subjects with known hypersensitivity to carboplatin, paclitaxel, or formulations containing polyethoxylated castor oil (Cremophor);
- Subject with prior mediastinal or thoracic radiotherapy. Prior tangential RT to prior breast cancer is acceptable;
- Subject with major surgery in the 4 weeks prior to randomization (VATS and/or mediastinoscopy is not considered major surgery);
- Subject with a previous or concurrent malignancy except for treated basal cell or squamous cell skin cancer, in situ cervical cancer, or other cancer for which the patient received potentially curative treatment and has been disease-free for 3 years or is considered cured by the investigator if has been disease-free for less than 3 years;
- Any medical condition, which in the opinion of the study investigator, places the subject at an unacceptably high risk for toxicities, or any subject circumstance that prohibits trial participation according to local law;
- Subject is pregnant or lactating;
- Subject with sensory peripheral neuropathy of \geq Grade 2 at baseline;
- Subject is unable to swallow medication;
- Subjects with prior history of seizure within the prior 12 months.

Investigational Product:	Veliparib (ABT-888) or Placebo
Dose(s):	60 – 240 mg BID (concurrent chemoradiotherapy); 120 – 240 mg BID (consolidation)
Mode of Administration:	Oral

Reference Therapy:	Carboplatin
Dose(s):	AUC 2 mg/mL/min (concurrent chemoradiotherapy); AUC 6 mg/mL/min (consolidation)
Mode of Administration:	Intravenous

Reference Therapy:	Paclitaxel
Dose(s):	45 mg/m ² (concurrent chemoradiotherapy); 200 mg/m ² (consolidation)
Mode of Administration:	Intravenous

Duration of Treatment:

Subjects without clinical progression of disease and with tolerable side effects should continue to receive treatment until completion of all prescribed cycles (chemoradiotherapy plus 2 cycles of consolidation chemotherapy).

Criteria for Evaluation:

Efficacy:

Progression-free survival (PFS) will be derived according to radiographic progression per RECIST version 1.1 (beginning with the second scan after completion of CRT) or death. Radiographic tumor assessments for response will be conducted at baseline, prior to consolidation chemotherapy, at 24 weeks after start of treatment, every 8 weeks until one year after beginning therapy, then every 12 weeks until radiographic progression or death. Subjects who require additional therapy, withdraw consent, or are lost to follow-up prior to radiographic progression will be censored at that time for the analysis of PFS.

Overall survival (OS) will be determined by the Investigator until radiographic progression. After radiographic progression, survival information will be collected via the electronic CRF at 8-week intervals (or as requested by sponsor to support data analysis).

Objective response rate (ORR), and duration of overall response (DOR) will be derived per RECIST version 1.1. Radiographic tumor assessments for response will be conducted at baseline, prior to consolidation chemotherapy, at 24 weeks after start of treatment, every 8 weeks until one year after beginning therapy, then every 12 weeks until radiographic progression or death. Subjects who require additional therapy, withdraw consent, or are lost to follow-up prior to radiographic progression will be censored at that time for the analysis of DOR.

ECOG performance status will be determined by the Investigator at each assessment. A quality of life assessment as measured by the EORTC QLQ-C15-PAL and the companion symptom module EORTC QLQ-LC13 will be performed at screening, prior to consolidation chemotherapy, at 24 weeks after start of treatment, every 8 weeks until one year after beginning therapy and at the final visit.

Pharmacokinetic:

Blood samples for veliparib assay will be collected for the determination of pharmacokinetic parameters of veliparib such as apparent oral clearance (CL/F) and volume of distribution (V/F).

Pharmacodynamic:

Research to find biomarkers that may serve as surrogates for clinical endpoints in future veliparib studies or that may be predictive of veliparib activity will be conducted. Serum, plasma, blood and archived tissue samples will be collected at designated time points throughout the study. Study-specific core biopsies are requested but are not required.

Safety:

Adverse events, laboratory profiles, physical examinations and vital signs will be assessed throughout the study. Results will be tabulated for each subject and summary statistics will be computed for each sampling time and each parameter.

Statistical Methods:

The following efficacy endpoint will be analyzed using data obtained from subjects in Phase 1:

Objective Response Rate (ORR)

The proportion of subjects with objective response as assessed by the investigator using RECIST version 1.1 will be calculated for all dosed subjects.

The following efficacy endpoints will be analyzed using data obtained from subjects in Phase 2:

Progression-Free survival (PFS)

Progression-Free Survival will be defined as the number of days from the date of randomization to the date of earliest radiographic disease progression or death. All radiographic disease progression will be included regardless whether the event occurred while the subject was taking study drug or had previously discontinued study drug. If the subject does not experience radiographic disease progression or death, then the data will be censored at the date of the last disease assessment.

Overall Survival (OS)

Overall survival will be defined as the number of days from the date of randomization to the date of death. For subjects who did not die, their data will be censored at the date of last study visit or the last known date to be alive, whichever is later.

Objective Response Rate (ORR)

The proportion of subjects with objective response as assessed by the investigator using RECIST version 1.1 will be evaluated for randomized subjects.

Duration of Overall Response (DOR)

Duration of overall response will be defined as the number of days from the date of first response (CR or PR) to the earliest documentation of radiographic progressive disease or death due to disease progression. If a subject is still responding, then the subject's data will be censored at the date of the subject's last available disease assessment. For subjects who never experience response, the subject's data will not be included in the analysis.

Quality of life (QoL) Measures

Changes and/or percent changes from baseline will be summarized using descriptive statistics for each scheduled post-baseline visit and for the Final Visit for quality of life measures using the EORTC QLQ-C15-PAL and EORTC QLQ-LC13 questionnaires. The QoL will be used as an exploratory endpoint and not tested against pre-specified hypothesis.

Performance Status

Changes and/or percent changes from baseline will be summarized using descriptive statistics for each scheduled post-baseline visit and for the Final Visit for ECOG performance status. Post-baseline measurements more than 30 days after the last dose of study drug will not be included. Subjects that do not have a baseline measurement or do not have any post-baseline measurements will not be included.

Efficacy Analysis:

The primary Phase 2 efficacy analysis will test if concurrent paclitaxel/carboplatin/radiotherapy/veliparib followed by consolidation paclitaxel/carboplatin/veliparib (Arm A) will improve PFS versus concurrent paclitaxel/carboplatin/radiotherapy/placebo followed by consolidation paclitaxel/carboplatin/placebo (Arm C).

Statistical Methods (Continued):

Efficacy Analysis (Continued):

The secondary Phase 2 efficacy analyses will test (in the following order):

1) if concurrent paclitaxel/carboplatin/radiotherapy/veliparib followed by consolidation paclitaxel/carboplatin/placebo (Arm B) results in improved Progression-Free survival (PFS) versus Arm C;

2a) if Arm A or

2b) if Arm B results in improved overall survival (OS) versus Arm C;

3a) if Arm A or

3b) if Arm B results in improved overall response rate (ORR) versus Arm C;

4a) if Arm A or

4b) if Arm B results in improved duration of overall response (DOR) versus Arm C.

Sample Size:

Assuming a hazard ratio of 0.6 for Arm A (Concurrent paclitaxel/carboplatin/radiotherapy/veliparib followed by consolidation paclitaxel/carboplatin/veliparib) versus Arm C (Concurrent paclitaxel/carboplatin/radiotherapy/placebo followed by consolidation paclitaxel/carboplatin/placebo), a total of 71 PFS events in Arm A and Arm C combined will provide an expected 95% confidence interval of 0.38 to 0.96 for the estimated hazard ratio. Assuming a hazard ratio of 0.75 for Arm B (Concurrent paclitaxel/carboplatin/radiotherapy/veliparib followed by consolidation paclitaxel/carboplatin/placebo) versus Arm C, a total of 107 PFS events will be observed across all three arms at the time when 71 PFS events are observed for Arm A and Arm C combined. A total of approximately 156 subjects (52 subjects per treatment arm) will be enrolled into the Phase 2 portion of study to obtain the 107 PFS events.

Section 1.3 List of Abbreviations and Definition of Terms

Subsection Abbreviations:

Add:

DLCO Diffusing Capacity of the Lung for Carbon Monoxide

Section 4.0 Study Objective

First paragraph previously read:

The primary objectives of the study are to establish the recommended Phase 2 dose (RPTD) of veliparib in combination with concurrent paclitaxel/carboplatin-based chemoradiotherapy (CRT) and to assess whether the addition of oral veliparib versus placebo to paclitaxel/carboplatin-based chemoradiotherapy with consolidation paclitaxel/carboplatin will improve progression-free survival (PFS) in patients with Stage III non-small cell lung cancer (NSCLC).

Has been changed to read:

The primary objectives of the study are to establish the recommended Phase 2 dose (RPTD) of veliparib in combination with concurrent paclitaxel/carboplatin-based chemoradiotherapy (CRT) and paclitaxel/carboplatin-based consolidation chemoradiotherapy and to assess whether the addition of oral veliparib versus placebo to paclitaxel/carboplatin-based chemoradiotherapy with consolidation paclitaxel/carboplatin will improve progression-free survival (PFS) in patients with Stage III non-small cell lung cancer (NSCLC).

Section 5.1 Overall Study Design and Plan: Description

Previously read:

This two-phase study consists of 1) dose-escalation of veliparib to determine an RPTD for combination with concurrent paclitaxel/carboplatin-based CRT; and 2) a randomized, double-blinded study to determine whether veliparib improves outcome relative to placebo when added to paclitaxel/carboplatin based CRT followed by consolidation paclitaxel/carboplatin in subjects with previously untreated Stage III NSCLC.

Has been changed to read:

This two-phase study consists of 1) dose-escalation of veliparib to determine an RPTD for combination with concurrent paclitaxel/carboplatin-based CRT and paclitaxel/carboplatin-based consolidation chemoradiotherapy; and 2) a randomized, double-blinded study to determine whether veliparib improves outcome relative to placebo when added to paclitaxel/carboplatin based CRT followed by consolidation paclitaxel/carboplatin in subjects with previously untreated Stage III NSCLC.

Section 5.2 Selection of Study Population

First paragraph, first sentence previously read:

The study was designed to enroll approximately 186 subjects with Stage III NSCLC (approximately 30 in the dose escalation portion and approximately 156 in the randomized portion) at approximately 50 – 75 study centers to meet scientific and

regulatory objectives without enrolling an undue number of subjects in alignment with ethical considerations.

Has been changed to read:

The study was designed to enroll approximately 206 subjects with Stage III NSCLC (approximately 50 in the dose escalation portion and approximately 156 in the randomized portion) at approximately 50 – 75 study centers to meet scientific and regulatory objectives without enrolling an undue number of subjects in alignment with ethical considerations.

Table 1. Dose Escalation

Previously read:

Dose Level	Number of Subjects	Veliparib (mg)
1	3 – 6	60
2	3 – 6	80
3	3 – 6	120
4	3 – 6	200
5	3 – 6	240
-1	0 – 6	40

Has been changed to read:

Dose Escalation in the Concurrent Chemoradiotherapy

Cohort	Dose Level	Number of Subjects	Veliparib (mg)
1	1	3 – 6	60
2	2	3 – 6	80
3	3	3 – 6	120
4	4	3 – 6	200
5	5	3 – 6	240
	-1	0 – 6	40

Dose Escalation in the Consolidation Chemotherapy

Cohort	Dose Level	Number of Subjects	Veliparib (mg)
1 – 5		3 – 6	120
6		3 – 6	240

Section 5.2 Selection of Study Population
Subsection Dose Escalation Portion (Phase 1)
Third paragraph previously read:

Dose limiting toxicity (DLT) events will be collected for each dosing cohort until a new dosing cohort is opened or until the RPTD is identified. The DLT period for each subject will be from the start of veliparib dosing through 28 days following completion of RT or until consolidation chemotherapy is initiated, and the DLT period for all subjects at each dose level will end upon initiation of the next dose level. The consolidation dose of veliparib will be 120 mg BID + carboplatin (AUC 6 mg/mL/min) + paclitaxel (200 mg/m²) for up to two 21-day cycles.

Has been changed to read:

Dose limiting toxicity (DLT) events will be collected for each dosing cohort until a new dosing cohort is opened or until the RPTD is identified. During CRT dose escalation, the DLT period for each subject will be from the start of veliparib dosing through 28 days following completion of RT or until consolidation chemotherapy is initiated, and the DLT period for all subjects at each dose level will end upon initiation of the next dose level. CRT dose escalation will occur with a consolidation dose of veliparib of 120 mg BID + carboplatin (AUC 6 mg/mL/min) + paclitaxel (200 mg/m²) for up to two 21-day cycles. Once the concurrent CRT RPTD is identified, an additional cohort will be enrolled to explore the tolerability of a consolidation dose of veliparib at 240 mg BID + carboplatin (AUC 6 mg/mL/min) + paclitaxel (200 mg/m²) for up to two 21-day cycles.

Subjects overenrolled in Cohort 5 will be allowed to roll over into Cohort 6 as long as they have not started the consolidation phase, and at the discretion of the Investigators and the AbbVie Medical Monitor.

For Cohort 6, the DLT period will be 21 days from start of consolidation chemotherapy or until the start of Cycle 2 consolidation therapy.

For this cohort, if 3 or less subjects were able to take Cycle 2 of consolidation chemotherapy, the reason of dose reduction and treatment discontinuation will be reviewed as part of consideration to determine MTD/RPTD of veliparib for the consolidation phase.

Section 5.2.1 Inclusion Criteria

Add: new Criterion 4

Subject must consent to provide archived tissue or cytology sample of NSCLC lesion for analysis;

Section 5.2.1 Inclusion Criteria

Subsection Rationale for Inclusion Criteria

Previously read:

- 1 – 6 To select the appropriate subject population with sufficient disease severity for evaluation
- 7 The impact of veliparib plus paclitaxel/carboplatin-based chemoradiotherapy followed by paclitaxel/carboplatin consolidation on the unborn fetus is unknown; therefore, these criteria ensure that adequate precautions are taken to avoid pregnancy
- 8 In accordance with harmonized Good Clinical Practice (GCP)

Has been changed to read:

- 1 – 7 To select the appropriate subject population with sufficient disease severity for evaluation
- 8 The impact of veliparib plus paclitaxel/carboplatin-based chemoradiotherapy followed by paclitaxel/carboplatin consolidation on the unborn fetus is unknown; therefore, these criteria ensure that adequate precautions are taken to avoid pregnancy
- 9 In accordance with harmonized Good Clinical Practice (GCP)

Table 2. Study Activities (Phase 1 and 2)
Activity "PFT^m" and "Chemistry/Hematology^p" previously read:

Activity	Screening ^a	Concurrent (Chemoradiotherapy)					Post CRT Visit ^c	Consolidation ^d			Post-Treatment Visit ^e	Final Visit ^f	30-Day FU Visit ^g	Survival Period
		Wk 1 Day -3	Wk 1-3 Day 1	Wk 4 Day -3	Wk 4-9 ^b Day 1	Wk 7 Day -3 ^b		Cycle 1 Day -2	Cycle 1 Day 1	Cycle 2 Day 1				
PFT ^m	X													
Chemistry/Hematology ^p	X	X		X		X	X		X					

Has been changed to read:

Activity	Screening ^a	Concurrent (Chemoradiotherapy)					Post CRT Visit ^c	Consolidation ^d			Post-Treatment Visit ^e	Final Visit ^f	30-Day FU Visit ^g	Survival Period
		Wk 1 Day -3	Wk 1-3 Day 1	Wk 4 Day -3	Wk 4-9 ^b Day 1	Wk 7 Day -3 ^b		Cycle 1 Day -2	Cycle 1 Day 1	Cycle 2 Day 1				
PFT ^m	X									X				
Chemistry/Hematology ^p	X	X		X		X	X	X	X	X				

Table 2. Study Activities (Phase 1 and 2)

Table note "m."

Add: new second and third sentence

PFT will be performed at 12 months post start of radiation therapy. If subject is no longer coming in for Post-Treatment Visits, every effort should be made to still collect the PFT at this 12 month timepoint.

Table 2. Study Activities (Phase 1 and 2)

Table note "p."

Add: new last sentence

Blood Draw (hemoglobin only) to be collected in the Post Treatment visit at 12 months post start of radiation therapy.

**Table 3. Schedule of Pharmacogenetic and Pharmacodynamic Assessments
Procedure "Archived Tissue Sample Collection* (optional)" previously read:**

Archived Tissue Sample Collection* (optional)

Has been changed to read:

Archived Tissue Sample Collection

Table 3. Schedule of Pharmacogenetic and Pharmacodynamic Assessments

Table note "c."

Add: new second, third and fourth sentence

Subjects must consent to provide available archival tissue for analysis. It is preferred to send FFPE blocks, however slides prepared by the local pathology laboratory are acceptable and should be prepared as described in the study specific laboratory manual. If there is not enough tissue to provide the number of slides specified in the laboratory manual, sites should provide as many slides as possible with the available tissue.

Section 5.3.1.1 Study Procedures

Subsection Informed Consent

First paragraph, third and fourth sentence previously read:

Archived tissue collection is optional. Subjects must consent to provide available archival tissue for analysis.

Has been changed to read:

Archived tissue collection is optional for all subjects participating in Cohort 1 – 5. Subjects participating in Cohort 6 must consent to provide archived tissue or cytology sample for analysis.

Section 5.3.1.1 Study Procedures

Subsection Pulmonary Function Test Procedure (PFT)

Add: new subsection title and text

Pulmonary Function Test procedure (PFT)

The PFT procedure will be performed per [Table 2](#). The Pulmonary function test should include spirometry with FEV1 and DLCO documentation. Hemoglobin lab assessment will be needed to generate a DLCO (Hb).

Section 5.3.1.3 Collection and Handling of Pharmacodynamic Variables

Subsection Archived Tissue Collection

First sentence previously read:

If available, fixed samples from most recent biopsy should be collected from subjects who have consented, while subject is active on study.

Has been changed to read:

If available, fixed samples from most recent biopsy should be collected from subjects participating in Cohort 1 – 5 who have consented, while subject is active on study.

Section 5.3.1.3 Collection and Handling of Pharmacodynamic Variables

Subsection Archived Tissue Collection

Add: new third and fourth sentence

Subjects participating in Cohort 6 must consent to provide available archived tumor for analysis. It is recognized that the availability of the samples suitable for analysis may not be known at the time of consent for all subjects.

Section 5.3.7 Pharmacodynamic Variables

Second paragraph, second sentence previously read:

These characterizations may be included, but are not limited, characterization of gene methylation/mutational status or copy number changes of genes, particularly those involved in DNA repair pathways.

Has been changed to read:

These characterizations may be included, but are not limited, characterization of gene expression, methylation/mutational status or copy number changes of genes, particularly those involved in DNA repair pathways.

Section 5.5.1 Treatments Administered
Subsection Concurrent Chemoradiotherapy
Delete: last paragraph

AbbVie will review available safety data from all subjects in the dose escalation portion of the study and determine the recommended Phase 2 dose (RPTD) for veliparib during chemoradiotherapy. Subjects in the randomized portion of the study will receive the veliparib RPTD or placebo during chemoradiotherapy.

Section 5.5.1 Treatments Administered
Subsection Consolidation Chemotherapy
First sentence previously read:

No more than 8 weeks after completion of concurrent chemoradiotherapy, veliparib/placebo 120 mg BID will be administered beginning 2 days prior to the start of paclitaxel/carboplatin infusion and will continue through Day 5 of each 21-day cycle.

Has been changed to read:

No more than 8 weeks after completion of concurrent chemoradiotherapy, veliparib/placebo 120 mg or 240 mg BID will be administered beginning 2 days prior to the start of paclitaxel/carboplatin infusion and will continue through Day 5 of each 21-day cycle.

Section 5.5.1 Treatments Administered

Subsection Phase 2 Treatment Regimen: RPTD or Placebo

Add: new subsection title and text

Phase 2 Treatment Regimen: RPTD or Placebo

AbbVie will review available safety data from all subjects in the dose escalation portion of the study and determine the CRT and consolidation RPTDs. Subjects in the randomized portion of the study will receive the veliparib RPTD or placebo during CRT and consolidation.

Section 5.6.4 Selection of Doses in the Study

Previously read:

The doses of standard therapy (radiotherapy, carboplatin, paclitaxel) are guideline recommended or based on randomized studies of subjects with advanced NSCLC.³ The dose escalation portion of this study will determine the appropriate dose of veliparib with standard-dose concurrent chemoradiotherapy by the 3 + 3 cohort design commonly used for determining tolerability. During consolidation therapy, doses of standard therapy and the dose of investigational agent (veliparib) in this study are identical to those used in a randomized, double-blind placebo controlled Phase 2 study of carboplatin and paclitaxel ± veliparib for advanced metastatic NSCLC. As described in Section 3.0, preliminary data from this study show the combination is well-tolerated, showed delivery of carboplatin and paclitaxel were not substantially compromised, and suggested improved efficacy in subjects who received veliparib.

The maximum dose of veliparib/placebo for any subject in this study is 240 mg BID continuously during chemoradiotherapy followed by 120 mg BID for 7 of 21 days over 2 cycles.

Has been changed to read:

The doses of standard therapy (radiotherapy, carboplatin, paclitaxel) are guideline recommended or based on randomized studies of subjects with advanced NSCLC.³ The dose escalation portion of this study will determine the appropriate dose of veliparib with

standard-dose concurrent chemoradiotherapy and consolidation chemotherapy by a 3 + 3 cohort design.

Both 120 mg BID veliparib and 240 mg BID (or higher) have been used in Phase 2 and Phase 3 studies in combination with platinum doublet in different patient population. In Cohorts 1 – 5, the 120 mg BID dose of investigational agent (veliparib) in the consolidation portion was selected based on a randomized, double-blind placebo controlled Phase 2 study of carboplatin and paclitaxel ± veliparib for advanced metastatic NSCLC, and to ensure the capability to escalate veliparib dose in combination with Chemo-RT.

Once the CRT RPTD is determined, a 6th cohort will be enrolled with subjects at 240 mg BID dose in the consolidation portion as indicated in [Table 1](#). The dose selection of 240 mg BID was supported by safety data in Phase 1 studies with veliparib in combination with carboplatin/paclitaxel, an ongoing Phase 2 study of 240 mg BID of veliparib in combination of carboplatin/etoposide for extended stage of small cell lung cancer, and a Phase 3 study of 300 mg BID veliparib in combination of carboplatin/paclitaxel in front line ovarian cancer patients. As described in [Section 3.0](#), preliminary data from this study show the combination is well-tolerated, showed delivery of carboplatin and paclitaxel were not substantially compromised, and suggested improved efficacy in subjects who received veliparib.

The maximum dose of veliparib/placebo for any subject in this study is 240 mg BID continuously during chemoradiotherapy followed by 240 mg BID for 7 of 21 days over 2 cycles of consolidation chemotherapy.

Section 6.6.3 Reporting Serious Adverse Events

"Primary Study Designated Physician:" previously read:

[REDACTED]

AbbVie

[REDACTED]

1 North Waukegan Road
North Chicago, IL 60064

Office:

Fax:

Mobile:

Email:

[REDACTED]

Has been changed to read:

[REDACTED]

AbbVie

[REDACTED]

1 North Waukegan Road
North Chicago, IL 60064

Office:

Fax:

Mobile:

Email:

[REDACTED]

Section 6.8.1 Dose Limiting Toxicities

First paragraph, seventh sentence previously read:

The DLT period for each subject will be from start of veliparib dosing through 28 days following completion of CRT or until consolidation chemotherapy is initiated, and the DLT period for all patients at each dose level will end upon initiation of next dose level.

Has been changed to read:

The DLT period for each subject in the concurrent CRT dose escalation will be from start of veliparib dosing through 28 days following completion of CRT or until consolidation chemotherapy is initiated, and the DLT period for all patients at each dose level will end upon initiation of next dose level. The DLT period for each subject during consolidation chemotherapy dose (Cohort 6), will be 21 days from start of consolidation or until the start of Cycle 2 of the consolidation therapy or treatment discontinuation.

Section 6.8.3 Determination of the RPTD

First and second sentence previously read:

AbbVie will review available safety data from all subjects in the dose escalation portion of the study and determine the RPTD for veliparib during chemoradiotherapy. Subjects in the randomized portion of the study will receive the veliparib RPTD or placebo during chemoradiotherapy.

Has been changed to read:

AbbVie will review available safety data from all subjects in the dose escalation portion of the study and determine the RPTD for veliparib during chemoradiotherapy and consolidation chemotherapy. Subjects in the randomized portion of the study will receive the veliparib CRT RPTD or placebo during chemoradiotherapy and the veliparib consolidation RPTD or placebo during consolidation.

Table 10. Suggested Guidelines for Veliparib + Paclitaxel/Carboplatin Independent Dose Reduction

Previously read:

Dose Level	Carboplatin	Paclitaxel	Veliparib/Placebo
Starting Dose Level	AUC 6	200 mg/m ²	120 mg BID
Dose Level -1	AUC 5	175 mg/m ²	80 mg BID
Dose Level -2	AUC 4	150 mg/m ²	40 mg BID

Has been changed to read:

Dose Level	Carboplatin	Paclitaxel	Veliparib/Placebo
Starting Dose Level (for subjects participating in Cohort 6)	AUC 6	200 mg/m ²	240 mg BID
Starting Dose Level -1			120 mg BID
Dose Level -2	AUC 5	175 mg/m ²	80 mg BID
Dose Level -3	AUC 4	150 mg/m ²	60 mg BID

Section 7.0 Protocol Deviations

"Medical Monitor:" previously read:

[REDACTED]

AbbVie

[REDACTED]

1 North Waukegan Road
North Chicago, IL 60064

Office: [REDACTED]

Fax: [REDACTED]

Cell: [REDACTED]

Email: [REDACTED]

Has been changed to read:

[REDACTED]

AbbVie

[REDACTED]

1 North Waukegan Road
North Chicago, IL 60064

Office: [REDACTED]

Fax: [REDACTED]

Mobile: [REDACTED]

Email: [REDACTED]

Section 7.0 Protocol Deviations

Delete: "Clinical Monitor"

Clinical Monitor



1 North Waukegan Road
North Chicago, IL 60064

Office:

Fax:

Cell:

Email:



Section 8.2 Determination of Sample Size

First paragraph previously read:

Approximately 30 subjects will be enrolled in the dose escalation portion of the study.

Has been changed to read:

Approximately 50 subjects will be enrolled in the dose escalation portion of the study.

Section 9.3 Subject Information and Consent

Last paragraph previously read:

Archived tissue analysis will only be performed if the subject has voluntarily consented for tissue sampling on the informed consent, approved by an IRB/IEC, after the nature of the testing has been explained and the subject has had an opportunity to ask questions. If the subject does not consent to the archived tissue analysis, it will not impact the subject's participation in the study.

Has been changed to read:

For subjects participating in Cohort 1 – 5, archived tissue analysis will only be performed if the subject has voluntarily consented for tissue sampling on the informed consent, approved by an IRB/IEC, after the nature of the testing has been explained and the subject has had an opportunity to ask questions. If the subject does not consent to the archived tissue analysis, it will not impact the subject's participation in the study. Subjects in Cohort 6 must consent to provide available archival tumor for analysis. It is recognized that the availability of the samples suitable for analysis may not be known at the time of consent for all subjects.

Appendix B. List of Protocol Signatories
Previously read:

Name	Title	Functional Area
		Clinical
		GDSM
		Clinical
		Clinical
		Statistics
		Clinical Pharmacology & Pharmacometrics
		Bioanalysis
		Biometrics

Has been changed to read:

Name	Title	Functional Area
		Clinical
		GDSM
		Clinical
		Clinical
		Statistics
		Clinical Pharmacology & Pharmacometrics
		Bioanalysis
		Biometrics