1.0 Title Page

Clinical Study Protocol M14-359

A Randomized, Open-Label, Multicenter, Phase 3 Trial Comparing Veliparib Plus Carboplatin and Paclitaxel Versus Investigator's Choice of Standard Chemotherapy in Subjects Receiving First Cytotoxic Chemotherapy for Metastatic or Advanced Non-Squamous Non-Small Cell Lung Cancer (NSCLC) and Who Are Current or Former Smokers

Incorporating Amendments 1, 2, 3 and 4

AbbVie Investigational Product:	Veliparib (ABT-888)
Date:	09 May 2018
Development Phase:	3
Study Design:	A Randomized, Open-Label, Multicenter, Phase 3 Trial Comparing Veliparib Plus Carboplatin and Paclitaxel Versus Investigator's Choice of Standard Chemotherapy in Subjects Receiving First Cytotoxic Chemotherapy for Metastatic or Advanced Non-Squamous Non-Small Cell Lung Cancer (NSCLC) and Who Are Current or Former Smokers.
EudraCT Number:	2014-002565-30
Investigator:	Multicenter Study: Investigator information is on file at AbbVie Inc. (AbbVie).
Sponsor:	AbbVie Inc.*
Sponsor/Emergency Contact:	[redacted] Phone: [redacted] Cell: [redacted] AbbVie [redacted] 200 Sidney Street Cambridge, MA 02139

*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.

1.1 Protocol Amendment: Summary of Changes

Previous Protocol Versions

Protocol	Date
Original	10 July 2014
Amendment 1	20 October 2014
Amendment 2	10 December 2014
Amendment 3	17 July 2015

The primary purpose of this amendment is to revise the patient population for the primary endpoint with related statistical analysis changes and to provide clarifications across certain study-specific procedures and includes the following changes as follows:

- The patient population for the primary endpoint of overall survival (OS) is being amended from current smokers to subjects who are positive for the Lung Subtyping Panel (LSP) signature; subjects who are LSP positive will also replace the current smoker population for other key efficacy analyses. This change does not impact the patient management aspects of the protocol or the associated informed consent. This change impacts: Section 1.2, Synopsis; Section 3.0, Introduction; Section 3.5, Study Rationale; Section 4.0, Study Objectives; Section 5.3.3, Efficacy Variables; Section 8.1.2, Efficacy Endpoints; Section 8.1.3, Timing of Efficacy Analyses and Safety Evaluations; Section 8.1.4, Primary Analysis of Efficacy; Section 8.1.5, Secondary Analysis of Efficacy; Section 8.1.6, Tertiary Analyses of Efficacy; Section 8.1.7, Additional Exploratory Efficacy Analyses; Section 8.1.8, Statistical Analysis of Safety.

  Rationale: *Change is to focus the analyses on the patient population most likely to derive clinical benefit from veliparib, based on recent analyses of Phase 2 and Phase 3 studies which suggest that LSP status may be predictive of a possible veliparib treatment effect in combination with carboplatin and paclitaxel in subjects with NSCLC.*
- Update number of subjects to be enrolled from approximately 525 to 595 subjects.

Rationale: *Change is to include accurate/updated enrollment targets.*

- Remove language in footnote "i." of Study Activities Table 2 referencing exclusion of the 72-hour window allowance for C1D-2 lab samples.

  Rationale: *Change is to provide clarification that C1D-2 lab samples have the same 72 hour window allowance as all other lab samples.*

- Include full emergency contact details for Study Designated Physician in Section 6.6.1 Reporting Serious Adverse Events.

  Rationale: *Change is to assure full appropriate emergency contact details are reflected.*

- Revise throughout to reflect updates in the latest version of the investigator's brochure.

  Rationale: *Change is for accuracy ensuring most recent investigator's brochure is referenced and accompanying changes to investigator's brochure are reflected.*

An itemized list of all changes made to the protocol under this amendment is found in Appendix I.

1.2 Synopsis

AbbVie Inc.	**Protocol Number:** M14-359
Name of Study Drug: Veliparib (ABT-888)	**Phase of Development:** 3
Name of Active Ingredient: Not applicable	**Date of Protocol Synopsis:** 09 May 2018
Protocol Title: A Randomized, Open-Label, Multicenter, Phase 3 Trial Comparing Veliparib Plus Carboplatin and Paclitaxel Versus Investigator's Choice of Standard Chemotherapy in Subjects Receiving First Cytotoxic Chemotherapy for Metastatic or Advanced Non-Squamous Non-Small Cell Lung Cancer (NSCLC) and Who Are Current or Former Smokers	
Objectives: The primary objective of the study is to assess if treatment with veliparib plus carboplatin and paclitaxel results in improved survival compared to Investigator's choice of standard chemotherapy in Lung Subtype Panel (LSP) positive subjects with metastatic or advanced NSCLC. The secondary objectives of the study are to assess if treatment with veliparib plus carboplatin and paclitaxel results in improved survival compared to Investigator's choice of standard chemotherapy in the entire study population; to compare progression-free survival (PFS) and to compare objective response rate (ORR) between the two treatment arms in LSP positive subjects or in entire study population. The tertiary objectives are to compare duration of overall response (DOR), ECOG performance status and Quality of Life (QoL) between the two treatment arms in LSP positive subjects or in the entire study population.	
Investigators: Multicenter	
Study Sites: 150	
Study Population: Subjects receiving first cytotoxic chemotherapy for Metastatic or Advanced Non-Squamous Non-Small Cell Lung Cancer (NSCLC) who are current or former smokers. Chemotherapy for adjuvant or neoadjuvant treatment of NSCLC received greater than 12 months prior to Cycle 1 Day –2 (C1D-2) will be allowed.	
Number of Subjects to be Enrolled: 595	

Methodology:

This is a Phase 3, randomized, open-label, multi-center study evaluating the efficacy, safety, and tolerability of veliparib plus carboplatin and paclitaxel versus Investigator's choice of standard chemotherapy in subjects receiving first cytotoxic chemotherapy for advanced or metastatic non-squamous NSCLC who are current or former smokers. Subjects will be randomized in a 1:1 ratio to a maximum of 6 cycles of carboplatin/paclitaxel plus 120 mg BID of veliparib or a maximum of 6 cycles of Investigator's choice of platinum doublet chemotherapy (carboplatin/paclitaxel, cisplatin/pemetrexed, or carboplatin/pemetrexed), unless treatment is discontinued for toxicity or cancer progression. Investigators may elect to administer maintenance pemetrexed regardless of which therapy their subjects are randomized to receive. Following completion of platinum doublet therapy, maintenance pemetrexed is strongly encouraged for all subjects who are suitable candidates. Subjects LSP status (positive or negative) will be determined from tissue samples obtained to confirm diagnosis of NSCLC with a commercially developed RNA seq based LSP classifier developed in partnership with Qiagen.

Subject randomization will be stratified by smoking status (current versus former), by the Investigators' preferred platinum doublet therapy (carboplatin/paclitaxel versus cisplatin/pemetrexed versus carboplatin/pemetrexed), by gender (male versus female) and by ECOG performance status (0 versus 1).

Subjects randomized to receive veliparib will begin oral veliparib dosing 2 days prior to the start of the carboplatin/paclitaxel infusion on C1D-2 and will continue twice a day (BID) through C1D5 (7 consecutive days).

Subjects randomized to receive carboplatin/paclitaxel/veliparib will receive carboplatin (AUC 6 mg/mL•min) and paclitaxel (200 mg/m^2) IV infusion starting on Day 1 of each cycle. Subjects will receive a maximum of 6 cycles of treatment, unless toxicity requires cessation of therapy, or radiographic progression occurs prior to completing 6 cycles. Carboplatin/paclitaxel plus veliparib may be delayed or dose-modified due to toxicity. Should a subject not receive carboplatin and paclitaxel on Day 1 of any cycle, the cycle will be restarted with veliparib at the newly designated Day –2 when the subject is able to do so.

Subjects randomized to receive Investigator's choice of platinum doublet therapy will receive therapy on Day 1 of each cycle. Subjects will receive a maximum of 6 cycles of treatment, unless toxicity requires cessation of therapy, or radiographic progression occurs prior to completing 6 cycles. Platinum doublet therapy may be delayed or dose-modified due to toxicity. Dose delays and modification will be at the discretion of the Investigator per local standard practice.

Suitable subjects in either arm will receive pemetrexed maintenance therapy after completion of platinum doublet chemotherapy regimen. Maintenance pemetrexed will be administered on Day 1 of each 21-day cycle. Maintenance therapy may be delayed or dose-modified due to toxicity. Subjects will continue to receive maintenance therapy until toxicity requires cessation of therapy, or radiographic progression occurs. Veliparib will not be administered during the maintenance phase.

Methodology (Continued):

Subjects will have physician visits q3 weeks while receiving platinum doublet and maintenance therapy. After cessation of therapy, physician visits and quality of life measures will be performed q9 weeks until 1 year after beginning treatment (C1D-2) (or beyond 1 year until maintenance therapy is discontinued), then q12 weeks until radiographic progression. Tumor assessments will be performed at baseline prior to treatment on Cycle 3 Day 1 and Cycle 5 Day 1. After cessation of platinum doublet therapy, tumor assessments will be performed q9 weeks until 1 year after beginning treatment (C1D-2) (or beyond 1 year until maintenance therapy is discontinued), then q12 weeks until radiographic progression or death. Radiographic information will be collected to determine response according to the Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1. Toxicities will be graded at each study visit according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

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. It is preferable that final visit procedures be conducted prior to the initiation of another anticancer therapy.

All subjects who have a Final visit ≤ 30 days after the last dose of Study drug will have a Follow-Up Visit approximately 30 days after the last dose of Study drug. 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.

Subjects no longer undergoing clinical assessments will have survival information reported at 2-month intervals (or as requested by the sponsor to support data analysis) beginning at the last clinical assessment and continuing until the endpoint of death, the subject has become lost to follow-up, or AbbVie terminates the study.

Diagnosis and Main Criteria for Inclusion/Exclusion:

Diagnosis: Metastatic or advanced non-squamous Non-Small Cell Lung Cancer

Main Inclusion:

1. Subject must be ≥ 18 years of age.
2. Life expectancy > 12 weeks (as per Investigator's clinical assessment).
3. Subject must have cytologically or histologically confirmed advanced or metastatic non-squamous NSCLC. Subjects with mixed histology tumors will be eligible if the tumor is predominant non-squamous histology and does not include tumor with small cell histology. Subjects must have a pathologist's report confirming non-squamous NSCLC available for collection by the sponsor. Subjects with EGFR mutation (exon 19 deletion or L858R mutation in exon 21) and/or ALK gene rearrangement must have progressed after first line monotherapy treatment with targeted therapy.
4. Subject must have NSCLC that is not amenable to surgical resection or radiation with curative intent at time of study Screening.
5. Subjects must be current smokers (defined as having > 100 smoking events lifetime and having smoked within the past year) or former smokers (defined as having > 100 smoking events lifetime and having not smoked within the past year).

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

Main Inclusion (Continued):

6. Subject must have at least 1 unidimensional measurable NSCLC lesion on a CT scan as defined by RECIST (version 1.1).
7. Subject must consent to provide archived tissue or cytology sample of NSCLC lesion (primary or metastatic) for analysis if available.
8. Subject must have no history of brain metastases or evidence of CNS tumors at screening assessment. Subjects with signs or symptoms of CNS involvement will undergo MRI (or CT scan if MRI is contraindicated) to confirm absence of CNS metastases.
9. Subject must have an Eastern Cooperative Oncology Group (ECOG) Performance Score of 0 – 1.
10. Subjects with fluid retention, including ascites or pleural effusion, may be allowed at the discretion of the Investigator.
11. Subject must have adequate bone marrow, renal and hepatic function as follows:
    - Bone Marrow: Absolute neutrophil count (ANC) $\geq$ 1,500/mm^3 (1.5 $\times$ 10^9/L);
    - Platelets $\geq$ 100,000/mm^3 (100 $\times$ 10^9/L); Hemoglobin $\geq$ 9.0 g/dL;
    - Renal function: serum calculated creatinine clearance > 50 mL/min according to the Cockcroft-Gault formula; confirmation of creatinine clearance/GFR may be done by a local direct measurement method (e.g., 24 hour urine collection or radioisotope) at the investigator's discretion;
    - Hepatic function: AST and ALT $\leq$ 2.5 $\times$ ULN unless liver metastases are present, then AST and ALT < 5.0 $\times$ ULN; bilirubin $\leq$ 1.5 $\times$ ULN; unless Gilbert's Syndrome is present, then bilirubin $\geq$ 1.5 $\times$ ULN.
12. 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 partners should practice at least one of the methods of birth control listed below during study and for at least 6 months after treatment with paclitaxel chemotherapy. Male subjects and their female partners of childbearing potential should practice at least one of the methods of birth control listed below during study and for at least 6 months after treatment with chemotherapy:
    - total abstinence from sexual intercourse (if it is the subject's preferred and usual lifestyle; for 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.
13. Subject must be capable of understanding and complying with parameters as outlined in the protocol and able to sign and date the informed consent approved by an Independent Ethics Committee (IEC)/Institutional Review Board (IRB), prior to the initiation of any screening or study-specific procedures.

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

Main Exclusion:

1. Subject has a known hypersensitivity to paclitaxel or to other drugs formulated with polyethoxylated castor oil (Cremophor).
2. Subject has a known hypersensitivity to platinum compounds.
3. Subjects with peripheral neuropathy ≥ grade 2.
4. Subjects with squamous NSCLC, or those with an untreated EGFR mutation (exon 19 deletion or L858R mutation in exon 21) and/or ALK gene rearrangement. Subjects' EGFR mutation and ALK gene rearrangement status must be known prior to study entry.
5. A history of seizure within 12 months prior to study entry.
6. Subject has received prior cytotoxic chemotherapy or chemoradiotherapy for NSCLC, except adjuvant or neoadjuvant therapy > 12 months prior to C1D-2 or subject has received targeted small molecule monotherapy for EGFR and/or ALK-positive disease ≤ 14 days prior to C1D-2 or biologic therapy ≤ 21 days prior to C1D-2.
7. Subject has received anti-cancer Chinese medicine or anti-cancer herbal remedies within 14 days prior to C1D-2.
8. Subject has undergone focal External Beam Radiation Therapy (EBRT) to bone ≤ 2 weeks prior to C1D-2; or subject has undergone EBRT to larger fields (i.e., 100 cm^2 to thorax) ≤ 4 weeks prior to C1D-2.
9. Any medical condition, which in the opinion of the Investigator, places the subject at an unacceptably high risk for toxicities, or any subject circumstance which prohibits trial participation according to local law.
10. Subject is pregnant or lactating.
11. Subject has previously been treated with a PARP inhibitor.
12. The subject has a history of another cancer within the past 3 years except cervical cancer in situ, in situ carcinoma of the bladder, squamous or basal cell carcinoma of the skin or another in situ cancer that is considered cured by the Investigator (e.g., in situ prostate cancer).

Investigational Products:	Veliparib (ABT-888)
Doses:	120 mg BID Days –2 through 5 of 21-day cycle
Mode of Administration:	Oral
Reference Therapy or Investigational products:	Carboplatin Day 1 of 21-day cycle
Dose:	AUC 6 mg/mL•min
Mode of Administration:	Intravenous
Reference Therapy or Investigational products:	Paclitaxel Day 1 of 21-day cycle
Dose:	200 mg/m^2
Mode of Administration:	Intravenous

Reference Therapy:	Pemetrexed
Dose:	500 mg/m^2
Mode of Administration:	Intravenous
Reference Therapy:	Cisplatin
Dose:	75 mg/m^2
Mode of Administration:	Intravenous

Duration of Treatment:

Subjects will receive veliparib in combination with carboplatin/paclitaxel for a maximum of 6 treatment cycles or Investigator's choice of chemotherapy for a maximum of 6 cycles unless toxicity requires cessation of therapy, or radiographic progression occurs prior to completing 6 cycles. Following completion of platinum doublet therapy, maintenance pemetrexed is strongly encouraged for all subjects who are suitable candidates.

Criteria for Evaluation:

Overall survival (OS): will be reported by the Investigator until radiographic progression or death. After the final visit, survival information will be collected at 2-month intervals (or as requested by sponsor to support data analysis).

Progression-free survival (PFS): will be derived according to radiographic progression per RECIST version 1.1 or death. Radiographic tumor assessments for response will be conducted by CT scanning prior to C3D1, prior to C5D1, every 9 weeks until 1 year after beginning treatment (or beyond 1 year until maintenance therapy is discontinued), and then every 12 weeks.

Objective response rate (ORR): will be derived per RECIST version 1.1. Radiographic tumor assessments for response will be conducted by CT scanning prior to C3D1, prior to C5D1, every 9 weeks until 1 year after beginning treatment (or beyond 1 year until maintenance therapy is discontinued), and then every 12 weeks.

Duration of overall response (DOR): will be derived according to radiographic progression per RECIST version 1.1. Radiographic tumor assessments for response will be conducted by CT scanning prior to C3D1, prior to C5D1, every 9 weeks until 1 year after beginning treatment (or beyond 1 year until maintenance therapy is discontinued), and then every 12 weeks.

ECOG performance status: will be determined by the Investigator at each assessment.

Quality of Life (QoL): will be assessed at baseline prior to veliparib dosing on C1D-2, C3D1, C5D1 and at the Final Visit, every 9 weeks until 1 year after beginning treatment (or beyond 1 year until maintenance therapy is discontinued), then every 12 weeks and at the Final Visit until radiographic progression via the NCCN-Functional Assessment of Cancer Therapy (FACT) Lung Symptom Index-17 (NFLSI-17) questionnaire and the European Quality of Life-5 Dimensions (EQ-5D-5L) questionnaires.

Safety:

Adverse events, laboratory profiles, physical examinations and vital signs will be assessed throughout the study.

Pharmacokinetic/Pharmacogenetics:

Blood samples for pharmacokinetics of veliparib will be collected at designated timepoints throughout the study and will be analyzed in LSP-defined populations as well as the entire study population.

Criteria for Evaluation (Continued):

LSP status:

Available archived tumor tissue will be used to determine the subjects' tumor LSP status with a commercially developed RNA seq based LSP classifier developed in partnership with Qiagen.

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 tissue samples will be collected at designated time points throughout the study.

Statistical Methods:

For all statistical analyses, statistical significance will be determined by a two-sided *P* value ≤ 0.05. The date of randomization (enrollment) is defined as the date that the IRT issues a randomization number.

Sample Size:

Sample size determination for the original protocol: Assuming the true hazard ratio of overall survival (OS) for current smokers in favor of the veliparib 120 mg BID + carboplatin/paclitaxel treatment group is 0.64, a total of 210 death events among current smokers will be needed for the study to have approximately 90% power at one-sided α level of 0.025 to detect a statistically significant treatment effect for the veliparib 120 mg BID + carboplatin/paclitaxel group using the log rank test for OS. A total of approximately 300 current smokers will be enrolled to obtain the 210 death events.

During the enrollment period for the approximate 300 current smokers, it is anticipated that approximately 225 former smokers will enroll concurrently. Assuming the true hazard ratio of overall survival (OS) for all subjects (including current plus former smokers) in favor of the veliparib 120 mg BID + carboplatin/paclitaxel treatment group is 0.71, a total of 369 death events in all subjects will be needed for the study to have approximately 90% power at one-sided α level of 0.025 to detect a statistically significant treatment effect for the veliparib 120 mg BID + carboplatin/paclitaxel group using the log rank test for OS.

Sample size consideration for OS analysis in LSP+ subgroup:

Based on 452 subjects having tissue samples (assumed 76% LSP sample availability rate, out of 595 enrolled subjects), the below table provides the power and number of events (assuming 80% event rate at final analysis) for a range of likely LSP+ rates if the treatment allocation ratio is 1:1 in the LSP+ subgroup and true HR of OS is 0.65 in LSP+ subgroup.

Number of LSP+ Subjects (LSP+ rate)	Number of Events in LSP+	Power for OS in LSP+ Subgroup (one-sided alpha = 0.025)
271 (60%)	216	89%
226 (50%)	180	82%
180 (40%)	144	73%

1.3 List of Abbreviations and Definition of Terms

Abbreviations

ADP	Adenosine Diphosphate
AE	Adverse Event
ALK	Anaplastic Lymphoma Kinase
ALT	Alanine transaminase
ANC	Absolute Neutrophil Count
ANCOVA	Analysis of Covariance
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
CNS	Central Nervous System
CR	Complete Response
CRF or eCRF	Case Report Form or Electronic Case Report Form
CS	Clinically Significant
CSF	Colony-Stimulating Factor
CT	Computed Tomography
CTEP	Cancer Therapy Evaluation Program
C_{max}	Maximum Drug Concentration
CYP	Cytochrome P450
D	Day
DDI	Drug-Drug Interaction
DLT	Dose Limiting Toxicity
DNA	Deoxyribonucleic Acid
DOR	Duration of Overall Response
EBRT	External Beam Radiation Treatment
ECG	Electrocardiogram

ECOG	Eastern Cooperative Oncology Group
EDC	Electronic Data Capture
EGFR	Epidermal Growth Factor
ERCC1	Excision Repair Cross-Complementary Group 1 Protein
EMA	European Medicines Agency
ESMO	European Society for Medical Oncology
FDA	US Food and Drug Administration
FFPE	Formalin fixed, paraffin embedded
GCP	Good Clinical Practice
GFR/eGFR	Glomerular Filtration Rate/estimated Glomerular Filtration Rate
hCG	Human Chorionic Gonadotropin
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IIA	Investigator Information and Agreement
IIS	Investigator initiated studies
IMP	Investigational Medicinal Product
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
IV, i.v.	Intravenous
LD	Longest Diameter
LDH	Lactate Dehydrogenase
LSP	Lung Subtype Panel
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
mL	Milliliter
MRI	Magnetic Resonance Imaging
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
PBMC	Peripheral Blood Mononuclear Cells
PD	Pharmacodynamic or Progressive Disease
PFS	Progression Free Survival
PG	Pharmacogenetic
PK	Pharmacokinetic
PO	Oral Route of Administration
POR	Proof of Receipt
PR	Partial Response
QA	Quality Assurance
QC	Quality Control
QTc	QT interval corrected for heart rate
QoL	Quality of Life
RBC	Red Blood Cell
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
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
TNM	Tumor size, Nodes and Metastasis presence
ULN	Upper Limit of Normal
US	Ultrasound or United States
VAS	Visual Analogue Scale
WBC	White Blood Cell

Definition of Terms

AUC	Area under the concentration-time curve
C_{max}	Maximum observed concentration
nM	Nanomolar
T_{max}	Time to maximum observed plasma concentration

2.0 Table of Contents

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3.0 Introduction

3.1 NSCLC (Non-Small Cell Lung Cancer)

Lung cancer is the leading cause of cancer-related mortality in both men and women throughout the world. The prevalence of lung cancer is second only to that of prostate cancer in men and breast cancer in women. Lung cancer recently surpassed heart disease as the leading cause of smoking-related mortality. Most lung carcinomas are diagnosed at an advanced stage, conferring a poor prognosis. In 2008, an estimated 1.52 million new cases of lung cancer were diagnosed globally, accounting for approximately 12% of the global cancer burden, and an estimated 1.31 million lung cancer deaths occurred.[1]

The incidence of non-small cell lung cancer (NSCLC) increases with age; 60% occur in subjects aged 60 years and older, and 30% to 40% occur in subjects aged 70 years and older. Eighty-five percent of subjects either present with or will eventually develop advanced or recurrent NSCLC and are considered candidates for systemic chemotherapy.[2,3] Non-small cell lung cancer is divided further into adenocarcinoma, squamous cell carcinoma, and large cell carcinoma histologies. Currently, about 40% of NSCLC cases are adenocarcinoma subtypes and about 40% are squamous tumors.[3]

National Comprehensive Cancer Network (NCCN) 2014 guidelines[3] and ESMO guidelines[4] recommend that first-line treatment with cytotoxic chemotherapy for metastatic non-small cell lung cancer should include a platinum combination. Several randomized controlled studies have failed to show a clear superiority of one platinum-containing combination over another. A landmark Eastern Cooperative Oncology Group (ECOG) study comparing cisplatin-gemcitabine, cisplatin-paclitaxel, cisplatin-docetaxel, and carboplatin-paclitaxel, suggested similar overall response rates (approximately 19%), and median survival (7.9 months). 1- and 2-year overall survival was also similar at 33% and 11%, respectively.[5] Thus, significant unmet medical need exists to improve outcome for the majority of NSCLC subjects.

A recent Phase 3 randomized trial showed that continuing pemetrexed as a single agent after the completion of pemetrexed-based platinum doublet therapy (continuation maintenance therapy) increased PFS and OS for subjects with non-squamous NSCLC [http://www.ncbi.nlm.nih.gov/pubmed/23835707]. A separate randomized trial showed PFS and OS benefit for pemetrexed maintenance therapy initiated after the completion of platinum doublet therapy with agents other than pemetrexed in subjects with non-squamous NSCLC (switch maintenance therapy) [ref http://www.ncbi.nlm.nih.gov/pubmed/19767093]. Even with maintenance chemotherapy, median survival time in these trials was 13 – 14 months. Thus, significant unmet medical need exists to improve outcome for the majority of NSCLC subjects.

Large scale genomic characterization efforts including those conducted by the TCGA and the Lung Cancer Mutation Consortium (LCMC) have been conducted to identify molecular features that differ between NSCLC subtypes. These different features may explain the differential therapeutic responses among different NSCLC subtypes, e.g., of squamous and non-squamous NSCLC. The importance of molecular phenotyping has become increasingly clear as The Cancer Genome Atlas (TCGA) contributed results from a massive specific tumor type sequencing effort that provided a significant landmark for understanding the genetic mutation and gene expression profile of lung cancer in well characterized and distinct histologic subtypes.

Genomic-based classification methods are more likely to capture the molecular characteristics of the cancer cell and therefore classify NSCLC into prognostically informative subgroups. One such approach, termed LSP, is a gene expression profile established using a panel of 57 genes (52 classification genes plus 5 housekeeping genes) for the mRNA expression signature. This panel became known as the Lung Subtype Panel (LSP). Analysis in these three independent adenocarcinoma NSCLC cohorts demonstrated that LSP positive (LSP+) group of patients who had poor prognosis.[6]

3.2 Carboplatin and Paclitaxel

NCCN and ESMO guidelines include carboplatin AUC of 6 mg/mL•min and paclitaxel 200 mg/m^2 (administered every 3 weeks) among several recommended platinum doublet chemotherapy combinations for the treatment of metastatic NSCLC.[3,4]

Carboplatin is a commonly used platinum compound that acts by binding to deoxyribonucleic acid (DNA) and interrupting cell division. It is approved for the treatment of subjects with ovarian cancer. It is also used for the treatment of non-small cell lung cancer (NSCLC), small cell lung cancer (SCLC), head and neck cancer, endometrial cancer, metastatic seminoma and breast cancer. Carboplatin is eliminated by renal excretion, and the clearance is related to the glomerular filtration rate (GFR). Therefore it is dosed based on the GFR and the target area under the concentration versus time curve (AUC). The main side effect of carboplatin is myelosuppression. Other toxicities include nausea, vomiting, renal and neurotoxicity.[7,8]

Paclitaxel is an antimicrobial agent that promotes the assembly of microtubule formation and stabilizes them by preventing depolymerization. It is insoluble in water and is therefore formulated in cremophor. It is approved for the treatment of ovarian cancer, breast cancer, non-small cell lung cancer and Kaposi's sarcoma. It is also in use for the treatment of several other solid tumor malignancies. Main toxicities associated with the use of paclitaxel include myelosuppression, neuropathy and hypersensitivity reactions.[9,10]

Myelosuppression is the principal toxicity of a carboplatin/paclitaxel regimen in NSCLC, and peripheral neuropathy is a dose limiting toxicity of this regimen. In the ECOG study of systemic treatment for advanced NSCLC, grade 3/4 granulocytopenia was reported in 57% and 35% of subjects after the first and second cycles, but remained ≤ 22% during subsequent cycles. Grade 3/4 thrombocytopenia and anemia were reported in 47% and 33% of subjects, respectively. Grade 3/4 peripheral neuropathy was reported in 10% of subjects. Overall, 25% of the subjects discontinued therapy due to toxicities.[11,12]

3.3 PARP Inhibition for Cancer Treatment

Poly(ADP-ribose)-polymerase (PARP) is a nuclear enzyme that recognizes deoxyribonucleic acid (DNA) damage and facilitates DNA repair.[13-15] Inactive PARPs 1 and 2 bind to damaged DNA, which leads to their auto-activation. The resulting activated PARP then poly(ADP-ribosyl)ates many nuclear target proteins, including those that facilitate DNA repair of both single-stranded or double-stranded DNA breaks. Thus, inhibition of PARP results in less efficient DNA repair following a DNA damaging insult.

DNA-damaging agents, including cytotoxic chemotherapy and radiation therapy, remain a mainstay of treatment for advanced cancer. Since cancer cells are genetically unstable, often exhibiting complex karyotypes that include large deletions, insertions, and unbalanced translocations of chromosomal fragment, these cells are more susceptible than normal tissues to cytotoxicity induced by DNA-damaging agents.[16] Deficiencies in mismatch repair and homologous recombination render cells more dependent on PARP for DNA repair and, hence, are more prone to cytotoxicity induced by PARP inhibition.[17] In particular, tumor cells with BRCA1 or BRCA2 deficiencies are exquisitely sensitive to PARP inhibition, even in the absence of any other insults.[18,19]

Consistent with the observation that PARP activity may act as a resistance factor in some tumors, PARP inhibitors have been shown in preclinical models to sensitize tumors to a variety of DNA-damaging agents, including cross-linking chemotherapy agents such as carboplatin and ionizing radiation therapy. It is unknown whether the pattern or prevalence of DNA damage in tumors is correlated with PARP inhibitor efficacy. A direct correlation of this nature would support the use of PARP inhibitors in tumors with more DNA damage, such as lung tumors arising in smokers. DNA damage is 10-fold more prevalent in lung tumors from smokers compared to tumors from non-smokers, and many DNA changes in subjects who smoke are not reversed despite smoking cessation.[20-22]

3.4 Veliparib

A detailed discussion of the preclinical toxicology, metabolism, and pharmacology of veliparib can be found in the veliparib Investigator's Brochure.[23] Veliparib is a potent PARP inhibitor that delays the repair of DNA damage induced by chemotherapeutics. Veliparib increases sensitivity of tumor cells to DNA-damaging agents in vitro and in vivo, and inhibits PARP in murine tumors in vivo, human peripheral blood mononuclear cells (PBMCs) ex vivo, and human tumors ex vivo.

3.4.1 Preclinical Studies and Toxicology

Veliparib is a novel small molecule that is a potent inhibitor of both PARP-1 and PARP-2 with Ki's of 5 nM and 3 nM, respectively. In cells under oxidative stress, veliparib inhibits the PARP induced formation of poly-(ADP-ribose) (PAR) with an EC_{50} of 2.4 nM. In cellular assays, veliparib increases sensitivity of tumor cells to DNA-damaging agents including platinum agents, irinotecan, cyclophosphamide, temozolomide (TMZ) and radiation. In preclinical tumor models, veliparib enhances the anti-tumor efficacy of crosslinking agents (cisplatin, carboplatin), alkylating/methylating agents (TMZ, cyclophosphamide), topoisomerase inhibitors (irinotecan) and radiation.

Veliparib has been shown to enhance the efficacy of carboplatin or of carboplatin plus paclitaxel in several xenograft tumor models. In the BRCA1 deficient MX-1 model, veliparib administered at doses as low as 25 mg/kg/day significantly enhanced the efficacy of carboplatin. Veliparib administered at 50 and 100 mg/kg/day in combination with carboplatin 50 mg/kg/day intraperitoneally + paclitaxel 10 mg/kg/day IV caused regression of implanted MX-1 tumors, whereas veliparib alone or carboplatin + paclitaxel without veliparib did not.[24]

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 (convulsions, tremors), hematopoietic system (bone marrow depletion), 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). All findings were dose-dependent and reversible or self-limited. Veliparib was 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 photosensitivity tests.

3.4.2 Veliparib Pharmacokinetics/Pharmacodynamics

Clinical pharmacokinetic (PK) data available from Phase 1 studies indicate that exposure of veliparib is approximately dose-proportional over 10 through 500 mg BID dose range. The absorption of veliparib after oral dosing is rapid, and veliparib plasma concentrations peak at approximately 1 to 2 hours after dosing across dose levels. The terminal half-life of veliparib is about 6 hours, with minimal accumulation following multiple BID dosing. Food does not have a significant effect on veliparib bioavailability. On average, 73% and 86% of the orally administered veliparib dose were recovered in urine as the parent drug alone and as the parent drug plus an M8 metabolite, which indicates that veliparib is highly absorbed after oral dosing and the renal excretion is the 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 have been or are being evaluated in veliparib combination studies. There was no significant PK interaction between veliparib and TMZ, and preliminary results indicate the absence of a DDI between veliparib and carboplatin/gemcitabine, between veliparib and FOLFIRI, between veliparib and carboplatin/paclitaxel, or between veliparib and capecitabine/5-FU.

In Phase 0 Study A10-161, substantial inhibition of PARP activity was observed in tumor biopsies collected 3 to 6 hours after dosing in all 3 subjects who received a single-dose of 25 mg veliparib (92%, 95%, and 100%). For subjects receiving 50 mg, PARP activity inhibition in tumor biopsies averaged 75% at 3 to 6 hours after dosing (N = 3) and averaged 74% at 24 hours after dosing (N = 3). Therefore, both 25 mg and 50 mg veliparib doses were biologically active.

3.4.3 Veliparib Clinical Studies

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 radiation therapy.

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.[21] Data from non-AbbVie sponsored studies show veliparib has activity as monotherapy for treatment of ovarian cancer[25] and activity in combination with carboplatin + paclitaxel for treatment of early breast cancer.[26] 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 squamous NSCLC.

Phase 1 data from subjects treated with veliparib, carboplatin, and paclitaxel for advanced NSCLC are available from CTEP Study 7967.[27] Subjects had advanced solid tumors, received ≤ 3 prior chemotherapy regimens for advanced disease, and had ECOG performance status 0 to 2. Veliparib was given PO BID on Days 1 to 7 of each 21-day cycle, and paclitaxel and carboplatin were administered on Day 3. Dose escalation was started at veliparib 20 mg BID, paclitaxel 150 mg/m^2, and carboplatin AUC 5. Backbone therapy was escalated to paclitaxel 200 mg/m^2 and carboplatin AUC 6 in later cohorts. Among 68 initial subjects, partial responses were seen in 11 subjects and complete response in 2 subjects. Among 11 subjects with NSCLC (8 evaluable), 4 subjects had

responses and 3 additional subjects had stable disease at first tumor evaluation. 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/m^2, 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).

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/m^2 (IV) every 3 weeks plus veliparib/placebo 120 mg BID (PO) on 7 days around chemotherapy administration. All subjects have completed therapy. Data showed an improvement in median progression-free survival of 1.3 months (HR 0.38, 95% CI: 0.21 – 0.67) and an improvement in overall survival of 7.1 months (HR 0.43, 95% CI: 0.26 – 0.70) in 95 current smokers with NSCLC.[28] Similar effect on PFS and OS was observed in non-squamous NSCLC current smokers (data on file with 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 (± 3%) with or without veliparib.

At present, AbbVie's safety database for veliparib is based on the exposure of approximately 3,700 cancer subjects 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 subjects 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.

3.5 Study Rationale

Most NSCLC subjects are diagnosed at an advanced stage, conferring a poor prognosis. Current standard therapy for NSCLC provides time-to-progression of 4 to 6 months and overall survival of 10 to 12 months.[29] Phase 1 data and Phase 2 data described above suggest the addition of veliparib to carboplatin and paclitaxel may improve outcome of LSP+ subjects and/or current-smokers with advanced or metastatic NSCLC. Current smokers and former smokers will be enrolled into the trial, based on the findings from other research showing that DNA damage is 10-fold more prevalent in lung tumors from smokers compared to tumors from non-smokers, and that many DNA changes in smokers are not reversed despite smoking cessation.[20-22] All enrolled subjects with available tumor tissue will be evaluated for the LSP gene expression signature status. This study will investigate carboplatin and paclitaxel with veliparib with or without maintenance therapy compared to different platinum doublet chemotherapies for non-squamous NSCLC.

3.6 Differences Statement

The current study is the first randomized, open-label, multicenter, Phase 3 trial comparing veliparib plus carboplatin and paclitaxel versus Investigator's choice of standard chemotherapy in previously untreated subjects with metastatic or advanced non-squamous non-small cell lung cancer (NSCLC), now as defined by LSP status.

3.7 Benefits and Risks

This study proposes to establish improved clinical outcomes for subjects with advanced NSCLC through the addition of veliparib to standard therapy with carboplatin and paclitaxel. Preclinical data demonstrate that veliparib potentiates the anti-tumor activity of platinums, and data from early-phase studies (completed or preliminary) is consistent with these observations. As described above, non-squamous NSCLC study subjects

receiving veliparib with carboplatin and paclitaxel have shown favorable results for the current smokers group (as presented above) and the LSP+ group for the endpoints of overall survival. Overall survival is a clinically meaningful endpoint for NSCLC, as shown in several studies that have influenced treatment for the disease over the last 15 years.[31-34]

Risks in this study include toxicity from the addition of veliparib to standard therapy. Safety data from a blinded, randomized Phase 2 study of the proposed combination therapy in subjects with advanced NSCLC suggest low rates of additional toxicities and no compromise to the delivery of carboplatin and paclitaxel. Standard clinical practices to manage the toxicity of carboplatin + paclitaxel 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 Objectives

The primary objective of the study is to assess if treatment with veliparib plus carboplatin and paclitaxel results in improved survival compared to Investigator's choice of standard chemotherapy in LSP positive subjects with metastatic or advanced NSCLC.

The secondary objectives of the study are to assess if treatment with veliparib plus carboplatin and paclitaxel results in improved survival compared to Investigator's choice of standard chemotherapy in the entire study population with metastatic or advanced NSCLC; to compare progression-free survival (PFS) and to compare objective response rate (ORR) between the two treatment arms in LSP positive subjects or in the entire study population.

The tertiary objectives are to compare duration of overall response (DOR), ECOG performance status and Quality of Life (QoL) between the two treatment arms in LSP positive subjects or in the entire study population.

5.0 Investigational Plan

5.1 Overall Study Design and Plan: Description

This is a Phase 3, randomized, open-label, multi-center study evaluating the efficacy, safety, and tolerability of veliparib plus carboplatin and paclitaxel versus Investigator's choice of standard chemotherapy in subjects receiving first cytotoxic chemotherapy for advanced or metastatic non-squamous NSCLC who are current or former smokers. Subjects will be randomized in a 1:1 ratio to a maximum of 6 cycles of carboplatin/paclitaxel plus 120 mg BID of veliparib or a maximum of 6 cycles of Investigator's choice of platinum doublet chemotherapy (carboplatin/paclitaxel, cisplatin/pemetrexed, or carboplatin/pemetrexed). Following completion of platinum doublet therapy, maintenance pemetrexed is strongly encouraged for all subjects who are suitable candidates. Subject randomization will be stratified by smoking status (current versus former), by the Investigators' preferred platinum therapy (carboplatin/paclitaxel versus cisplatin/pemetrexed versus carboplatin/pemetrexed), by gender (male versus female) and by ECOG performance status (0 versus 1).

Subjects randomized to receive veliparib will begin oral veliparib dosing 2 days prior to the start of the carboplatin/paclitaxel infusion on C1D-2 and will continue twice a day BID through C1D5 (7 consecutive days). Subjects randomized to receive carboplatin/paclitaxel/veliparib will receive carboplatin (AUC 6 mg/mL•min) and paclitaxel (200 mg/m^2) IV infusion starting on Day 1 of each cycle. Subjects will receive a maximum of 6 cycles of treatment, unless toxicity requires cessation of therapy, or radiographic progression occurs prior to completing 6 cycles. Carboplatin/paclitaxel plus veliparib may be delayed or dose-modified due to toxicity. Should a subject not receive carboplatin and paclitaxel on Day 1 of any cycle, the cycle will be restarted with veliparib at the newly designated Day –2 when the subject is able to do so.

Subjects randomized to receive Investigator's choice of platinum doublet therapy will receive therapy on Day 1 of each cycle. Subjects will receive a maximum of 6 cycles of treatment, unless toxicity requires cessation of therapy, or radiographic progression occurs

prior to completing 6 cycles. Platinum doublet therapy may be delayed or dose-modified due to toxicity. Dose delays and modification will be at the discretion of the Investigator per local standard practice.

Suitable subjects in either arm will receive pemetrexed maintenance therapy after completion of platinum doublet chemotherapy regimen. Maintenance pemetrexed will be administered on Day 1 of each 21-day cycle. Maintenance therapy may be delayed or dose-modified due to toxicity. Subjects will continue to receive maintenance therapy until toxicity requires cessation of therapy, or radiographic progression occurs.

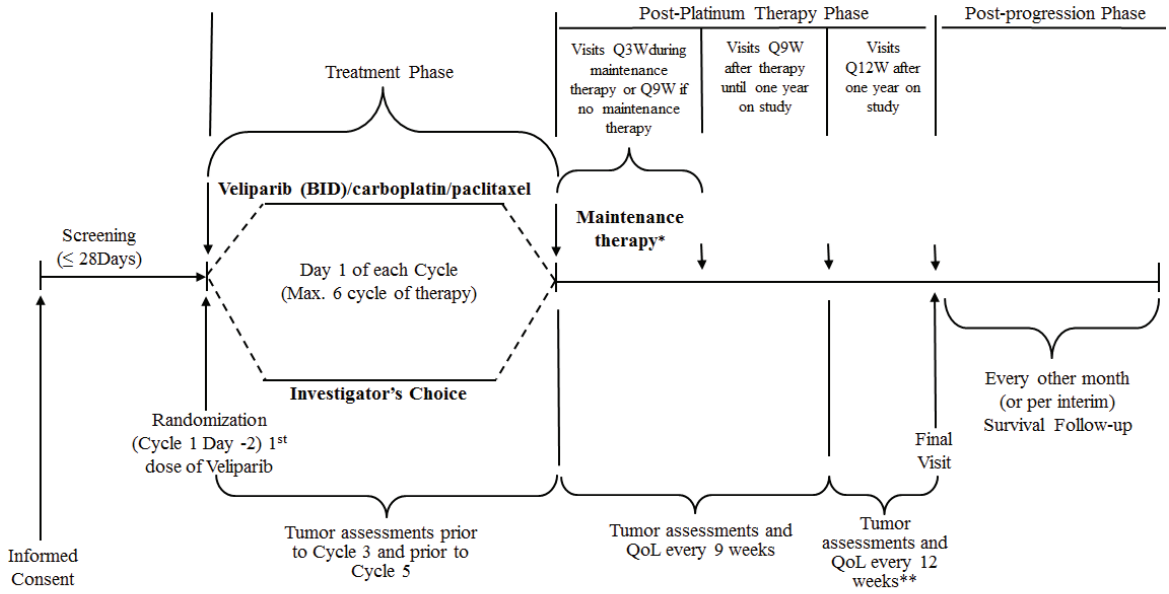
Subjects will have physician visits q3 weeks while receiving platinum doublet and maintenance therapy. After cessation of therapy, physician visits and quality of life measures will be performed q9 weeks until one year after randomization (or beyond 1 year until maintenance therapy is discontinued), then q12 weeks until radiographic progression or death. Tumor assessments will be performed at baseline, prior to treatment on Cycle 3 Day 1 and Cycle 5 Day 1. After cessation of platinum doublet therapy, tumor assessments will be performed q9 weeks until 1 year after C1D-2 (or beyond 1 year until maintenance therapy is discontinued), then q12 weeks until radiographic progression or death. Radiographic information will be collected to determine response according to the Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1.[38] Toxicities will be graded at each study visit according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.[36]

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 who have a Final Visit ≤ 30 days after the last dose of study drug will have a Follow-Up Visit approximately 30 days after the last dose of study drug. 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.

Subjects no longer undergoing clinical assessments will have survival information reported via the eCRF at two month intervals (or as requested by sponsor to support data analysis) beginning at the last clinical assessment and continuing until the endpoint of death, the subject has become lost to follow-up, or AbbVie terminates the study. In addition, all post treatment therapy, if applicable and available, will be collected in the survival follow-up period.

Figure 1. Study Schedule Schematic



*Until unacceptable toxicity or progression of disease
**Subjects still on maintenance therapy will continue tumor assessments and QoL every 9 weeks

Table 1. Treatment Schema for Each Cycle (Maximum of 6 Cycles)

Days	–2	–1	1	2	3	4	5	6 – 19
veliparib	Twice a day	Twice a day	Twice a day	Twice a day	Twice a day	Twice a day	Twice a day	
paclitaxel			Once					
carboplatin			Once					
Investigator's choice of Standard Doublet Chemotherapy			Once					

5.2 Selection of Study Population

The study population will consist of adult subjects who are current or former smokers with cytologically or histologically confirmed locally advanced or metastatic non-squamous NSCLC that is not amenable to surgical resection or radiation with curative intent, and who have not received prior cytotoxic chemotherapy or chemoradiotherapy for their NSCLC. Chemotherapy or chemoradiotherapy-received previously for adjuvant or neoadjuvant treatment will be allowed if last treatment was greater than 12 months prior to C1D-2. Subjects must meet all inclusion criteria and none of the exclusion criteria within 28 days of randomization. Subjects should be assessed for eligibility based on the most recent data collected prior to randomization.

5.2.1 Inclusion Criteria

1. Subject must be ≥ 18 years of age.
2. Life expectancy > 12 weeks (as per Investigator's clinical assessment).
3. Subject must have cytologically or histologically confirmed advanced or metastatic non-squamous NSCLC. Subjects with mixed histology tumors will be eligible if the tumor is predominant non-squamous histology and does not include tumor with small cell histology. Subjects must have a pathologist's report confirming non-squamous NSCLC available for collection by the sponsor. Subjects with EGFR mutation (exon 19 deletion or L858R mutation in exon 21) and/or ALK

gene rearrangement must have progressed after first line monotherapy treatment with targeted therapy.

4. Subject must have NSCLC that is not amenable to surgical resection or radiation with curative intent at time of study Screening.
5. Subjects must be current smokers (defined as having > 100 smoking events lifetime and having smoked within the past year) or former smokers (defined as having > 100 smoking events lifetime and having not smoked within the past year).
6. Subject must have at least 1 unidimensional measurable NSCLC lesion on a CT scan as defined by RECIST (version 1.1).
7. Subject must consent to provide archived tissue or cytology sample of NSCLC lesion (primary or metastatic) for analysis if available.
8. Subject must have no history of brain metastases or evidence of CNS tumors at screening assessment. Subjects with signs or symptoms of CNS involvement will undergo MRI (or CT scan if MRI is contraindicated) to confirm absence of CNS metastases.
9. Subject must have an Eastern Cooperative Oncology Group (ECOG) Performance Score of 0 – 1.
10. Subjects with fluid retention, including ascites or pleural effusion, may be allowed at the discretion of the Investigator.
11. Subject must have adequate bone marrow, renal and hepatic function as follows:
    - Bone Marrow: Absolute neutrophil count (ANC) $\geq 1{,}500/mm^3$ ($1.5 \times 10^9/L$); Platelets $\geq 100{,}000/mm^3$ ($100 \times 10^9/L$); Hemoglobin ≥ 9.0 g/dL;
    - Renal function: Serum calculated creatinine clearance > 50 mL/min according to the Cockcroft-Gault formula; confirmation of creatinine clearance/GFR may be done by a local direct measurement method (e.g., 24 hour urine collection or radioisotope) at the investigator's discretion;

- Hepatic function: AST and ALT ≤ 2.5 × ULN unless liver metastases are present, then AST and ALT < 5.0 × ULN; bilirubin ≤ 1.5 × ULN unless Gilbert's Syndrome is present, then bilirubin ≥ 1.5 × ULN.

12. 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 partners should practice at least one of the methods of birth control listed below during study and for at least 6 months after treatment with paclitaxel chemotherapy. Male subjects and their female partners of childbearing potential should practice at least one of the methods of birth control listed below during study and for at least 6 months after treatment with chemotherapy.
    - total abstinence from sexual intercourse (if it is the subject's preferred and usual lifestyle; for 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.
13. Subject must be capable of understanding and complying with parameters as outlined in the protocol and able to sign and date the informed consent approved by an Independent Ethics Committee (IEC)/Institutional Review Board (IRB), prior to the initiation of any screening or study-specific procedures.

Rationale for Inclusion Criteria

(1 – 10) These criteria were selected to ensure the appropriate subject population with sufficient disease severity for evaluation.

(11) This is standard criteria to ensure general good health and safety of the subjects.

(12) The impact of veliparib/carboplatin/paclitaxel on the unborn fetus is unknown, therefore, this criteria ensures that adequate precautions are taken to avoid pregnancy.

(13) This is standard criteria in accordance with harmonized Good Clinical Practice.

5.2.2 Exclusion Criteria

1. Subject has a known hypersensitivity to paclitaxel or to other drugs formulated with polyethoxylated castor oil (Cremophor).
2. Subject has a known hypersensitivity to platinum compounds.
3. Subjects with peripheral neuropathy ≥ grade 2.
4. Subjects with squamous NSCLC, or those with an untreated EGFR mutation (exon 19 deletion or L858R mutation in exon 21) and/or ALK gene rearrangement. Subjects' EGFR mutation and ALK gene rearrangement status must be known prior to study entry.
5. A history of seizure within 12 months prior to study entry.
6. Subject has received prior cytotoxic chemotherapy or chemoradiotherapy for NSCLC, except adjuvant or neoadjuvant therapy > 12 months prior to C1D-2, or subject has received targeted small molecule monotherapy for EGFR and/or ALK-positive disease ≤ 14 days prior to C1D-2 or biologic therapy ≤ 21 days prior to C1D-2.
7. Subject has received anti-cancer Chinese medicine or anti-cancer herbal remedies within 14 days prior to C1D-2.
8. Subject has undergone focal External Beam Radiation Therapy (EBRT) to bone ≤ 2 weeks prior to C1D-2; or subject has undergone EBRT to larger fields (i.e., 100 cm^2 to thorax) ≤ 4 weeks prior to C1D-2.

9. Any medical condition, which in the opinion of the Investigator, places the subject at an unacceptably high risk for toxicities, or any subject circumstance which prohibits trial participation according to local law.
10. Subject is pregnant or lactating.
11. Subject has previously been treated with a PARP inhibitor.
12. The subject has a history of another cancer within the past 3 years except cervical cancer in situ, in situ carcinoma of the bladder, squamous or basal cell carcinoma of the skin or another in situ cancer that is considered cured by the Investigator (e.g., in situ prostate cancer).

Rationale for Exclusion Criteria

(1 – 8, 11, 12) These criteria were selected to ensure the appropriate subject population with sufficient disease severity for evaluation.

(9) This is standard criteria to ensure general good health and safety of the subjects.

(10) The impact of veliparib/carboplatin/paclitaxel on the unborn fetus is unknown, therefore, this criteria ensures exclusion of pregnant 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.

For purposes of this protocol, anti-tumor treatment may be defined as, but is not limited to, anti-cancer agents (cytotoxic chemotherapy, immunotherapy, biologic and targeted therapy), radiotherapy and investigational agents. An investigational agent is any drug or therapy not currently approved for use in humans.

The AbbVie study designated physician (identified in Section 6.6.1) should be contacted if there are any questions regarding concomitant or prior therapies.

5.2.3.1 Prior Therapy

Subjects who have not received prior cytotoxic chemotherapy or chemoradiotherapy after diagnosis of non-squamous NSCLC are considered eligible for the study, except previous adjuvant/or neoadjuvant chemotherapy (with or without radiotherapy) for NSCLC will be allowed if completed greater than 12 months prior to C1D-2. Prior targeted small molecule monotherapy for EGFR and/or ALK-positive disease will be allowed if received > 14 days prior to C1D-2 and prior biologic treatment if received > 21 days prior to C1D-2.

Previous focal EBRT to a metastatic lesion will be allowed if completed greater than 2 weeks prior to C1D-2, or if greater than 4 weeks prior to C1D-2 if delivered to a larger field (i.e., 100 cm^2). Radiated lesions may not be considered target lesions.

5.2.3.2 Concomitant Therapy for Carboplatin/Paclitaxel

The locally approved product label or applicable Summary of Product Characteristics (SmPC) for carboplatin/paclitaxel and pemetrexed 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 H_2 antagonists).
Anti-cancer agents:	No anti-cancer agents or investigational agents may be taken throughout the study until after the Final Visit. 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 guidelines or ASCO guidelines. For anti-emetic therapy, ASCO guidelines recommend a two drug combination of palonosetron and dexamethasone. If palonosetron is not available, any of the first generation 5-HT^3 receptor antagonists may be used, preferably ondansetron or granisetron. ASCO dosing guidelines are as follows: Palonosetron: 0.25 mg 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-HT_3 receptor antagonist dosing Dexamethasone: 12 mg on Day 1 only[35] The use of bisphosphonates or denosumab for bone metastases is permitted, but it is strongly encouraged that first time administration of a bisphosphonate or denosumab should be delayed until after cycle 1 so as to not introduce both the veliparib and bisphosphonate/denosumab together for the first time.
Growth factors:	Biologic response modifiers administered for erythropoiesis (e.g., erythropoietin, darbepoetin alpha) may be administered during dosing of veliparib and carboplatin/paclitaxel. 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. After C1D1, growth factors may be given with the intent to prevent dose reductions or delays after C1D1.
Radiation:	Radiation therapy is not allowed during the study, except for palliative radiation to a non-target lesion. Sites to be radiated should be assessed for radiographic progression, prior to beginning radiotherapy. If the subject requires radiotherapy during the study, the AbbVie medical monitor must be contacted.

Surgery:	If the subject requires surgery during the study, the AbbVie medical monitor must be contacted.
Alternate therapy:	No herbal remedies or non-prescription anti-cancer supplements may be taken for cancer treatment concurrently with veliparib (a 14-day washout period from C1D-2 must be documented).
Therapies to take caution with when administered with paclitaxel or carboplatin	Carboplatin: Ototoxic and nephrotoxic drugs such as aminoglycosides, vancomycin, capreomycin and diuretics, may increase or exacerbate toxicity due to carboplatin induced changes in renal function. Paclitaxel: Caution should also be taken when administering paclitaxel concomitantly with known substrates (e.g., midazolam, buspirone, felodipine, lovastatin, eletriptan, repaglinide, rosiglitazone, sildenafil, simvastatin, and triazolam), inhibitors (e.g., atazanavir, clarithromycin, erythromycin, fluoxetine, gemfibrozil, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, and telithromycin), and inducers (e.g., rifampin, carbamazepine, phenytoin, phenobarbital, efavirenz, and nevirapine) of CYP3A4 or CYP2C8. Recommendations per the local label should be observed.

The locally approved product label or applicable Summary of Product Characteristics (SmPC) for cisplatin and pemetrexed (if randomized to Investigator's choice of standard chemotherapy) should be referenced for any concomitant therapy guidelines.

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.

Table 2. Study Activities

Activity	SCR[a]	Cycle 1 Day –2	Cycle 1 Day 1	Cycle 1 Day 15	Cycle 2 – 6 Day 1*	Final Visit[b]	30-day FU Visit[c]	Maintenance Therapy[d]	Post-Treatment Visits[p]	Survival Period
Informed Consent[e]	X									
Medical and Cancer History	X									
Physical Exam (including weight)	X[f]	X[f]			X	X	X	X	X	
Vital Signs	X	X		X	X	X	X	X	X	
12-Lead ECG	X					X				
Performance Status (ECOG)	X[q]	X[g]			X	X	X	X	X	
Documentation of Non-Childbearing Status or Pregnancy Test[h]	X	X			X					
Chemistry/Hematology[i]	X	X		X	X	X	X	X		
Urinalysis[i]	X					X				
aPTT, INR[i]	X									
Tumor Assessments	X[j]				X[j]	X[k]		X	X[j,k]	
MRI of the Brain[l]	X									
QoL Questionnaires[m]		X			X	X		X	X	
Adverse Event and Concomitant Medication Assessment	X	X		X	X	X	X	X	X	X[r]
Randomization[g]		X[g]								
Dispense veliparib[n]		X	X		X					
Administer premedication			X		X			X		
Administer platinum doublet chemotherapy[o]			X		X					
Administer maintenance pemetrexed								X		
Survival[r]										X

SCR = Screening

* Subjects who complete up to 6 treatment cycles or who discontinue treatment prior to reaching an event of disease progression are to continue visits and radiographic assessments until progression.

a. The Screening Visit must be performed within 28 days of randomization.

b. When an Investigator has determined that a subject should discontinue the study, a Final Visit will be conducted.

c. A Follow-Up visit is required if the Final Visit is < 30 days from the last administration of drug.

Table 2. Study Activities (Continued)

d. Following completion of platinum doublet therapy, maintenance pemetrexed 500 mg q3 weeks is strongly encouraged for all subjects who are suitable candidates. For those subjects in maintenance therapy, tumor assessments will be completed q9 weeks until radiographic progression.

e. Must be performed prior to initiation of any screening or study-specific procedures. Informed Consent may be obtained before 28 day screening window.

f. Physical exam not required, if performed within 7 days prior to randomization. Height is only measured at Screening.

g. May occur up to 4 calendar days before C1D-2 to facilitate dispensing and morning administration of Study Drug.

h. Serum pregnancy test will be done at Screening. Urine pregnancy test will be done prior to dosing at C1D-2 unless the serum pregnancy test was collected within 7 days of C1D-2. Local urine pregnancy testing should also be performed at each subsequent Cycle Day 1 visit. 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 per the discretion of the Investigator at any time during the study.

i. Study samples for central laboratory analysis may be performed within 72 hours of the scheduled day. A qualified (e.g., certification or accreditation) local laboratory may be used to perform laboratory analyses for treatment decisions but this cannot replace the central laboratory analysis on a protocol defined visit.

j. Baseline tumor assessments must be conducted within 28 days (inclusive) of randomization. Post-baseline tumor assessment will be conducted within 7 days prior to chemotherapy on C3D1 and C5D1, every 9 weeks ± 7 days from the last scan after treatment discontinuation until 1 year on study (or beyond 1 year until maintenance therapy is discontinued), and then every 12 weeks ± 7 days. If desired, tumor assessments during protocol therapy may be coordinated to occur on treatment initiation Days C3D1 and C5D1.

k. An unscheduled tumor assessment should be performed if the subject discontinues from the study for a reason other than radiographic progression, and no scan has been performed within the last 4 weeks.

l. Baseline MRI of the brain only for subjects with suspected metastases due to neurologic signs or symptoms. A CT scan may be performed if an MRI is contraindicated.

m. Questionnaires for the assessment of quality of life will be collected prior to dosing on C1D-2, C3D1, C5D1 and at the Final Visit, every 9 weeks until 1 year after beginning therapy (C1D-2) ± 7 days (or beyond 1 year until maintenance therapy is discontinued), then every 12 weeks ± 7 days and at the Final Visit.

n. Sufficient medication will be dispensed to cover the entire cycle. The site is advised to contact the subject on the morning of Day –2 to reiterate the dosing instructions of pre--chemotherapy-veliparib. It is recommended the site contact the subject on Day 5 to instruct about ceasing dosing.

o. Carboplatin and paclitaxel are to be given only after veliparib dosing on cycle Day –2 and Day –1 are confirmed.

p. Following treatment discontinuation, subjects will have post-treatment visits q9 weeks until one year after randomization, then q12 weeks until radiographic progression or death.

q. Screening ECOG may be used to stratify during a randomization call if randomization is performed prior to C1D-2.

r. All systemic post treatment anti-cancer therapy, if applicable and available, will be collected in the survival follow-up period.

Table 3. Schedule of Pharmacogenetic and Pharmacodynamic Assessments

Activity	Visit Schedule	Before Drug Administration	Sampling Plan Specimen Matrix
Optional with Consent PG Blood Sampling* Genetic (DNA)	C1D-2	Independent of dose	Whole Blood Frozen (as per the study specific laboratory manual)
PD Blood Sampling Plasma Markers[a]	C1D-2, C3D1	Pre-dose	Blood → Plasma Frozen (as per the study specific laboratory manual)
	Final Visit	At the time of the clinic visit	
Serum Markers	C1D-2, C3D1	Pre-dose	Blood → Serum Frozen (as per the study specific laboratory manual)
	Final Visit	At the time of the clinic visit	
Tissue Sample Collection	Screening or C1D-2		Archived FFPE tissue blocks (as per the study specific laboratory manual)

* (Optional) only to be collected after additional informed consent is obtained. If sample is not collected at C1D-2, it may be collected at any time throughout the study.

a. At C1D-2 and the Final Visit, 12 mL of blood for plasma markers will be collected. At C3D1, it will be 6 mL of blood.

Table 4. Schedule of Pharmacokinetic Assessments

Procedure	Visit Schedule	Before Drug Administration	After Veliparib AM Dose	Sampling Plan Specimen Matrix
Veliparib PK Sampling	C1D-2	--	1, 2, 3 h	Blood → Plasma Frozen (as per the study specific laboratory manual)
Veliparib PK Sampling[a]	C2D1, C3D1, C4D1.	0 h[a]	--	Blood → Plasma Frozen (as per the study specific laboratory manual)

a. Before the administration of the morning dose of veliparib.

5.3.1.1 Study Procedures

The study procedures outlined in Table 2 are discussed in detail in this section, with the exception of the monitoring of treatment compliance and adverse event information

(discussed in Section 5.5.6). All study data will be recorded on eCRFs with supporting source documentation.

Screening procedures will occur within 28 days prior to randomization. Radiographic assessments will occur within 28 days prior to randomization. For procedures performed at Screening and repeated prior to dosing on C1D-2, the later procedure performed prior to dosing will serve as baseline for clinical assessment. Subsequent study procedures should be performed within 4 days surrounding the scheduled study visit date during the post treatment phase a 7 day allowance is permitted. 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. Details about how informed consent will be obtained and documented are provided in Section 9.3.

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 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, tumor burden, metastatic sites, and prior treatment).

On C1D-2 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.

Physical Examination

A physical examination, including body weight, will be performed per Table 2. If the Screening physical examination is performed within 7 days of randomization, it is not required to repeat the exam on C1D-2 unless clinically indicated. 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.

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 post-menopausal 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 C1D-2. A urine pregnancy test should also be performed prior to dosing on C1D-2 if > 7 days since obtaining Screening serum test results. Local urine pregnancy testing should also be performed at each subsequent Cycle Day 1 visit. 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 per 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 5.

All laboratory samples will be assessed using a certified central laboratory and these data will be used for all data analysis. The central laboratory will provide instructions regarding the collection, processing and shipping of samples. All laboratory samples will be shipped to the central laboratory. A qualified (e.g., certification or accreditation) local laboratory may be used to perform laboratory analyses for treatment decisions as per standard of care. 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 6.1.1.

Table 5. Clinical Laboratory Tests

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

* Collected at Screening only.

** A renal function assessment will be done on all subjects at screening to assess eligibility.

*** 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) will be used in the evaluation of tumor responses, as per Table 2 (the estimated amount of radiation per CT scan would be 1700 mrem [17mSv] {700mrem [7mSv] for chest + 1000 mrem [10mSv] for abdomen and pelvis} as per http://www.ans.org/pi/resources/dosechart/). 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) can be conducted in cases where local laws/requirements mandate, but should have Sponsor approval prior to performing the MRI.

A baseline MRI (or CT if MRI is contraindicated) of the brain is to be performed on any subject with signs or symptoms suggesting CNS involvement by tumor.

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. An unscheduled assessment should be obtained in such subjects if a Final Visit will not be conducted. Subjects are to continue monitoring by the same methods unless evidence of tumor metastasis warrants otherwise or a medical contraindication is noted.

Randomization and Subject Number Assignment

An Interactive Response Technology system (IRT) will be utilized to register subjects.

Subjects who complete all Screening procedures and meet the eligibility criteria will proceed to randomization. The site will access the system within 4 calendar days prior to or on the subject's C1D-2 visit and a unique randomization number will be provided. 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.

Dispensing Study Drug

Randomized subjects will receive sufficient quantities of veliparib for Cycle 1 Days –2 and –1. Beginning with C1D1, subjects will receive veliparib for Days 1 – 5 of the current cycle and a separate bottle for Days –2, –1 of the following cycle. This dispensing schedule will allow subjects to begin veliparib dosing prior to Cycle 2 through Cycle 6 carboplatin and paclitaxel administration without requiring a return to the investigative site on Day –2. The IRT will assign every bottle of study drug to be dispensed to a subject. Prior to each scheduled drug dispensation visit (per Table 2), site personnel must contact IRT for the next bottle number assignment. Study medication cannot be

dispensed without contacting the IRT. AbbVie or designee will provide specific instructions on the use of IRT.

Trained site personnel will administer the carboplatin/paclitaxel intravenously on Day 1 of each 21-day cycle. Subjects will be supervised at the time of the infusion.

Quality of Life Assessment

Advanced lung cancer, is often symptomatic; thus the goals of treatment include maintenance of function and palliation of symptoms. Symptom management requires validated systematic symptom assessment by subjects. To assess the subject's health-related quality of life and symptoms, two questionnaires will be administered: the NCCN-Functional Assessment of Cancer Therapy (FACT) Lung Symptom Index-17 (NFLSI-17) questionnaire and the European Quality of Life-5 Dimensions (EQ-5D-5L). To minimize response bias, the questionnaires will be administered before drug administration and before subjects are informed of their tumor assessment. Subjects in both arms 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 NFLSI-17 is a validated scale developed as a brief version of the longer validated FACT-L questionnaire to overcome concerns about subject burden, interruption of clinic flow, and interpretability associated with longer questionnaires. The NFLSI-17 is a validated scale which has 17 items broken into the following: a 10-item disease-related symptoms-physical subscale (DRS-P), and a 3-item treatment side effect subscale, plus 4 additional items of importance to subjects regarding emotional health and quality of life. The NFLSI-17 was developed and validated along the steps that are consistent with the PRO guidance from the FDA, based on additional input from both advanced lung cancer subjects and clinical experts.

The EuroQol 5 Dimensions 5 Level (EQ-5D-5L) is a generic preference instrument that has been validated in numerous populations. The EQ-5D-5L is composed of 5 questions

that can be converted into a utility score for use in an economic evaluation to adjust life- years gained by the subject's health-related quality of life. The EQ-5D-5L also contains a visual analog scale (VAS) to assess the subject's overall health.

Survival Information

Subjects no longer undergoing clinical assessments will have survival information reported at 2-month intervals (or as requested by sponsor to support data analysis) beginning at the last clinical assessment and continuing until the endpoint of death, the subject has become lost to follow-up, or AbbVie terminates the study. 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. Post-study anti-cancer therapy information (including type of agent, initiation date, end date, and clinical response), if known, will also be collected in the survival follow-up period.

5.3.1.2 Blood Samples for Pharmacogenetic Analysis (Optional)

One 4 mL whole blood sample for DNA isolation will be collected on C1D-2 from each subject who consents to provide a sample for pharmacogenetic analysis. The procedure for obtaining and documenting informed consent is discussed in Section 9.3. If the sample is not collected on C1D-2, it may be collected at any time throughout the study.

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 ABT-888 (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 Markers

Approximately 12 mL (Baseline and Final Visit) or 6 mL (all other timepoints) of 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.

Blood Collection for Serum Markers

Approximately 5 mL of blood will be collected pre-dose by venipuncture as outlined in Table 3. The collection should be performed as described in the study specific laboratory manual. The complete process of clot formation, centrifugation, transfer to cryovials and freezing should be accomplished in less than 90 minutes from the time of blood draw.

Tissue Collection

Subjects must consent to provide available archival tumor (biopsy preferred, or cytology) for analysis. It is recognized that samples suitable for analysis will not be available from all consenting subjects. Tissue biopsies (10 – 15 slides with quality controls) or cytology slides (if no tissue specimen was obtained) may be provided to AbbVie as detailed in the study specific laboratory manual. Study-specific biopsies are not required for subject participation.

Shipment of Pharmacodynamic Samples

All pharmacodynamics samples should be labeled and shipped as outlined in the study specific laboratory manual. Also, pathology reports showing histologic confirmation of NSCLC should be labeled and shipped as outlined in the study specific laboratory manual. An inventory of the samples being shipped will accompany the package.

5.3.2 Drug Concentration Measurements

5.3.2.1 Collection of Samples for Pharmacokinetic Analysis

Veliparib Pharmacokinetic Specimen Collection

Approximately 3 mL of blood will be collected by venipuncture for veliparib concentrations at 0 hours (just before morning dose of veliparib) and other timepoints as specified per Table 4. The date/time of collection of each blood sample will be recorded. 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 validated methods under the supervision of the Drug Analysis Department at AbbVie. Plasma concentrations of veliparib metabolite(s) may be determined using validated or non-validated methods.

5.3.3 Efficacy Variables

The primary efficacy endpoint is overall survival (OS) in LSP+ subgroup. The secondary efficacy endpoints are: progression free survival (PFS) in LSP+ subgroup, objective response rate (ORR) in LSP+ subgroup, OS in all subjects, PFS in all subjects, and ORR in all subjects. The tertiary efficacy endpoints are duration of response, ECOG performance status and Quality of Life (QoL) in LSP+ subgroup and in all subjects.

5.3.4 Safety Variables

AbbVie will assess adverse events, laboratory data, ECGs and vital signs throughout the study. Adverse events intensity and laboratory evaluation changes will be assessed by utilizing NCI CTCAE version 4.0.

During the conduct of the study, the AbbVie medical and safety team will be monitoring blinded, subject laboratory results and serious adverse event data as they are reported.

5.3.5 Pharmacokinetic Variables

A nonlinear mixed effect modeling analysis will be conducted to estimate the population pharmacokinetic parameters of veliparib including apparent oral clearance (CL/F) and volume of distribution (V/F). Additional parameters may be calculated 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, 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, other 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 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 cancer-directed radiotherapy or surgery related to clinical disease progression, or alternate anti-cancer agents during the study period. Palliative radiation to a symptomatic bone lesion is permitted during study if no radiographic progression is visible on radiographic assessments.
- The subject experiences treatment toxicity which, in the Investigator's opinion, prohibits further therapy 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 decides to withdraw consent for any reason.
- Any other medical reason that AbbVie or the study Investigator deems appropriate.

Discontinued subjects will not be replaced.

5.4.1 Discontinuation of Individual Subjects

Subjects who complete therapy or who discontinue treatment prior to reaching an event of disease progression are to continue assessments until disease progression. Refer to Section 5.3.1 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 an investigator identifies disease progression or at which a subject meets other criteria for study discontinuation will be considered the Final Visit. The reason(s) for the discontinuation from the study will be recorded and assessments will be performed per Table 2. It is preferable that Final Visit procedures be conducted prior to the initiation of another anticancer therapy. However, these procedures should not interfere with the initiation of any new treatments or therapeutic modalities that the Investigator feels are necessary to treat the subject's condition.

Subjects who have a Final Visit within 30 days of therapy will have one Follow-Up Visit approximately 30 days after the last dose of study drug. This Follow-Up Visit does not need to be performed for subjects who have had a Final Visit conducted ≥ 30 days after last dose of study drug.

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.

Subjects no longer undergoing clinical assessments will have survival information reported at 2-month intervals (or as requested by sponsor to support data analysis) beginning at the last clinical assessment and continuing until the endpoint of death, the subject has become lost to follow-up, or AbbVie terminates the study.

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 7.0.

5.4.1.1 Discontinuation of Veliparib and Carboplatin/Paclitaxel and Pemetrexed

Subjects will receive veliparib, carboplatin and paclitaxel up to a maximum of 6 cycles 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 (e.g., discontinuation of paclitaxel for neurotoxicity). The subject may continue on therapy with the remaining agent in combination with veliparib. If toxicities have resulted in discontinuation of both carboplatin and paclitaxel, veliparib will also be discontinued. At the Investigator's discretion, carboplatin and/or paclitaxel administration may continue after veliparib has been discontinued. Suitable subjects will receive pemetrexed maintenance therapy until reaching a protocol defined event of disease progression or experiencing unmanageable toxicity.

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.

If AbbVie terminates the study for safety reasons, AbbVie will immediately notify the Investigator by telephone and subsequently provide written instructions for study termination.

5.5 Treatments

5.5.1 Treatments Administered

Subjects will receive the following:

- Veliparib 120 mg BID Days –2 through 5; carboplatin AUC 6 mg/mL•min administered on Day 1; and paclitaxel 200 mg/m^2 administered on Day 1 of each 21-day cycle;
- Investigator's choice of standard doublet chemotherapy (one of the following three options, to be administered on Day 1 of each 21-day cycle):
  - Carboplatin AUC 6 mg/mL•min + paclitaxel 200 mg/m^2
  - Cisplatin 75 mg/m^2 + pemetrexed 500 mg/m^2
  - Carboplatin AUC 6 or AUC 5 mg/mL•min + pemetrexed 500 mg/m^2
- Maintenance therapy after completion of up to 6 cycles of either veliparib/carboplatin/paclitaxel or Investigator's choice of chemotherapy. Maintenance therapy consists of pemetrexed or no maintenance therapy (observational). Maintenance pemetrexed will be administered as 500 mg/m^2 on Day 1 of each 21-day cycle. Following completion of platinum doublet therapy, maintenance pemetrexed is strongly encouraged for all subjects who are suitable candidates.

5.5.1.1 Administration of Veliparib

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

It is recommended that if a subject misses a scheduled dose of veliparib 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, 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 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 was administered. Subjects will be instructed to store veliparib according to specific directions included in Section 5.5.2.3. Subjects should return bottles of veliparib (empty, partially filled or full) to the study site prior to each cycle and at the Final Visit.

5.5.1.2 Administration of Carboplatin/Paclitaxel with Veliparib

Carboplatin and paclitaxel will be administered intravenously on Day 1 of every 21-day cycle. Carboplatin and paclitaxel are to be given only after veliparib dosing on cycle Day –2 and Day –1 are confirmed. If veliparib was not taken by the subject on Day –2 and Day –1, a new supply of veliparib is to be dispensed, and Day –2 and Day –1 are to be repeated for that cycle. Paclitaxel will be infused prior to carboplatin. Investigators should evaluate subjects for carboplatin and paclitaxel treatment per the locally approved product label, local practice, or applicable SmPC. Paclitaxel will be administered intravenously over 3 hours at a dose of 200 mg/m^2. Carboplatin will be administered intravenously over approximately 15 to 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:[37]

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 = 6, the maximum dose is 6 × 150 = 900 mg
- For a target AUC = 5, the maximum dose is 5 × 150 = 750 mg*
- For a target AUC = 4, the maximum dose is 4 × 150 = 600 mg*

* Only for subjects who have had dose modifications.

5.5.2 Identity of Investigational Product

Information regarding the veliparib formulation to be used in this study is presented in Table 6.

Table 6. Identity of Investigational Product

Study Drug	Dosage Form	Strength	Route of Administration	Manufacturer
Veliparib (ABT-888)	Capsule	40 mg active	Oral	AbbVie
Carboplatin*	Vials**	150 mg and/or 450 mg	Intravenous (IV)	various***
Paclitaxel*	Vials**	100 mg	Intravenous (IV)	various***

* Carboplatin and paclitaxel will be supplied as investigational medicinal products in required countries for the veliparib treatment arm only.

** Carboplatin and paclitaxel dosage forms could vary based on the supplier as a powder for solution for injection, a concentrate for solution for infusion, or a solution for infusion/injection.

*** Carboplatin and paclitaxel will be sourced from approved marketed products from various commercial manufacturers depending on availability.

5.5.2.1 Medicinal Products for Combination Treatment

The non-investigational medicinal products available for use within the Investigator's choice of standard chemotherapy treatment arm are listed in Table 7. Unless directed otherwise by AbbVie, sites are responsible for obtaining the non-investigational products listed below as needed to conduct this study at their site. For operational or logistical purposes, AbbVie may supply non-investigational products depending on need.

Table 7. Non-Investigational Medicinal Products (Investigator's Choice Treatment Arm)

Study Treatment	Dosage Form	Route of Administration
Carboplatin (commercially available)*	Vial**	Intravenous (IV)
Paclitaxel (commercially available)*	Vial**	Intravenous (IV)
Cisplatin (commercially available)*	Vial**	Intravenous (IV)
Pemetrexed (commercially available)*	Vial**	Intravenous (IV)

* Carboplatin, paclitaxel, cisplatin and pemetrexed formulations may vary based on regional source. Carboplatin, paclitaxel, cisplatin and pemetrexed supplied by AbbVie will be sourced from approved marketed products from various commercial manufacturers depending on availability.

** Carboplatin, paclitaxel, cisplatin, pemetrexed dosage forms could vary based on the supplier as a powder for solution for injection, a concentrate for solution for infusion, or a solution for infusion/injection.

5.5.2.2 Packaging and Labeling

Veliparib will be packaged in bottles containing 15 or 33 of the 40 mg strength capsules. This will allow for the 2 or 5 days of administration with one 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.

Carboplatin, paclitaxel, cisplatin and pemetrexed supplied by AbbVie will be provided in commercial primary packaging with a study label affixed to the primary container and/or secondary packaging.

Instructions for the handling of study supplies to the study site are available in the veliparib IB, study Dosing Cards and from participants at the Site Initiation Visit.

5.5.2.3 Storage and Disposition of Study Drug

Veliparib

Table 8. Study Drug Storage Conditions

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

Paclitaxel

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

Pemetrexed

Vials must be stored between 15° to 25°C (59° to 77°F) (or per locally approved label or SmPC).

Cisplatin

Vials must be stored between 15° to 25°C (59° to 77°F) and protected from light or as directed per locally approved label or SmPC).

Carboplatin

Vials must be stored between 15° to 25°C (59° to 77°F) and protected from light or as directed per locally approved label or SmPC.

5.5.3 Preparation of Intravenous Solutions

All chemotherapy agents administered as part of this protocol should be prepared for administration by clinicians experienced in the preparation and handling of parenteral cancer chemotherapeutic agents. For complete product information, site personnel should consult their locally approved commercial product labeling or current Summary of Product Characteristics (SmPC) if applicable.

1. Carboplatin

Carboplatin is commercially available as both premixed aqueous solutions and lyophilized powders containing 50 mg, 150 mg, or 450 mg of carboplatin per vial. All forms of carboplatin are intended for administration by intravenous infusion after further dilution in a suitable parenteral solution such as 5% Dextrose in Water (D5W) or 0.9% Sodium Chloride Injection.

2. Paclitaxel

Paclitaxel is commercially available as a nonaqueous solution containing 30 mg, 100 mg or 300 mg paclitaxel per vial. All forms of paclitaxel are intended for administration by intravenous infusion after further dilution in a suitable parenteral solution such as 5% Dextrose in Water (D5W) or 0.9% Sodium Chloride Injection.

3. Cisplatin

Cisplatin is commercially available as both premixed aqueous solutions and lyophilized powders containing 50 mg, 100 mg, or 200 mg cisplatin per vial. Cisplatin is intended for administration by slow intravenous infusion after further

dilution in a suitable parenteral solution such as 5% Dextrose in Water (D5W) or 0.9% Sodium Chloride Injection.

4. Pemetrexed

Pemetrexed (ALIMTA) is commercially supplied as a white to either light yellow or green-yellow lyophilized powder in a vial containing 100 mg or 500 mg pemetrexed. Both forms of pemetrexed are intended for administration by intravenous infusion after further dilution in a suitable parenteral solution such as 5% Dextrose in Water (D5W) or 0.9% Sodium Chloride Injection.

5.5.4 Method of Assigning Subjects to Treatment Groups

All subjects in the study 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 system 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 randomized into the study, the reason for screen failure will be documented in the source document and in the eCRF. For others, the site will access the system on or prior to (within 4 calendar days) the subject's C1D-2 and a unique randomization number will be provided.

The stratification factors used for the randomization should be the last values on the date of randomization and should be consistent with those on the eCRF.

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.

5.5.5 Selection and Timing of Dose for Each Subject

All subjects randomized to the experimental arm will receive 120 mg of veliparib orally for BID dosing for 7 of 21 days in each treatment cycle (maximum 6 cycles) as described above. No other doses or schedules of veliparib are being investigated in this 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 should be taken as directed by the Investigator. Carboplatin, paclitaxel, cisplatin and pemetrexed will be administered intravenously by trained site personnel.

Subjects will be instructed to return all veliparib bottles (empty, partially filled or full) to the study site personnel prior to each cycle, their first post-treatment visit and/or at the Final Visit. The site staff will document the bottles returned and the number of capsules per bottle on the appropriate form.

Unless otherwise directed by the Investigator, a subject will be considered compliant with study drug, veliparib, 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, paclitaxel, cisplatin and pemetrexed given to each subject in the source documents and on the eCRF. If the Investigator will obtain carboplatin, paclitaxel, cisplatin and pemetrexed commercially, site inventory and accountability of carboplatin, paclitaxel, cisplatin and pemetrexed will not be performed, and drug accountability forms will not be provided. If the investigative site has received carboplatin, paclitaxel, cisplatin and pemetrexed centrally sourced by AbbVie, site inventory and accountability of these drugs will be performed in the IRT system and drug accountability forms will be provided.

Upon receipt of a shipment of veliparib and if applicable carboplatin, paclitaxel, cisplatin and pemetrexed, the representative at each site will; 1) open and inspect the shipment; 2) verify that the veliparib 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. 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 supplied by AbbVie 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 and if applicable carboplatin, paclitaxel, cisplatin and pemetrexed 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.

Upon completion or termination of the study, all original bottles/cartons containing unused veliparib and if applicable carboplatin, paclitaxel, cisplatin and pemetrexed (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/cartons 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 3.4.2 and Section 3.4.3 suggest the addition of veliparib to carboplatin and paclitaxel may improve outcome of non-squamous NSCLC subjects who are current or former smokers. This randomized,

open-label study will evaluate the effect of veliparib added to carboplatin and paclitaxel for treatment of advanced or metastatic non-squamous NSCLC in subjects who are current or former smokers.

ESMO[4] and National Comprehensive Cancer Network (NCCN) guidelines[3] recommend first-line cytotoxic chemotherapy treatment for metastatic non-small cell lung cancer with a platinum doublet combination. Commonly used platinum doublets for advanced NSCLC are cisplatin-gemcitabine, cisplatin-paclitaxel, cisplatin-docetaxel, carboplatin-paclitaxel, and cisplatin-pemetrexed (non-squamous NSCLC only). Several randomized controlled studies have failed to show a clear superiority of one platinum-containing combination over another for squamous NSCLC. Furthermore, Phase 3 randomized trials showed that continuing pemetrexed as a single agent after the completion of platinum doublet therapy increased PFS and OS for subjects with non-squamous NSCLC [http://www.ncbi.nlm.nih.gov/pubmed/23835707]. Thus, platinum doublet chemotherapy followed by pemetrexed maintenance therapy is a suitable treatment for the control subjects in this study.

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. Overall survival is a widely accepted endpoint of clinical importance for the evaluation of subjects with previously untreated advanced or metastatic NSCLC. Multiple prior studies have led to changes in standard practice after demonstrating a survival advantage in such subjects.[30-34] The secondary endpoints of progression-free survival and overall response rate may add supporting evidence to a finding of improved overall survival with veliparib combination therapy. Additionally, RECIST 1.1 is a validated guideline for the measurement of responses in subjects with advanced or metastatic solid tumors.

5.6.3 Suitability of Subject Population

Subjects who are either current or former smokers with pathologically documented and previously untreated advanced or metastatic non-squamous NSCLC will be selected to participate in this study. The proposed inclusion and exclusion criteria are anticipated to result in a study subjects population representative of advanced or metastatic non-squamous NSCLC subjects who are current or former smokers and who receive cytotoxic therapy according to current practice guidelines.[3,4] The poor prognosis of subjects with advanced or metastatic NSCLC suggests that potential late adverse events, such as the theoretical risk of secondary malignancies due to inhibition of DNA repair by PARP inhibitors, are unlikely to be encountered in this study. Of note, the risk of secondary malignancies after veliparib combined with carboplatin and paclitaxel will be assessed in a large randomized study of subjects with early breast cancer.

5.6.4 Selection of Doses in the Study

The doses of standard therapy (carboplatin, paclitaxel, cisplatin, pemetrexed) are guideline-recommended for advanced NSCLC.[3,4] Doses of standard therapy (carboplatin and paclitaxel) 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 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 showed an improvement in overall survival of 8.0 months in current smokers with non-squamous NSCLC.

The maximum dose of veliparib for any subject in this study is 120 mg BID for 7 of 21 days per cycle.

5.7 Dose Reductions or Delays

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 9 and Appendix G. 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 the next cycle.

All dose reductions are considered permanent. Re-escalation of chemotherapy treatments or veliparib doses is not allowed.

If a subject experiences an adverse event that results in a delay in starting chemotherapy or requires that study regimen is delayed or interrupted during a cycle, Day 1 of a treatment cycle may follow the prior cycle Day 1 by greater than 21 days. In this case, study activities should be aligned with newly designated cycle Day 1 as per Section 5.3.1. For modification of agents that are not administered with veliparib (i.e., Investigator's choice platinum doublet chemotherapy, maintenance pemetrexed), the Investigator should follow procedures as defined in the locally approved product label or applicable Summary of Product Characteristics (SmPC).

Table 9. Suggested Guidelines for Veliparib + Carboplatin/Paclitaxel Independent Dose Reductions

Dose Level	carboplatin	paclitaxel	veliparib
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

5.7.1 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 carboplatin/paclitaxel 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 Cycle Day –2 but subsequently experiences an event requiring delay of the carboplatin/paclitaxel 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 ≥ grade 2 event of seizure attributed to veliparib, veliparib is to be discontinued and the event should be discussed with the AbbVie medical monitor.

5.7.2 Carboplatin/Paclitaxel 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 carboplatin/paclitaxel if above information is not available are summarized in Appendix G. 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.

Carboplatin and paclitaxel are to be delayed if veliparib was not taken by the subject on Day –2 and Day –1. In such a case, a new supply of veliparib is to be dispensed, and Day –2 and Day –1 are to be repeated for that cycle.

5.7.2.1 Suggested Guidelines for Carboplatin and Paclitaxel Dose Reductions and Delays

Hematologic Toxicity

For absolute neutrophil count (ANC) < 1,500/mm^3 or platelet count < 100,000/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.

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 × ULN with increased ALT above ULN that is attributed to protocol therapy, paclitaxel is to be held until bilirubin is ≤ 1.5 × ULN, and the dose is to be reduced by one level when treatment is resumed.

For ALT > 5 × ULN with bilirubin < 1.5 × 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.

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, 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 Events

An adverse event (AE) is defined as any untoward medical occurrence in a subject 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), then 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.

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, compression of adjacent thoracic structures or distant metastases are presented in Appendix F 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.

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)	Death.

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.

6.3.1 Deaths

For this protocol, mortality is an efficacy endpoint. Deaths that occur during the protocol specified adverse event reporting period (Section 6.6.1) 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 subject 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 subject 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.

6.3.2 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 be captured as adverse events, but will not be subject to expedited reporting unless locally required.

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 (for the purpose of this section, study drug is considered veliparib, carboplatin, paclitaxel, cisplatin or pemetrexed):

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 paclitaxel, to cisplatin, to pemetrexed, and to NSCLC. Most events will be reasonably related to one treatment or to the underlying 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.

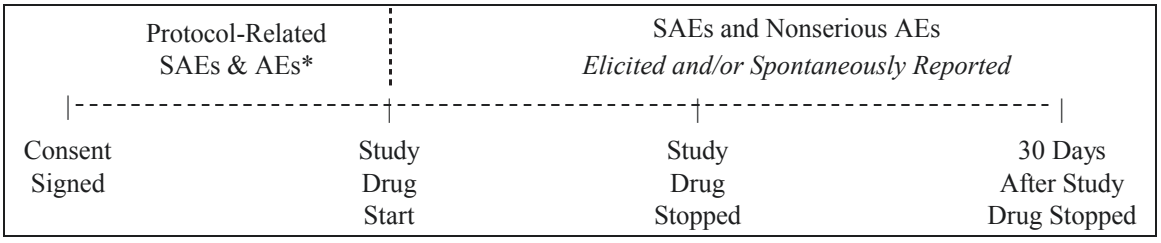
If an Investigator's opinion of no reasonable possibility of being related to study drug or NSCLC is given, an Other cause of event must be provided by the Investigator for the serious adverse event.

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 2.

Figure 2. 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 Reporting Serious Adverse Events

In the event of a serious adverse event, whether associated with study drug or not, the Investigator will notify the 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 operable should be faxed or emailed to the Clinical Pharmacovigilance within 24 hours of 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 Section 6.2 or Appendix F would not be expedited as individual safety case reports to regulatory authorities unless locally required.

FAX to:
Email to: [redacted]

For safety related concerns, contact the Oncology Safety Management Team at:

Oncology Group Safety Management
AbbVie
[redacted]
1 North Waukegan Road, IL 60064

Office:
Fax:
Email: [redacted]

Or the physician through the operator at:

Phone: [redacted]

Primary Study Designated Physician:

[redacted]
AbbVie
[redacted]
200 Sidney Street
Cambridge, MA 02139

Office:
Mobile:
Email: [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 or Summary of Product Characteristics (SmPC) for carboplatin, paclitaxel, cisplatin and pemetrexed.

In Japan, the principal investigator will provide documentation of all serious adverse events to the Director of the investigative site and the Sponsor.

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 Oncology Group Safety Management Team listed in protocol Section 6.6.1 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 (or per local labels) 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 or female partner 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

Management of toxicity should be performed by Investigators according to standard medical practice and according to local label for toxicity due to chemotherapy treatment. See Section 5.7 for dose delay and modification guidelines to adjust study treatment medication for any observed 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:

[redacted]
AbbVie
8401 TransCanada Highway
Saint-Laurent, Quebec
H4S 1Z1 Canada

Office: [redacted]
Fax:
Cell:

Medical Monitor:

[redacted]
AbbVie
[redacted]
200 Sidney Street
Cambridge, MA 02139

Office: [redacted]
Cell:
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.

In Japan, the Investigator will record all protocol deviations in the appropriate medical records at site.

8.0 Statistical Methods and Determination of Sample Size

8.1 Statistical and Analytical Plans

For all statistical analyses, statistical significance will be determined by a two-sided P value ≤ 0.05. The date of randomization (enrollment) is defined as the date that the IRT issues a randomization number.

The primary, secondary, and tertiary efficacy analyses will be performed on all subjects randomized in the study.

8.1.1.1 Demographics

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.

8.1.1.2 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 analysis will be a comparison of OS distributions between the 120 mg of veliparib BID + carboplatin/paclitaxel and Investigators' choice of platinum therapy groups in LSP + subgroup.

Time to death for a given subject will be defined as the number of days from the date that the subject was randomized to the date of the subject's death. All events of death will be included, regardless of whether the event occurred while the subjects was still taking study drug, or after the subject discontinued study drug. If a subject has not died, then the data will be censored at the date when the subject was last known to be alive.

8.1.2.2 Secondary Efficacy Endpoints

Fixed sequence testing procedure will be used for analyses of the primary and secondary efficacy endpoints to control for the family-wise error rate (FWER). If veliparib treatment group is not statistically significantly better than the Investigator's choice of platinum therapy group for the primary efficacy endpoint of OS in LSP + subgroup, then statistical significance will not be declared for any of the secondary efficacy endpoints, regardless of the observed *P* values.

P values for the secondary efficacy analyses will be subject to multiple comparison adjustments using the fixed sequence test method, with the analyses performed in the following order: progression-free survival (PFS) in LSP+ subgroup, objective response rate (ORR) in LSP+ subgroup, OS in all subjects, PFS in all subjects, ORR in all subjects.

PFS will be defined as the number of days from the date that the subject was randomized to the date the subject experiences an event of disease progression or to the date of death (all causes of mortality) if disease progression is not reached. All events of disease progression will be included, regardless of whether the event occurred while the subject was still taking study drug or had previously discontinued study drug. However, if a disease progression event occurs after a subject misses two or more consecutive disease assessments, then this subject's data will be censored at the last disease progression assessment prior to the missing disease assessments. All events of death will be included for subjects who had not experienced disease progression provided the death occurred within 18 weeks of the last tumor assessment. If the subject does not have an event of disease progression nor has the subject died, the subject's data will be censored at the date of the subject's last disease assessment.

ORR is defined as the proportion of subjects with complete or partial response using measurements according to RECIST (version 1.1). For the measurement of ORR, only confirmed responses will be considered.

8.1.2.3 Tertiary Efficacy Endpoints

In addition to the primary and secondary efficacy analyses, the tertiary objectives are to compare DOR, ECOG performance status and Quality of Life (QoL) via the NCCN-Functional Assessment of Cancer Therapy (FACT) Lung Symptom Index-17 (NFLSI-17) questionnaire and the European Quality of Life-5 Dimensions (EQ-5D-5L) in LSP+ subjects and in the entire study population between the two treatment groups.

The duration of overall response for a given subject will be defined as the number of days from the day the criteria are met for CR or PR (whichever is recorded first) to the date that PD is objectively documented or subject's death. If a subject is still responding then the subject's data will be censored at date of the last available disease progression assessment. For subjects who never experienced CR or PR, the subject's data will not be included in the DOR analysis.

8.1.3 Timing of Efficacy Analyses and Safety Evaluations

When LSP status is determined by the Qiagen assay for all submitted tissue samples, there will be a final review of the eCRF data. 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 clinical database data will be extracted for documentation and statistical analyses of the efficacy and safety data. The exact data cutoff date for the analyses of primary and secondary efficacy endpoints will be specified in the statistical analysis plan (SAP) prior to database lock.

8.1.4 Primary Analysis of Efficacy

For the LSP+ subgroup, the distribution of OS will be estimated for each treatment group using Kaplan-Meier methodology and compared between the two treatment groups (HR and 95%CI) using Cox proportional hazard model with treatment group, important prognostic factors (e.g., ECOG, Investigator's choice of platinum therapy, and smoking status) as the covariates.

8.1.5 Secondary Analysis of Efficacy

8.1.5.1 Progression Free Survival in LSP + Subgroup

For the LSP+ subgroup, the distribution of PFS will be estimated for each treatment group using Kaplan-Meier methodology and compared between the two treatment groups (HR and 95% CI) using Cox proportional hazard model with treatment group, important prognostic factors (e.g., ECOG, Investigator's choice of platinum therapy and smoking status) as covariates.

8.1.5.2 Objective Response Rate in LSP+ Subgroup

For the LSP+ subgroup, the ORR (proportion of subjects with a complete or partial response based on RECIST (version 1.1) will be estimated and compared between the two treatment groups using Fisher's exact test. In addition, 95% confidence interval will be constructed for the estimated proportion.

8.1.5.3 Overall Survival in All Subjects

For all subjects, the distribution of OS will be estimated for each treatment group using Kaplan-Meier methodology and compared between the two treatment groups (HR and 95% CI) using the Cox Proportional hazard model with treatment group, important prognostic factors (e.g., ECOG, smoking history (current versus former smokers), and Investigator's choice of platinum therapy) as the covariates.

8.1.5.4 Progression Free Survival in All Subjects

For all subjects, the distribution of PFS will be estimated for each treatment group using Kaplan-Meier methodology and compared between the two treatment groups (HR and 95%CI) using Cox proportional hazard model with treatment group, important prognostic factors (e.g., ECOG, and Investigator's choice of platinum therapy, smoking status) as the covariates.

8.1.5.5 Objective Response Rate in All Subjects

For all subjects, the ORR will be estimated and compared between the two treatment groups using Cochran-Mantel-Haenszel (CMH) test; stratified by ECOG, smoking history (current versus former smokers), and Investigator's preferred platinum therapy. In addition, 95% confidence interval will be constructed for the estimated proportion.

8.1.6 Tertiary Analyses of Efficacy

8.1.6.1 Duration of Overall Response

The distribution of duration of overall response (DOR) will be estimated for each treatment group using Kaplan-Meier methodology for LSP+ as well as for all subjects.

8.1.6.2 General Quality of Life

European Quality of Life-5 Dimensions (EQ-5D-5L)

Descriptive statistics will be calculated for individual 5 items and the utility score, and the EQ-5D-5L VAS score including mean change from baseline to each scheduled post-baseline visit.

EQ-5D-5L will be evaluated for subjects with a baseline assessment and at least one post-baseline EQ-5D-5L assessment that generate a score. Scores at baseline and change from baseline scores for each time point will be quantified using descriptive statistics. The EQ-5D-5L data may be used for additional health economic analyses whose results may be reported separately from the Clinical Study Report.

Subject Reported Symptoms and QOL (NFLSI-17)

The objective is to compare subject reported symptoms and QOL following treatment with the veliparib treated arm and the comparator arm for both the LSP+ subgroup and the whole population using the NFLSI-17 questionnaire. Summary statistics of the NFLSI-17 questionnaire including the individual questions and the 4 subscales and their changes from baseline will be calculated at each assessment time point for both study arms. Appropriate multivariate repeated measures models will be used to compare changes from baseline between the arms. Specific hypotheses, statistical methods and analysis plan details of these subject-reported outcomes will be provided in the Statistical Analysis Plan. For the development of the hypotheses, the DRS-P subscale score will be the primary PRO variable to estimate the differences in disease-related symptoms between the treatment arms.

8.1.6.3 Performance Status

Changes from baseline in ECOG performance status will be summarized using descriptive statistics for each scheduled post-baseline visit and for LSP+ as well as all subjects. Subjects that do not have a baseline measurement or do not have any post-baseline measurements will not be included. Changes from baseline to each scheduled post-

baseline visit in ECOG performance status will be compared between the two treatment groups, using an analysis of covariance (ANCOVA) model with treatment group as the factor and baseline value as a covariate.

8.1.7 Additional Exploratory Efficacy Analyses

In addition to the covariate-adjusted Cox PH analyses for the primary and secondary efficacy endpoints, the unstratified log-rank test and unstratified and unadjusted Cox proportional hazards model may be used for the comparison of OS and PFS between the two treatment groups.

For those subjects who take other chemotherapies during the study or after they withdraw from the study, the primary efficacy OS and secondary efficacy endpoint of PFS will be censored at the date of subject's initiation of other chemotherapies. These modified primary and secondary efficacy endpoints will be analyzed using the same methodology as detailed in previous sections.

For OS and PFS, additional analyses may also be performed, such as 1) including only data and events occurring on treatment or within 30 days of the last dose of study drug, 2) using a Cox proportional hazard model to explore the effect of baseline factors including (but not limited to) the following: LSP subgroup, LSP status unknown, tumor stage (locally advanced versus metastatic), smoking history (current smoker versus former smoker), gender, ECOG performance status (0 versus 1), Investigator's preferred platinum doublet therapy, and others, 3) subgroup analysis by LSP subgroup, LSP status unknown, smoking history (current smoker versus former smoker), gender, ECOG performance status (0 versus 1), Investigator's preferred platinum doublet therapy, post-study anti-cancer therapy (e.g., anti-PD-1, IO etc.) and others. Alternative statistical analyses may be performed if deemed as necessary and helpful in understanding the drug effect.

8.1.8 Statistical Analysis of Safety

Statistical analyses of safety data described below will be performed for three study population separately: LSP+ subgroup, LSP– subgroup, entire study population. The

safety of veliparib BID + carboplatin/paclitaxel will be assessed by evaluating study drug exposure, adverse events, serious adverse events, all deaths, as well as changes in laboratory determinations and vital sign parameters. Subjects who were randomized but did not receive study drug will not be included in the analyses of safety.

8.1.8.1 Duration of Study Drug

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

8.1.8.2 Adverse Events

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. 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 summarized by preferred terms within a System and Organ Class according to the most current MedDRA dictionary. In addition, the percentage of subjects experiencing an adverse event at a NCI CTCAE version 4.0 toxicity grade, and relationship to study drug will be provided. The percentages of subjects experiencing an adverse event will be presented by treatment group.

8.1.8.3 Serious Adverse Events

Serious adverse events will be summarized using the same methods as Adverse Events described above.

8.1.8.4 Deaths

The number of subject deaths will be summarized 1) for deaths occurring within 30 days of the last dose of study drug, 2) for deaths occurring more than 30 days of 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.

8.1.8.5 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 vital sign parameters. If more than one measurement exists for a subject on a particular day, then 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 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.

8.1.8.6 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 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 last post-baseline measurement collected no more than 30 days after the last dose of study drug. The percentage of subjects experiencing a shift from baseline grades of 0 to 2 to maximum post-baseline grades of 3 to 4, and from baseline grades of 0 to 2 to final post-baseline grades of 3 to 4 between veliparib BID + carboplatin/paclitaxel and Investigators' preferred platinum therapy will be presented. 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.

8.2 Determination of Sample Size

Sample size calculation for the original protocol:

Assuming the true hazard ratio of overall survival (OS) for current smokers in favor of the veliparib 120 mg BID + carboplatin/paclitaxel treatment group is 0.64, a total of 210 death events in the current smokers will be needed for the study to have

approximately 90% power at one-sided α level of 0.025 to detect a statistically significant treatment effect for the veliparib 120 mg BID + carboplatin/paclitaxel group using the log-rank test for OS. A total of approximately 300 current smokers will be enrolled to acquire the 210 death events.

During the enrollment period for approximately 300 current smokers, it is anticipated that approximately 225 former smokers will enroll concurrently. Assuming the true hazard ratio of OS for current plus former smokers in favor of the veliparib 120 mg BID + carboplatin/paclitaxel treatment group is 0.71, a total of 369 death events in current plus former smokers will be needed for the study to have approximately 90% power at one-sided α level of 0.025 to detect a statistically significant treatment effect for the veliparib 120 mg BID + carboplatin/paclitaxel group using the log-rank test for OS.

Sample size consideration for OS analysis in LSP+ subgroup

Based on 452 subjects having LSP tissue samples (assumed 76% LSP sample availability rate), the below table provides the power and number of events with different assumed LSP+ rate if the treatment allocation ratio is 1:1 in the LSP+ subgroup and true HR of OS is 0.65 in LSP+ subgroup.

Number of LSP+ Subjects (LSP+ rate)	Number of Events in LSP+	Power for OS in LSP+ Subgroup (one-sided alpha = 0.025)
271 (60%)	216	89%
226 (50%)	180	82%
180 (40%)	144	73%

8.3 Randomization Methods

The randomization numbers of the study will assign subjects in a 1:1 ratio to either the 120 mg of veliparib BID + carboplatin/paclitaxel treatment group or the Investigators' preferred platinum therapy treatment group. Subject randomization will be stratified by smoking status (current versus former), Investigators' preferred platinum therapy (carboplatin/paclitaxel versus cisplatin/pemetrexed versus carboplatin/pemetrexed),

ECOG (0 versus 1) and gender (male versus female). Current smokers are defined as subjects having > 100 smoking events lifetime and having smoked within the past year while former smokers are defined as subjects having > 100 smoking events lifetime and having not smoked within the past year.

A set of subject randomization schedules 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.

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. On-site monitoring will be performed before, during and after the trial to assure appropriate conduct of the trial in accordance with ICH GCP. 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.

9.3.1 Informed Consent Form and Explanatory Material

In Japan, the principal investigator will prepare the consent form and explanatory material required to obtain subject's consent to participate in the study with the cooperation of the sponsor and will revise these documents as required. The prepared or revised consent forms and explanatory material will be submitted to the sponsor. Approval of the IRB will be obtained prior to use in the study.

9.3.2 Revision of the Consent Form and Explanatory Material

In Japan, when important new information related to the subject's consent becomes available, the principal investigator will revise the consent form and explanatory material based on the information without delay and will obtain the approval of the IRB prior to use in the study. The investigator will provide the information, without delay, to each subject already participating in the study, and will confirm the intention of each subject to continue the study or not. The investigator shall also provide a further explanation using the revised form and explanatory material and shall obtain written consent from each subject of their own free will to continue participating in the study.

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 trial 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 subject 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 (Director of the Site in Japan) and AbbVie. Continuation of this study beyond this date must be mutually agreed upon in writing by both the Investigator (Director of the Site in Japan) 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. In the study site in Japan, the Investigator will provide a final report to the Director of the Site following conclusion of the study. Upon providing the report, the

Director of the Site will notify AbbVie or their representative and IEC/IRB of the conclusion of the study in Japan.

The Investigator (Director of the Site in Japan) must retain any records related to the study according to local requirements. If the Investigator (Director of the Site in Japan) 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 Medicines Agency (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. The sponsor may also end the study upon confirmation that the primary endpoint was statistically met.

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 Randomized, Open-Label, Multicenter, Phase 3 Trial Comparing Veliparib Plus Carboplatin and Paclitaxel Versus Investigator's Choice of Standard Chemotherapy in Subjects Receiving First Cytotoxic Chemotherapy for Metastatic or Advanced Non-Squamous Non-Small Cell Lung Cancer (NSCLC) and Who Are Current or Former Smokers
Protocol Date:	09 May 2018

Signature of Principal Investigator Date

Name of Principal Investigator (printed or typed)

15.0 Reference List

1. World Health Organization, International Agency for Research on Cancer. World cancer report: 2008.
2. Weir HK, Thun MJ, Hankey BF, et al. Annual report to the nation on the status of cancer, 1975-2000, featuring the uses of surveillance data for cancer prevention and control. J Natl Cancer Inst. 2003;95(17):1276-99.
3. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines). Non-Small Cell Lung Cancer, version 4. 2014. Available from: http://www.nccn.org/index.asp.
4. Peters S, Adjei AA, Gridelli C, et al. Metastatic non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2012 Oct;23 (Suppl 7):vii56-64.
5. Schiller JH, Harrington, D, Belani CP, et al. Comparison of Four Chemotherapy Regimens for Advanced Non-Small Cell Lung Cancer. New Engl J Med. 2002;346(2):92-8.
6. Mayhew G, Hayes N, Perou C, et al. Survival differences of adenocarcinoma lung tumors with squamous cell carcinoma or neuroendocrine profiles by gene expression subtyping. Abstract #384. Presented at the 16th World Conference on Lung Cancer, September 06-09, 2015; Denver, CO.
7. Carboplatin [package insert]. Irvine, CA; Teva Parenteral Medicines, Inc., 2010.
8. National Cancer Institute [updated 2011 May 5] Available from: http://www.cancer.gov/cancertopics/druginfo/carboplatin.
9. Paclitaxel [package insert]. Bedford, OH; Ben Venue Laboratories, Inc., 2010.
10. National Cancer Institute [updated 2010 July 2] Available from: http://www.cancer.gov/cancertopics/druginfo/paclitaxel.
11. Langer CJ, Leighton JC, Comis RL, et al. Paclitaxel and carboplatin in combination in the treatment of advanced non-small-cell lung cancer: a phase II toxicity, response and survival analysis. J Clin Onc. 1995;13(8):1860-70.

12. Rosell R, Gatzemeier U, Betticher DC, et al. Phase III randomised trial comparing paclitaxel/carboplatin with paclitaxel/cisplatin in patients with advanced non-small-cell lung cancer: a cooperative multinational trial. Ann Oncol. 2002;13(10):1539-49.
13. Chiarugi A. Poly (ADP-ribose) polymerase: killer or conspirator? The 'suicide hypothesis' revisited. Trends Pharmacol Sci. 2002;23(3):122-9.
14. Virag L, Szabo C. The therapeutic potential of poly(ADP-Ribose) polymerase inhibitors. Pharmacol Rev. 2002;54(3):375-429.
15. Schreiber V, Amé JC, Dollé P, et al. Poly(ADP ribose) polymerase-2 (PARP-2) is required for efficient base excision DNA repair in association with PARP-1 and XRCC1. J Biol Chem. 2002;277(25):23028-36.
16. Sharpless NE, DePinho RA. Telomeres, stem cells, senescence, and cancer. J Clin Invest. 2004;113(2):160-8.
17. Curtin NJ, Wang LZ, Yiakouvaki A, et al. Novel poly(ADP-ribose) polymerase-1 inhibitor, AG14361, restores sensitivity to temozolomide in mismatch repair-deficient cells. Clin Cancer Res. 2004;10(3):881-9.
18. Bryant HE, Schultz N, Thomas HD, et al. Specific killing of BRCA2-deficient tumours with inhibitors of poly(ADP-ribose) polymerase. Nature. 2005;434(7035):913-7.
19. Farmer H, McCabe N, Lord CJ, et al. Targeting the DNA repair defect in BRCA mutant cells as a therapeutic strategy. Nature. 2005;434(7035):917-21.
20. Govindan R, Ding L, Griffith M, et al. Genomic landscape of non-small cell lung cancer in smokers and never-smokers. Cell. 2012,150(6):1121-34.
21. Mao L, Lee JS, Kurie JM, et al. Clonal genetic alterations in the lungs of current and former smokers. J Natl Cancer Inst. 1997;89(12):857-62.
22. Beane J, Sebastiani P, Liu G, et al. Reversible and permanent effects of tobacco smoke exposure on airway epithelial gene expression. Genome Biol. 2007;8(9):R201.
23. AbbVie. Veliparib (ABT-888) Investigator Brochure, Edition 11. 22 June 2017.

24. AbbVie. R&D/10/098. Effects of veliparib (ABT-888) in syngeneic and xenograft tumors series 1. 2010.

25. Coleman RL, Sill M, Aghajanian CA, et al. Phase II evaluation of the potent, highly selective parp inhibitor veliparib in the treatment of persistent or recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer in patients who carry a germline BRCA1 or BRCA2 mutation – a gynecologic oncology group study. SGO 2013 Annual Meeting on Women's Cancer; March 2013; Los Angeles, CA.

26. Rugo HS, Olopade O, DiMichele A, et al. veliparib/carboplatin plus standard neoadjuvant therapy for high-risk breast cancer: First efficacy results from the I-SPY 2 TRIAL. In: Proceedings of the 2013 San Antonio Breast Cancer Symposium; 13 December, 2013; San Antonio, TX. Abstract S5-02.

27. Ramalingam S. A phase I study of veliparib (ABT-888) in combination with carboplatin and paclitaxel in advanced solid malignancies. J Clin Oncol 30, 2012 (suppl; abstr 3049).

28. Ramalingam SS, Blais N, Mazières J, et al. Smoking status to predict sensitivity to PARP inhibitor, veliparib, in patients with advanced NSCLC. 2015;33 (15 Suppl):8038.

29. Non-Small Cell Lung Cancer Treatment. National Cancer Institute. Available from: http://www.cancer.gov/cancertopics/pdq/treatment/non-small-cell-lung/healthprofessional/page11.

30. Wozniak AJ, Crowley JJ, Balcerzak SP, et al. Randomized trial comparing cisplatin with cisplatin plus vinorelbine in the treatment of advanced non-small-cell lung cancer: a Southwest Oncology Group study. J Clin Oncol. 1998;16(7):2459-65.

31. Sandler AB, Nemunaitis J, Denham C, et al. Phase III trial of gemcitabine plus cisplatin versus cisplatin alone in patients with locally advanced or metastatic non-small-cell lung cancer. J Clin Oncol. 2000;18(1):122-30.

32. Shepherd FA, Rodrigues P, Ciuleanu T, et al. Erlotinib in previously treated non-small-cell lung cancer. N Engl J Med. 2005;353(2):123-32.

33. Sandler A, Gray R, Perry MC, et al. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. N Engl J Med. 2006;355(24):2542-50.

34. Scagliotti GV, Parikh P, von Pawel J, et al. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naive patients with advanced-stage non-small-cell lung cancer. J Clin Oncol. 2008;26(21):3543-51.

35. Basch E, Prestrud AA, Hesketh PJ, et al. Antiemetics: American Society of Clinical Oncology clinical practice guideline update. J Clin Oncol. 2011;29(31):4189-98.

36. Common Terminology Criteria for Adverse Events, Version 4.0, DCTD, NCI, NIH, DHHS. 28 May 2009. Available from: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev4.pdf. Accessed on: 29 July 2009.

37. FDA Carboplatin Dosing Notification, 2010. Available from: http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm228974.htm.

38. Eisenhauer EA, Therasse P, Bogaerts B, et al. New response evaluation criteria in solid tumors: Revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45(2):228-47.

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
[redacted]	[redacted]	Clinical Program Development
		Oncology Development
		Oncology Development
		Statistics
		Pharmacokinetics

Appendix C. Japan Specific Information

1.0 Clinical Expense and Compensation

1.1 Expenditure of the Clinical Expense

The sponsor will pay the expenses related to this study to the investigative site in accordance with "Special Healthcare Expenditure." The expenses of screening test, etc. will be paid based on the contract concluded with each investigative site. To lighten the burden imposed on the subject with participation to the study, transportation expenses, etc. will be paid to the subjects via participating investigative site in accordance with the rules of the investigative site.

1.2 Compensation for Health Impairment and Insurance

1. If a subject suffers some sort of health impairment due to this study, the investigative site will provide treatment and take other necessary measures. Among the expenses required for the treatment, the amount not covered by health insurance that the patient must pay directly will be borne by the sponsor only when the event is associated with the use of the study drug.
2. When a subject suffers health impairment during this study and a dispute occurs or might occur between the investigative site and the subject, the investigative site will report it to the sponsor immediately, and resolve it. The sponsor will cooperate with the investigative site in resolving the problem.
3. When the investigative site must compensate to the subject's health impairment caused by this study, the compensation paid by the investigative site and the expenses related to any dispute will be borne in full by the sponsor, except in cases where the responsibility for the problem is attributed to the investigative site. This shall not apply to cases where the health impairment occurred because the investigative site performed the study with marked deviation from the GCP or the protocol or because of a deliberate action or a major error by investigative site.

4. When a subject suffers health impairment during this study and liability for compensation arises, the sponsor will compensate in accordance with the SOP regarding the compensation prepared in advance.
5. The sponsor will obtain clinical study insurance and will take other necessary measures to cover the claims and compensation required in such cases.

Appendix D. NFLSI-17

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

			Not at all	A little bit	Some-what	Quite a bit	Very much
DRS-P	GP1	I have a lack of energy	0	1	2	3	4
	GP4	I have pain	0	1	2	3	4
	C2	I am losing weight	0	1	2	3	4
	B1	I have been short of breath.....	0	1	2	3	4
	HI7	I feel fatigued.....	0	1	2	3	4
	L2	I have been coughing	0	1	2	3	4
	BP1	I have bone pain	0	1	2	3	4
	L4	Breathing is easy for me	0	1	2	3	4
	C6	I have a good appetite	0	1	2	3	4
DRS-E	GF5	I am sleeping well.....	0	1	2	3	4
	GE6	I worry that my condition will get worse	0	1	2	3	4
TSE	GP2	I have nausea	0	1	2	3	4
	B5	I am bothered by hair loss	0	1	2	3	4
	GP5	I am bothered by side effects of treatment ...	0	1	2	3	4
FWB	L1	My thinking is clear.....	0	1	2	3	4
	GF3	I am able to enjoy life	0	1	2	3	4
	GF7	I am content with the quality of my life right now	0	1	2	3	4

Appendix E. EQ-5D-5L Health Questionnaire

EQ-5D-5L

Health Questionnaire

(English version for the US)

Under each heading, please check the ONE box that best describes your health TODAY

Mobility

I have no problems walking ☐
I have slight problems walking ☐
I have moderate problems walking ☐
I have severe problems walking ☐
I am unable to walk ☐

Self-Care

I have no problems washing or dressing myself ☐
I have slight problems washing or dressing myself ☐
I have moderate problems washing or dressing myself ☐
I have severe problems washing or dressing myself ☐
I am unable to wash or dress myself ☐

Usual Activities (e.g., work, study, housework, family or leisure activities)

I have no problems doing my usual activities ☐
I have slight problems doing my usual activities ☐
I have moderate problems doing my usual activities ☐
I have severe problems doing my usual activities ☐
I am unable to do my usual activities ☐

Pain/Discomfort

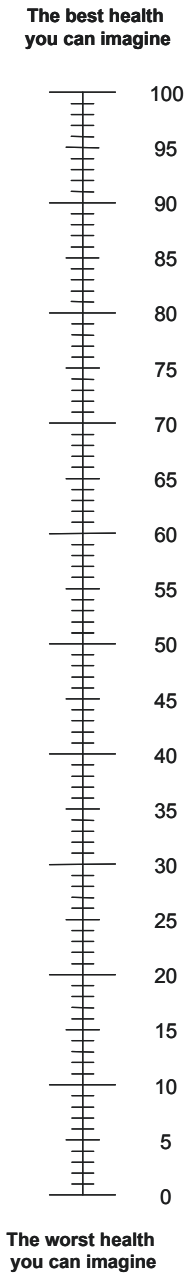
I have no pain or discomfort ☐
I have slight pain or discomfort ☐
I have moderate pain or discomfort ☐
I have severe pain or discomfort ☐
I have extreme pain or discomfort ☐

Anxiety/Depression

I am not anxious or depressed ☐
I am slightly anxious or depressed ☐
I am moderately anxious or depressed ☐
I am severely anxious or depressed ☐
I am extremely anxious or depressed ☐

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



Appendix F. 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

Appendix G. Suggested Guidelines for carboplatin/paclitaxel Dose Delay or Reduction

Adverse Event	Carboplatin Dose	Paclitaxel Dose
Grade 3/4 Neutropenia without fever	Wait until ANC ≥ 1,500/mm^3.	Wait until ANC ≥ 1,500/mm^3.
Grade 3/4 Febrile Neutropenia	Reduce to Dose Level –1 for 1st episode and Dose Level –2 for 2nd episode. Any further reduction after consultation with AbbVie medical monitor. Consider Prophylactic G-CSF after 1st episode	Reduce to Dose Level –1 for 1st episode and Dose Level –2 for 2nd episode. Any further reduction requires consultation with AbbVie medical monitor. Consider Prophylactic G-CSF after 1st episode.
Grade 3/4 nausea, vomiting despite standard supportive care, or grade 3/4 Stomatitis	Dose Level –1 for 1st episode and Dose Level –2 for 2nd episode. Any further reduction after consultation with AbbVie medical monitor.	Dose Level –1 for 1st episode and Dose Level –2 for 2nd episode. Any further reduction requires consultation with AbbVie medical monitor.
Grade 4 Thrombocytopenia	Dose Level –1 for 1st episode and Dose Level –2 for 2nd episode. Any further reduction after consultation with AbbVie medical monitor.	Dose Level –1 for 1st episode and Dose Level –2 for 2nd episode. Any further reduction requires consultation with AbbVie medical monitor.
Bilirubin > 1.5 × ULN with increased ALT above ULN	No Change	Hold until recovery, then reduce to Dose Level –1 for 1st episode and Dose Level –2 for 2nd episode. Any further reduction requires consultation with AbbVie medical monitor.
ALT > 5 × ULN with Bilirubin < 1.5 × ULN	No Change	Reduce to Dose Level –1 for 1st episode and Dose Level –2 for 2nd episode. Any further reduction requires consultation with AbbVie medical monitor.
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 H. 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: ● Longest diameter ≥ 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 ≥ 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 ≥ 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 subject, 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 × 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 subject who has visceral disease at baseline and while on study has a CT or MRI brain ordered which reveals metastases. The subject'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 I. 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] AbbVie [redacted] 381 Plantation Street Worcester, MA 01605	Phone: Cell: [redacted]

Has been changed to read:

Sponsor/Emergency Contact:	[redacted] AbbVie [redacted] 200 Sidney Street Cambridge, MA 02139	Phone: Cell: [redacted]

Section 1.2 Synopsis
Previously read:

AbbVie Inc.	**Protocol Number:** M14-359
Name of Study Drug: Veliparib (ABT-888)	**Phase of Development:** 3
Name of Active Ingredient: Not applicable	**Date of Protocol Synopsis:** 17 July 2015
Protocol Title: A Randomized, Open-Label, Multicenter, Phase 3 Trial Comparing Veliparib Plus Carboplatin and Paclitaxel Versus Investigator's Choice of Standard Chemotherapy in Subjects Receiving First Cytotoxic Chemotherapy for Metastatic or Advanced Non-Squamous Non-Small Cell Lung Cancer (NSCLC) and Who Are Current or Former Smokers	
Objectives: The primary objective of the study is to assess if treatment with veliparib plus carboplatin and paclitaxel results in improved survival compared to Investigator's choice of standard chemotherapy in current smokers with metastatic or advanced NSCLC. The secondary objectives of the study are to assess if treatment with veliparib plus carboplatin and paclitaxel results in improved survival compared to Investigator's choice of standard chemotherapy in current plus former smokers with metastatic or advanced NSCLC; to compare progression-free survival (PFS) and to compare objective response rate (ORR) between the two treatment arms in current smokers or in current plus former smokers. The tertiary objectives are to compare duration of overall response (DOR), ECOG performance status and Quality of Life (QoL) between the two treatment arms in current smokers or in current plus former smokers.	
Investigators: Multicenter	
Study Sites: 150	
Study Population: Subjects receiving first cytotoxic chemotherapy for Metastatic or Advanced Non-Squamous Non-Small Cell Lung Cancer (NSCLC) who are current or former smokers. Chemotherapy for adjuvant or neoadjuvant treatment of NSCLC received greater than 12 months prior to Cycle 1 Day –2 (C1D-2) will be allowed.	
Number of Subjects to be Enrolled: Approximately 525	

Methodology:

This is a Phase 3, randomized, open-label, multi-center study evaluating the efficacy, safety, and tolerability of veliparib plus carboplatin and paclitaxel versus Investigator's choice of standard chemotherapy in subjects receiving first cytotoxic chemotherapy for advanced or metastatic non-squamous NSCLC who are current or former smokers. Subjects will be randomized in a 1:1 ratio to a maximum of 6 cycles of carboplatin/paclitaxel plus 120 mg BID of veliparib or a maximum of 6 cycles of Investigator's choice of platinum doublet chemotherapy (carboplatin/paclitaxel, cisplatin/pemetrexed, or carboplatin/pemetrexed), unless treatment is discontinued for toxicity or cancer progression. Investigators may elect to administer maintenance pemetrexed regardless of which therapy their subjects are randomized to receive. Following completion of platinum doublet therapy, maintenance pemetrexed is strongly encouraged for all subjects who are suitable candidates.

Methodology (Continued):

Subject randomization will be stratified by smoking status (current versus former), by the Investigators' preferred platinum doublet therapy (carboplatin/paclitaxel versus cisplatin/pemetrexed versus carboplatin/pemetrexed), by gender (male versus female) and by ECOG performance status (0 versus 1).

Subjects randomized to receive veliparib will begin oral veliparib dosing 2 days prior to the start of the carboplatin/paclitaxel infusion on C1D-2 and will continue twice a day (BID) through C1D5 (7 consecutive days).

Subjects randomized to receive carboplatin/paclitaxel/veliparib will receive carboplatin (AUC 6 mg/mL•min) and paclitaxel (200 mg/m^2) IV infusion starting on Day 1 of each cycle. Subjects will receive a maximum of 6 cycles of treatment, unless toxicity requires cessation of therapy, or radiographic progression occurs prior to completing 6 cycles. Carboplatin/paclitaxel plus veliparib may be delayed or dose-modified due to toxicity. Should a subject not receive carboplatin and paclitaxel on Day 1 of any cycle, the cycle will be restarted with veliparib at the newly designated Day –2 when the subject is able to do so.

Subjects randomized to receive Investigator's choice of platinum doublet therapy will receive therapy on Day 1 of each cycle. Subjects will receive a maximum of 6 cycles of treatment, unless toxicity requires cessation of therapy, or radiographic progression occurs prior to completing 6 cycles. Platinum doublet therapy may be delayed or dose-modified due to toxicity. Dose delays and modification will be at the discretion of the Investigator per local standard practice.

Suitable subjects in either arm will receive pemetrexed maintenance therapy after completion of platinum doublet chemotherapy regimen. Maintenance pemetrexed will be administered on Day 1 of each 21-day cycle. Maintenance therapy may be delayed or dose-modified due to toxicity. Subjects will continue to receive maintenance therapy until toxicity requires cessation of therapy, or radiographic progression occurs. Veliparib will not be administered during the maintenance phase.

Subjects will have physician visits q3 weeks while receiving platinum doublet and maintenance therapy. After cessation of therapy, physician visits and quality of life measures will be performed q9 weeks until 1 year after beginning treatment (C1D-2) (or beyond 1 year until maintenance therapy is discontinued), then q12 weeks until radiographic progression. Tumor assessments will be performed at baseline prior to treatment on Cycle 3 Day 1 and Cycle 5 Day 1. After cessation of platinum doublet therapy, tumor assessments will be performed q9 weeks until 1 year after beginning treatment (C1D-2) (or beyond 1 year until maintenance therapy is discontinued), then q12 weeks until radiographic progression or death. Radiographic information will be collected to determine response according to the Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1. Toxicities will be graded at each study visit according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

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. It is preferable that final visit procedures be conducted prior to the initiation of another anticancer therapy.

All subjects who have a Final visit ≤ 30 days after the last dose of Study drug will have a Follow-Up Visit approximately 30 days after the last dose of Study drug. 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.

Methodology (Continued):

Subjects no longer undergoing clinical assessments will have survival information reported at 2-month intervals (or as requested by the sponsor to support data analysis) beginning at the last clinical assessment and continuing until the endpoint of death, the subject has become lost to follow-up, or AbbVie terminates the study.

Diagnosis and Main Criteria for Inclusion/Exclusion:

Diagnosis: Metastatic or advanced non-squamous Non-Small Cell Lung Cancer

Main Inclusion:

1. Subject must be ≥ 18 years of age.
2. Life expectancy > 12 weeks (as per Investigator's clinical assessment).
3. Subject must have cytologically or histologically confirmed advanced or metastatic non-squamous NSCLC. Subjects with mixed histology tumors will be eligible if the tumor is predominant non-squamous histology and does not include tumor with small cell histology. Subjects must have a pathologist's report confirming non-squamous NSCLC available for collection by the sponsor. Subjects with EGFR mutation (exon 19 deletion or L858R mutation in exon 21) and/or ALK gene rearrangement must have progressed after first line monotherapy treatment with targeted therapy.
4. Subject must have NSCLC that is not amenable to surgical resection or radiation with curative intent at time of study Screening.
5. Subjects must be current smokers (defined as having > 100 smoking events lifetime and having smoked within the past year) or former smokers (defined as having > 100 smoking events lifetime and having not smoked within the past year).
6. Subject must have at least 1 unidimensional measurable NSCLC lesion on a CT scan as defined by RECIST (version 1.1).
7. Subject must consent to provide archived tissue or cytology sample of NSCLC lesion (primary or metastatic) for analysis if available.
8. Subject must have no history of brain metastases or evidence of CNS tumors at screening assessment. Subjects with signs or symptoms of CNS involvement will undergo MRI (or CT scan if MRI is contraindicated) to confirm absence of CNS metastases.
9. Subject must have an Eastern Cooperative Oncology Group (ECOG) Performance Score of 0 – 1.
10. Subjects with fluid retention, including ascites or pleural effusion, may be allowed at the discretion of the Investigator.
11. Subject must have adequate bone marrow, renal and hepatic function as follows:
    - Bone Marrow: Absolute neutrophil count (ANC) ≥ 1,500/mm^3 (1.5×10^9/L);
    - Platelets ≥ 100,000/mm^3 (100×10^9/L); Hemoglobin ≥ 9.0 g/dL;
    - Renal function: serum calculated creatinine clearance > 50 mL/min according to the Cockroft-Gault formula; confirmation of creatinine clearance/GFR may be done by a local direct measurement method (e.g., 24 hour urine collection or radioisotope) at the investigator's discretion;
    - Hepatic function: AST and ALT ≤ 2.5 × ULN unless liver metastases are present, then AST and ALT < 5.0 × ULN; bilirubin ≤ 1.5 × ULN; unless Gilbert's Syndrome is present, then bilirubin ≥ 1.5 × ULN.

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

Main Inclusion (Continued):

12. 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 partners should practice at least one of the methods of birth control listed below during study and for at least 6 months after treatment with paclitaxel chemotherapy. Male subjects and their female partners of childbearing potential should practice at least one of the methods of birth control listed below during study and for at least 6 months after treatment with chemotherapy:
    - total abstinence from sexual intercourse (if it is the subject's preferred and usual lifestyle; for 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.
13. Subject must be capable of understanding and complying with parameters as outlined in the protocol and able to sign and date the informed consent approved by an Independent Ethics Committee (IEC)/Institutional Review Board (IRB), prior to the initiation of any screening or study-specific procedures.

Main Exclusion:

1. Subject has a known hypersensitivity to paclitaxel or to other drugs formulated with polyethoxylated castor oil (Cremophor).
2. Subject has a known hypersensitivity to platinum compounds.
3. Subjects with peripheral neuropathy ≥ grade 2.
4. Subjects with squamous NSCLC, or those with an untreated EGFR mutation (exon 19 deletion or L858R mutation in exon 21) and/or ALK gene rearrangement. Subjects' EGFR mutation and ALK gene rearrangement status must be known prior to study entry.
5. A history of seizure within 12 months prior to study entry.
6. Subject has received prior cytotoxic chemotherapy or chemoradiotherapy for NSCLC, except adjuvant or neoadjuvant therapy > 12 months prior to C1D-2 or subject has received targeted small molecule monotherapy for EGFR and/or ALK-positive disease ≤ 14 days prior to C1D-2 or biologic therapy ≤ 21 days prior to C1D-2.
7. Subject has received anti-cancer Chinese medicine or anti-cancer herbal remedies within 14 days prior to C1D-2.
8. Subject has undergone focal External Beam Radiation Therapy (EBRT) to bone ≤ 2 weeks prior to C1D-2; or subject has undergone EBRT to larger fields (i.e., 100 cm^2 to thorax) ≤ 4 weeks prior to C1D-2.

Diagnosis and Main Criteria for Inclusion/Exclusion (Continued): **Main Exclusion (Continued):** 9. Any medical condition, which in the opinion of the Investigator, places the subject at an unacceptably high risk for toxicities, or any subject circumstance which prohibits trial participation according to local law. 10. Subject is pregnant or lactating. 11. Subject has previously been treated with a PARP inhibitor. 12. The subject has a history of another cancer within the past 3 years except cervical cancer in situ, in situ carcinoma of the bladder, squamous or basal cell carcinoma of the skin or another in situ cancer that is considered cured by the Investigator (e.g., in situ prostate cancer).	
Investigational Products:	Veliparib (ABT-888)
Doses:	120 mg BID Days –2 through 5 of 21-day cycle
Mode of Administration:	Oral
Reference Therapy or Investigational products:	Carboplatin Day 1 of 21-day cycle
Dose:	AUC 6 mg/mL•min
Mode of Administration:	Intravenous
Reference Therapy or Investigational products:	Paclitaxel Day 1 of 21-day cycle
Dose:	200 mg/m^2
Mode of Administration:	Intravenous
Reference Therapy:	Pemetrexed
Dose:	500 mg/m^2
Mode of Administration:	Intravenous
Reference Therapy:	Cisplatin
Dose:	75 mg/m^2
Mode of Administration:	Intravenous
Duration of Treatment: Subjects will receive veliparib in combination with carboplatin/paclitaxel for a maximum of 6 treatment cycles or Investigator's choice of chemotherapy for a maximum of 6 cycles unless toxicity requires cessation of therapy, or radiographic progression occurs prior to completing 6 cycles. Following completion of platinum doublet therapy, maintenance pemetrexed is strongly encouraged for all subjects who are suitable candidates.	
Criteria for Evaluation: **Overall survival (OS):** will be reported by the Investigator until radiographic progression or death. After the final visit, survival information will be collected at 2-month intervals (or as requested by sponsor to support data analysis).	

Criteria for Evaluation (Continued):

Progression-free survival (PFS): will be derived according to radiographic progression per RECIST version 1.1 or death. Radiographic tumor assessments for response will be conducted by CT scanning prior to C3D1, prior to C5D1, every 9 weeks until 1 year after beginning treatment (or beyond 1 year until maintenance therapy is discontinued), and then every 12 weeks.

Objective response rate (ORR): will be derived per RECIST version 1.1. Radiographic tumor assessments for response will be conducted by CT scanning prior to C3D1, prior to C5D1, every 9 weeks until 1 year after beginning treatment (or beyond 1 year until maintenance therapy is discontinued), and then every 12 weeks.

Duration of overall response (DOR): will be derived according to radiographic progression per RECIST version 1.1. Radiographic tumor assessments for response will be conducted by CT scanning prior to C3D1, prior to C5D1, every 9 weeks until 1 year after beginning treatment (or beyond 1 year until maintenance therapy is discontinued), and then every 12 weeks.

ECOG performance status: will be determined by the Investigator at each assessment.

Quality of Life (QoL): will be assessed at baseline prior to veliparib dosing on C1D-2, C3D1, C5D1 and at the Final Visit, every 9 weeks until 1 year after beginning treatment (or beyond 1 year until maintenance therapy is discontinued), then every 12 weeks and at the Final Visit until radiographic progression via the NCCN-Functional Assessment of Cancer Therapy (FACT) Lung Symptom Index-17 (NFLSI-17) questionnaire and the European Quality of Life-5 Dimensions (EQ-5D-5L) questionnaires.

Safety:

Adverse events, laboratory profiles, physical examinations and vital signs will be assessed throughout the study.

Pharmacokinetic/Pharmacogenetics:

Blood samples for pharmacokinetics of veliparib will be collected at designated timepoints throughout the study.

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 tissue samples will be collected at designated time points throughout the study.

Statistical Methods:

For all statistical analyses, statistical significance will be determined by a two-sided P value ≤ 0.05. The date of randomization (enrollment) is defined as the date that the IRT issues a randomization number.

Sample Size:

Assuming the true hazard ratio of overall survival (OS) for current smokers in favor of the veliparib 120 mg BID + carboplatin/paclitaxel treatment group is 0.64, a total of 210 death events among current smokers will be needed for the study to have approximately 90% power at one-sided α level of 0.025 to detect a statistically significant treatment effect for the veliparib 120 mg BID + carboplatin/paclitaxel group using the log rank test for OS. A total of approximately 300 current smokers will be enrolled to obtain the 210 death events.

Statistical Methods (Continued):

Sample Size (Continued):

During the enrollment period for the approximate 300 current smokers, it is anticipated that approximately 225 former smokers will enroll concurrently. Assuming the true hazard ratio of overall survival (OS) for all subjects (including current plus former smokers) in favor of the veliparib 120 mg BID + carboplatin/paclitaxel treatment group is 0.71, a total of 369 death events in all subjects will be needed for the study to have approximately 90% power at one-sided α level of 0.025 to detect a statistically significant treatment effect for the veliparib 120 mg BID + carboplatin/paclitaxel group using the log rank test for OS.

Has been changed to read:

AbbVie Inc.	**Protocol Number:** M14-359
Name of Study Drug: Veliparib (ABT-888)	**Phase of Development:** 3
Name of Active Ingredient: Not applicable	**Date of Protocol Synopsis:** 09 May 2018
Protocol Title: A Randomized, Open-Label, Multicenter, Phase 3 Trial Comparing Veliparib Plus Carboplatin and Paclitaxel Versus Investigator's Choice of Standard Chemotherapy in Subjects Receiving First Cytotoxic Chemotherapy for Metastatic or Advanced Non-Squamous Non-Small Cell Lung Cancer (NSCLC) and Who Are Current or Former Smokers	
Objectives: The primary objective of the study is to assess if treatment with veliparib plus carboplatin and paclitaxel results in improved survival compared to Investigator's choice of standard chemotherapy in Lung Subtype Panel (LSP) positive subjects with metastatic or advanced NSCLC. The secondary objectives of the study are to assess if treatment with veliparib plus carboplatin and paclitaxel results in improved survival compared to Investigator's choice of standard chemotherapy in the entire study population; to compare progression-free survival (PFS) and to compare objective response rate (ORR) between the two treatment arms in LSP positive subjects or in entire study population. The tertiary objectives are to compare duration of overall response (DOR), ECOG performance status and Quality of Life (QoL) between the two treatment arms in LSP positive subjects or in the entire study population.	
Investigators: Multicenter	
Study Sites: 150	
Study Population: Subjects receiving first cytotoxic chemotherapy for Metastatic or Advanced Non-Squamous Non-Small Cell Lung Cancer (NSCLC) who are current or former smokers. Chemotherapy for adjuvant or neoadjuvant treatment of NSCLC received greater than 12 months prior to Cycle 1 Day –2 (C1D-2) will be allowed.	
Number of Subjects to be Enrolled: 595	

Methodology:

This is a Phase 3, randomized, open-label, multi-center study evaluating the efficacy, safety, and tolerability of veliparib plus carboplatin and paclitaxel versus Investigator's choice of standard chemotherapy in subjects receiving first cytotoxic chemotherapy for advanced or metastatic non-squamous NSCLC who are current or former smokers. Subjects will be randomized in a 1:1 ratio to a maximum of 6 cycles of carboplatin/paclitaxel plus 120 mg BID of veliparib or a maximum of 6 cycles of Investigator's choice of platinum doublet chemotherapy (carboplatin/paclitaxel, cisplatin/pemetrexed, or carboplatin/pemetrexed), unless treatment is discontinued for toxicity or cancer progression. Investigators may elect to administer maintenance pemetrexed regardless of which therapy their subjects are randomized to receive. Following completion of platinum doublet therapy, maintenance pemetrexed is strongly encouraged for all subjects who are suitable candidates. Subjects LSP status (positive or negative) will be determined from tissue samples obtained to confirm diagnosis of NSCLC with a commercially developed RNA seq based LSP classifier developed in partnership with Qiagen.

Subject randomization will be stratified by smoking status (current versus former), by the Investigators' preferred platinum doublet therapy (carboplatin/paclitaxel versus cisplatin/pemetrexed versus carboplatin/pemetrexed), by gender (male versus female) and by ECOG performance status (0 versus 1).

Subjects randomized to receive veliparib will begin oral veliparib dosing 2 days prior to the start of the carboplatin/paclitaxel infusion on C1D-2 and will continue twice a day (BID) through C1D5 (7 consecutive days).

Subjects randomized to receive carboplatin/paclitaxel/veliparib will receive carboplatin (AUC 6 mg/mL•min) and paclitaxel (200 mg/m^2) IV infusion starting on Day 1 of each cycle. Subjects will receive a maximum of 6 cycles of treatment, unless toxicity requires cessation of therapy, or radiographic progression occurs prior to completing 6 cycles. Carboplatin/paclitaxel plus veliparib may be delayed or dose-modified due to toxicity. Should a subject not receive carboplatin and paclitaxel on Day 1 of any cycle, the cycle will be restarted with veliparib at the newly designated Day –2 when the subject is able to do so.

Subjects randomized to receive Investigator's choice of platinum doublet therapy will receive therapy on Day 1 of each cycle. Subjects will receive a maximum of 6 cycles of treatment, unless toxicity requires cessation of therapy, or radiographic progression occurs prior to completing 6 cycles. Platinum doublet therapy may be delayed or dose-modified due to toxicity. Dose delays and modification will be at the discretion of the Investigator per local standard practice.

Suitable subjects in either arm will receive pemetrexed maintenance therapy after completion of platinum doublet chemotherapy regimen. Maintenance pemetrexed will be administered on Day 1 of each 21-day cycle. Maintenance therapy may be delayed or dose-modified due to toxicity. Subjects will continue to receive maintenance therapy until toxicity requires cessation of therapy, or radiographic progression occurs. Veliparib will not be administered during the maintenance phase.

Methodology (Continued):

Subjects will have physician visits q3 weeks while receiving platinum doublet and maintenance therapy. After cessation of therapy, physician visits and quality of life measures will be performed q9 weeks until 1 year after beginning treatment (C1D-2) (or beyond 1 year until maintenance therapy is discontinued), then q12 weeks until radiographic progression. Tumor assessments will be performed at baseline prior to treatment on Cycle 3 Day 1 and Cycle 5 Day 1. After cessation of platinum doublet therapy, tumor assessments will be performed q9 weeks until 1 year after beginning treatment (C1D-2) (or beyond 1 year until maintenance therapy is discontinued), then q12 weeks until radiographic progression or death. Radiographic information will be collected to determine response according to the Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1. Toxicities will be graded at each study visit according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

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. It is preferable that final visit procedures be conducted prior to the initiation of another anticancer therapy.

All subjects who have a Final visit ≤ 30 days after the last dose of Study drug will have a Follow-Up Visit approximately 30 days after the last dose of Study drug. 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.

Subjects no longer undergoing clinical assessments will have survival information reported at 2-month intervals (or as requested by the sponsor to support data analysis) beginning at the last clinical assessment and continuing until the endpoint of death, the subject has become lost to follow-up, or AbbVie terminates the study.

Diagnosis and Main Criteria for Inclusion/Exclusion:

Diagnosis: Metastatic or advanced non-squamous Non-Small Cell Lung Cancer

Main Inclusion:

1. Subject must be ≥ 18 years of age.
2. Life expectancy > 12 weeks (as per Investigator's clinical assessment).
3. Subject must have cytologically or histologically confirmed advanced or metastatic non-squamous NSCLC. Subjects with mixed histology tumors will be eligible if the tumor is predominant non-squamous histology and does not include tumor with small cell histology. Subjects must have a pathologist's report confirming non-squamous NSCLC available for collection by the sponsor. Subjects with EGFR mutation (exon 19 deletion or L858R mutation in exon 21) and/or ALK gene rearrangement must have progressed after first line monotherapy treatment with targeted therapy.
4. Subject must have NSCLC that is not amenable to surgical resection or radiation with curative intent at time of study Screening.
5. Subjects must be current smokers (defined as having > 100 smoking events lifetime and having smoked within the past year) or former smokers (defined as having > 100 smoking events lifetime and having not smoked within the past year).

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

Main Inclusion (Continued):

6. Subject must have at least 1 unidimensional measurable NSCLC lesion on a CT scan as defined by RECIST (version 1.1).
7. Subject must consent to provide archived tissue or cytology sample of NSCLC lesion (primary or metastatic) for analysis if available.
8. Subject must have no history of brain metastases or evidence of CNS tumors at screening assessment. Subjects with signs or symptoms of CNS involvement will undergo MRI (or CT scan if MRI is contraindicated) to confirm absence of CNS metastases.
9. Subject must have an Eastern Cooperative Oncology Group (ECOG) Performance Score of 0 – 1.
10. Subjects with fluid retention, including ascites or pleural effusion, may be allowed at the discretion of the Investigator.
11. Subject must have adequate bone marrow, renal and hepatic function as follows:
    - Bone Marrow: Absolute neutrophil count (ANC) $\geq$ 1,500/mm^3 (1.5 $\times$ 10^9/L);
    - Platelets $\geq$ 100,000/mm^3 (100 $\times$ 10^9/L); Hemoglobin $\geq$ 9.0 g/dL;
    - Renal function: serum calculated creatinine clearance > 50 mL/min according to the Cockcroft-Gault formula; confirmation of creatinine clearance/GFR may be done by a local direct measurement method (e.g., 24 hour urine collection or radioisotope) at the investigator's discretion;
    - Hepatic function: AST and ALT $\leq$ 2.5 $\times$ ULN unless liver metastases are present, then AST and ALT < 5.0 $\times$ ULN; bilirubin $\leq$ 1.5 $\times$ ULN; unless Gilbert's Syndrome is present, then bilirubin $\geq$ 1.5 $\times$ ULN.
12. 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 partners should practice at least one of the methods of birth control listed below during study and for at least 6 months after treatment with paclitaxel chemotherapy. Male subjects and their female partners of childbearing potential should practice at least one of the methods of birth control listed below during study and for at least 6 months after treatment with chemotherapy:
    - total abstinence from sexual intercourse (if it is the subject's preferred and usual lifestyle; for 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.
13. Subject must be capable of understanding and complying with parameters as outlined in the protocol and able to sign and date the informed consent approved by an Independent Ethics Committee (IEC)/Institutional Review Board (IRB), prior to the initiation of any screening or study-specific procedures.

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

Main Exclusion:

1. Subject has a known hypersensitivity to paclitaxel or to other drugs formulated with polyethoxylated castor oil (Cremophor).
2. Subject has a known hypersensitivity to platinum compounds.
3. Subjects with peripheral neuropathy ≥ grade 2.
4. Subjects with squamous NSCLC, or those with an untreated EGFR mutation (exon 19 deletion or L858R mutation in exon 21) and/or ALK gene rearrangement. Subjects' EGFR mutation and ALK gene rearrangement status must be known prior to study entry.
5. A history of seizure within 12 months prior to study entry.
6. Subject has received prior cytotoxic chemotherapy or chemoradiotherapy for NSCLC, except adjuvant or neoadjuvant therapy > 12 months prior to C1D-2 or subject has received targeted small molecule monotherapy for EGFR and/or ALK-positive disease ≤ 14 days prior to C1D-2 or biologic therapy ≤ 21 days prior to C1D-2.
7. Subject has received anti-cancer Chinese medicine or anti-cancer herbal remedies within 14 days prior to C1D-2.
8. Subject has undergone focal External Beam Radiation Therapy (EBRT) to bone ≤ 2 weeks prior to C1D-2; or subject has undergone EBRT to larger fields (i.e., 100 cm^2 to thorax) ≤ 4 weeks prior to C1D-2.
9. Any medical condition, which in the opinion of the Investigator, places the subject at an unacceptably high risk for toxicities, or any subject circumstance which prohibits trial participation according to local law.
10. Subject is pregnant or lactating.
11. Subject has previously been treated with a PARP inhibitor.
12. The subject has a history of another cancer within the past 3 years except cervical cancer in situ, in situ carcinoma of the bladder, squamous or basal cell carcinoma of the skin or another in situ cancer that is considered cured by the Investigator (e.g., in situ prostate cancer).

Investigational Products:	Veliparib (ABT-888)
Doses:	120 mg BID Days –2 through 5 of 21-day cycle
Mode of Administration:	Oral
Reference Therapy or Investigational products:	Carboplatin Day 1 of 21-day cycle
Dose:	AUC 6 mg/mL•min
Mode of Administration:	Intravenous
Reference Therapy or Investigational products:	Paclitaxel Day 1 of 21-day cycle
Dose:	200 mg/m^2
Mode of Administration:	Intravenous

Reference Therapy:	Pemetrexed
Dose:	500 mg/m^2
Mode of Administration:	Intravenous
Reference Therapy:	Cisplatin
Dose:	75 mg/m^2
Mode of Administration:	Intravenous

Duration of Treatment:

Subjects will receive veliparib in combination with carboplatin/paclitaxel for a maximum of 6 treatment cycles or Investigator's choice of chemotherapy for a maximum of 6 cycles unless toxicity requires cessation of therapy, or radiographic progression occurs prior to completing 6 cycles. Following completion of platinum doublet therapy, maintenance pemetrexed is strongly encouraged for all subjects who are suitable candidates.

Criteria for Evaluation:

Overall survival (OS): will be reported by the Investigator until radiographic progression or death. After the final visit, survival information will be collected at 2-month intervals (or as requested by sponsor to support data analysis).

Progression-free survival (PFS): will be derived according to radiographic progression per RECIST version 1.1 or death. Radiographic tumor assessments for response will be conducted by CT scanning prior to C3D1, prior to C5D1, every 9 weeks until 1 year after beginning treatment (or beyond 1 year until maintenance therapy is discontinued), and then every 12 weeks.

Objective response rate (ORR): will be derived per RECIST version 1.1. Radiographic tumor assessments for response will be conducted by CT scanning prior to C3D1, prior to C5D1, every 9 weeks until 1 year after beginning treatment (or beyond 1 year until maintenance therapy is discontinued), and then every 12 weeks.

Duration of overall response (DOR): will be derived according to radiographic progression per RECIST version 1.1. Radiographic tumor assessments for response will be conducted by CT scanning prior to C3D1, prior to C5D1, every 9 weeks until 1 year after beginning treatment (or beyond 1 year until maintenance therapy is discontinued), and then every 12 weeks.

ECOG performance status: will be determined by the Investigator at each assessment.

Quality of Life (QoL): will be assessed at baseline prior to veliparib dosing on C1D-2, C3D1, C5D1 and at the Final Visit, every 9 weeks until 1 year after beginning treatment (or beyond 1 year until maintenance therapy is discontinued), then every 12 weeks and at the Final Visit until radiographic progression via the NCCN-Functional Assessment of Cancer Therapy (FACT) Lung Symptom Index-17 (NFLSI-17) questionnaire and the European Quality of Life-5 Dimensions (EQ-5D-5L) questionnaires.

Safety:

Adverse events, laboratory profiles, physical examinations and vital signs will be assessed throughout the study.

Pharmacokinetic/Pharmacogenetics:

Blood samples for pharmacokinetics of veliparib will be collected at designated timepoints throughout the study and will be analyzed in LSP-defined populations as well as the entire study population.

Criteria for Evaluation (Continued):

LSP status:

Available archived tumor tissue will be used to determine the subjects' tumor LSP status with a commercially developed RNA seq based LSP classifier developed in partnership with Qiagen.

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 tissue samples will be collected at designated time points throughout the study.

Statistical Methods:

For all statistical analyses, statistical significance will be determined by a two-sided *P* value ≤ 0.05. The date of randomization (enrollment) is defined as the date that the IRT issues a randomization number.

Sample Size:

Sample size determination for the original protocol: Assuming the true hazard ratio of overall survival (OS) for current smokers in favor of the veliparib 120 mg BID + carboplatin/paclitaxel treatment group is 0.64, a total of 210 death events among current smokers will be needed for the study to have approximately 90% power at one-sided α level of 0.025 to detect a statistically significant treatment effect for the veliparib 120 mg BID + carboplatin/paclitaxel group using the log rank test for OS. A total of approximately 300 current smokers will be enrolled to obtain the 210 death events.

During the enrollment period for the approximate 300 current smokers, it is anticipated that approximately 225 former smokers will enroll concurrently. Assuming the true hazard ratio of overall survival (OS) for all subjects (including current plus former smokers) in favor of the veliparib 120 mg BID + carboplatin/paclitaxel treatment group is 0.71, a total of 369 death events in all subjects will be needed for the study to have approximately 90% power at one-sided α level of 0.025 to detect a statistically significant treatment effect for the veliparib 120 mg BID + carboplatin/paclitaxel group using the log rank test for OS.

Sample size consideration for OS analysis in LSP+ subgroup:

Based on 452 subjects having tissue samples (assumed 76% LSP sample availability rate, out of 595 enrolled subjects), the below table provides the power and number of events (assuming 80% event rate at final analysis) for a range of likely LSP+ rates if the treatment allocation ratio is 1:1 in the LSP+ subgroup and true HR of OS is 0.65 in LSP+ subgroup.

Number of LSP+ Subjects (LSP+ rate)	Number of Events in LSP+	Power for OS in LSP+ Subgroup (one-sided alpha = 0.025)
271 (60%)	216	89%
226 (50%)	180	82%
180 (40%)	144	73%

Section 1.3 List of Abbreviations and Definition of Terms
Subsection Abbreviations
Add:

LSP Lung Subtype Panel

Section 3.1 NSCLC (Non-Small Cell Lung Cancer)
Add: new fifth and sixth paragraph

Large scale genomic characterization efforts including those conducted by the TCGA and the Lung Cancer Mutation Consortium (LCMC) have been conducted to identify molecular features that differ between NSCLC subtypes. These different features may explain the differential therapeutic responses among different NSCLC subtypes, e.g., of squamous and non-squamous NSCLC. The importance of molecular phenotyping has become increasingly clear as The Cancer Genome Atlas (TCGA) contributed results from a massive specific tumor type sequencing effort that provided a significant landmark for understanding the genetic mutation and gene expression profile of lung cancer in well characterized and distinct histologic subtypes.

Genomic-based classification methods are more likely to capture the molecular characteristics of the cancer cell and therefore classify NSCLC into prognostically informative subgroups. One such approach, termed LSP, is a gene expression profile established using a panel of 57 genes (52 classification genes plus 5 housekeeping genes) for the mRNA expression signature. This panel became known as the Lung Subtype Panel (LSP). Analysis in these three independent adenocarcinoma NSCLC cohorts demonstrated that LSP positive (LSP+) group of patients who had poor prognosis.[6]

Section 3.5 Study Rationale
Third sentence previously read:

Phase 1 data and Phase 2 data described above suggest the addition of veliparib to carboplatin and paclitaxel may improve outcome of current-smokers with advanced or metastatic NSCLC.

Has been changed to read:

Phase 1 data and Phase 2 data described above suggest the addition of veliparib to carboplatin and paclitaxel may improve outcome of LSP+ subjects and/or current-smokers with advanced or metastatic NSCLC.

Section 3.5 Study Rationale
Add: new fifth sentence

All enrolled subjects with available tumor tissue will be evaluated for the LSP gene expression signature status.

Section 3.6 Differences Statement
Previously read:

The current study is the first randomized, open-label, multicenter, Phase 3 trial comparing veliparib plus carboplatin and paclitaxel versus Investigator's choice of standard chemotherapy in previously untreated subjects with metastatic or advanced non-squamous non-small cell lung cancer (NSCLC) who are current or former smokers.

Has been changed to read:

The current study is the first randomized, open-label, multicenter, Phase 3 trial comparing veliparib plus carboplatin and paclitaxel versus Investigator's choice of standard chemotherapy in previously untreated subjects with metastatic or advanced non-squamous non-small cell lung cancer (NSCLC), now as defined by LSP status.

Section 3.7 Benefits and Risks
First paragraph, third sentence previously read:

As described above, non-squamous NSCLC study subjects receiving veliparib with carboplatin and paclitaxel have shown favorable results for the current smokers group (as presented above) for the endpoints of overall survival.

Has been changed to read:

As described above, non-squamous NSCLC study subjects receiving veliparib with carboplatin and paclitaxel have shown favorable results for the current smokers group (as presented above) and the LSP+ group for the endpoints of overall survival.

Section 4.0 Study Objectives
Previously read:

The primary objective of the study is to assess if treatment with veliparib plus carboplatin and paclitaxel results in improved survival compared to Investigator's choice of standard chemotherapy in current smokers with metastatic or advanced NSCLC.

The secondary objectives of the study are to assess if treatment with veliparib plus carboplatin and paclitaxel results in improved survival compared to Investigator's choice of standard chemotherapy in current plus former smokers with metastatic or advanced NSCLC; to compare progression-free survival (PFS) and to compare objective response rate (ORR) between the two treatment arms in current smokers or in current plus former smokers.

The tertiary objectives are to compare duration of overall response (DOR), ECOG performance status and Quality of Life (QoL) between the two treatment arms in current smokers or in current plus former smokers.

Has been changed to read:

The primary objective of the study is to assess if treatment with veliparib plus carboplatin and paclitaxel results in improved survival compared to Investigator's choice of standard chemotherapy in LSP positive subjects with metastatic or advanced NSCLC.

The secondary objectives of the study are to assess if treatment with veliparib plus carboplatin and paclitaxel results in improved survival compared to Investigator's choice of standard chemotherapy in the entire study population with metastatic or advanced NSCLC; to compare progression-free survival (PFS) and to compare objective response

rate (ORR) between the two treatment arms in LSP positive subjects or in the entire study population.

The tertiary objectives are to compare duration of overall response (DOR), ECOG performance status and Quality of Life (QoL) between the two treatment arms in LSP positive subjects or in the entire study population.

Section 5.1 Overall Study Design and Plan: Description
Last paragraph
Add: new last sentence

In addition, all post treatment therapy, if applicable and available, will be collected in the survival follow-up period.

Table 2. Study Activities
Activity "Adverse Event and Concomitant Medication Assessment" and "Survival" previously read:

Activity	SCR[a]	Cycle 1 Day –2	Cycle 1 Day 1	Cycle 1 Day 15	Cycle 2 – 6 Day 1*	Final Visit[b]	30-day FU Visit[c]	Maintenance Therapy[d]	Post-Treatment Visits[p]	Survival Period
Adverse Event and Concomitant Medication Assessment	X	X		X	X	X	X	X	X	
Survival										X

Has been changed to read:

Activity	SCR[a]	Cycle 1 Day –2	Cycle 1 Day 1	Cycle 1 Day 15	Cycle 2 – 6 Day 1*	Final Visit[b]	30-day FU Visit[c]	Maintenance Therapy[d]	Post-Treatment Visits[p]	Survival Period
Adverse Event and Concomitant Medication Assessment	X	X		X	X	X	X	X	X	X[r]
Survival[r]										X

Table 2. Study Activities
Table note "i."
Delete: second sentence

This does not include C1D-2 as any sample prior to randomization is still considered to be screening.

Table 2. Study Activities
Add: new table note "r."

All systemic post treatment anti-cancer therapy, if applicable and available, will be collected in the survival follow-up period.

Section 5.3.1.1 Study Procedures
Subsection Survival Information
Add: new last sentence

Post-study anti-cancer therapy information (including type of agent, initiation date, end date, and clinical response), if known, will also be collected in the survival follow-up period.

Section 5.3.3 Efficacy Variables
Previously read:

The primary efficacy endpoint is overall survival (OS) in current smokers. The secondary efficacy endpoints are OS in all subjects (current and former smokers), progression-free

survival (PFS) in current smokers and in all subjects, objective response rate (ORR) in current smokers and in all subjects. The tertiary efficacy endpoints are duration of response, ECOG performance status and Quality of Life (QoL) in current smokers and in all subjects.

Has been changed to read:

The primary efficacy endpoint is overall survival (OS) in LSP+ subgroup. The secondary efficacy endpoints are: progression free survival (PFS) in LSP+ subgroup, objective response rate (ORR) in LSP+ subgroup, OS in all subjects, PFS in all subjects, and ORR in all subjects. The tertiary efficacy endpoints are duration of response, ECOG performance status and Quality of Life (QoL) in LSP+ subgroup and in all subjects.

Section 6.6.1 Reporting Serious Adverse Events
Add: "Primary Study Designated Physician:"

Primary Study Designated Physician:

[redacted]
AbbVie
[redacted]
200 Sidney Street
Cambridge, MA 02139

Office: [redacted]
Mobile:
Email:

Section 7.0 Protocol Deviations
Contact information previously read:

Clinical Team Lead:

[redacted]
AbbVie
[redacted]
1 North Waukegan Road
North Chicago, IL 60064

Office:
Fax: [redacted]

Medical Monitor:

[redacted]
AbbVie
[redacted]
381 Plantation Street
Worcester, MA 01605

Office:
Cell:
Email: [redacted]

Has been changed to read:

Clinical Team Lead:

[redacted]
AbbVie
8401 TransCanada Highway
Saint-Laurent, Quebec
H4S 1Z1 Canada

Office:
Fax:
Cell: [redacted]

Medical Monitor:

[redacted]
AbbVie
[redacted]
200 Sidney Street
Cambridge, MA 02139

Office:
Cell:
Email: [redacted]

Section 8.1.2.1 Primary Efficacy Endpoint
First paragraph previously read:

The primary efficacy analysis will be a comparison of OS distributions between the 120 mg of veliparib BID + carboplatin/paclitaxel and Investigators' preferred platinum therapy groups in current smokers.

Has been changed to read:

The primary efficacy analysis will be a comparison of OS distributions between the 120 mg of veliparib BID + carboplatin/paclitaxel and Investigators' choice of platinum therapy groups in LSP + subgroup.

Section 8.1.2.2 Secondary Efficacy Endpoints
First paragraph, last sentence previously read:

If veliparib treatment group is not statistically significantly better than the Investigator's preferred platinum therapy group for the primary efficacy endpoint of OS in current smokers, then statistical significance will not be declared for any of the secondary efficacy endpoints, regardless of the observed *P* values.

Has been changed to read:

If veliparib treatment group is not statistically significantly better than the Investigator's choice of platinum therapy group for the primary efficacy endpoint of OS in LSP + subgroup, then statistical significance will not be declared for any of the secondary efficacy endpoints, regardless of the observed *P* values.

Section 8.1.2.2 Secondary Efficacy Endpoints
Second paragraph previously read:

P values for the secondary efficacy analyses will be subject to multiple comparison adjustments using the fixed sequence test method, with the analyses performed in the following order: OS in current plus former smokers, progression-free survival (PFS) in current smokers, PFS in current plus former smokers, objective response rate (ORR) in current smokers, ORR in current plus former smokers.

Has been changed to read:

P values for the secondary efficacy analyses will be subject to multiple comparison adjustments using the fixed sequence test method, with the analyses performed in the

following order: progression-free survival (PFS) in LSP+ subgroup, objective response rate (ORR) in LSP+ subgroup, OS in all subjects, PFS in all subjects, ORR in all subjects.

Section 8.1.2.3 Tertiary Efficacy Endpoints
First paragraph previously read:

In addition to the primary and secondary efficacy analyses, the tertiary objectives are to compare DOR, ECOG performance status and Quality of Life (QoL) via the NCCN-Functional Assessment of Cancer Therapy (FACT) Lung Symptom Index-17 (NFLSI-17) questionnaire and the European Quality of Life-5 Dimensions (EQ-5D-5L) in current smokers and in current plus former smokers between the two treatment arms and ECOG performance status will be performed.

Has been changed to read:

In addition to the primary and secondary efficacy analyses, the tertiary objectives are to compare DOR, ECOG performance status and Quality of Life (QoL) via the NCCN-Functional Assessment of Cancer Therapy (FACT) Lung Symptom Index-17 (NFLSI-17) questionnaire and the European Quality of Life-5 Dimensions (EQ-5D-5L) in LSP+ subjects and in the entire study population between the two treatment groups.

Section 8.1.2.3 Tertiary Efficacy Endpoints
Last paragraph, first sentence previously read:

The duration of overall response for a given subject will be defined as the number of days from the day the criteria are met for CR or PR (whichever is recorded first) to the date that PD is objectively documented.

Has been changed to read:

The duration of overall response for a given subject will be defined as the number of days from the day the criteria are met for CR or PR (whichever is recorded first) to the date that PD is objectively documented or subject's death.

Section 8.1.3 Timing of Efficacy Analyses and Safety Evaluations
First sentence previously read:

When both the 210th death event in the current smokers and the 369th death event in current plus former smokers occur, there will be a final review of the eCRF data.

Has been changed to read:

When LSP status is determined by the Qiagen assay for all submitted tissue samples, there will be a final review of the eCRF data.

Section 8.1.4 Primary Analysis of Efficacy
Previously read:

For the current smokers, the distribution of OS will be estimated for each treatment group using Kaplan-Meier methodology and compared between the two treatment groups using the log-rank test, stratified by ECOG and Investigator's preferred platinum therapy.

Has been changed to read:

For the LSP+ subgroup, the distribution of OS will be estimated for each treatment group using Kaplan-Meier methodology and compared between the two treatment groups (HR and 95%CI) using Cox proportional hazard model with treatment group, important prognostic factors (e.g., ECOG, Investigator's choice of platinum therapy, and smoking status) as the covariates.

Section 8.1.5 Secondary Analysis of Efficacy
Previously read:

8.1.5 Secondary Analysis of Efficacy

8.1.5.1 Overall Survival in Current Plus Former Smokers

For current plus former smokers, the distribution of OS will be estimated for each treatment group using Kaplan-Meier methodology and compared between the two treatment groups using the log-rank test, stratified by ECOG, smoking history (current versus former smokers), and Investigator's preferred platinum therapy.

8.1.5.2 Progression Free Survival in Current Smokers

For the current smokers, the distribution of PFS will be estimated for each treatment group using Kaplan-Meier methodology and compared between the two treatment groups using the log-rank test, stratified by ECOG and Investigator's preferred platinum therapy.

8.1.5.3 Progression Free Survival in Current Plus Former Smokers

For current plus former smokers, the distribution of PFS will be estimated for each treatment group using Kaplan-Meier methodology and compared between the two treatment groups using the log-rank test, stratified by ECOG, smoking history (current versus former smokers), and Investigator's preferred platinum therapy.

8.1.5.4 Objective Response Rate in Current Smokers

For the current smokers, the ORR (proportion of subjects with a complete or partial response based on RECIST (version 1.1) will be estimated and compared between the two treatment groups using Cochran-Mantel-Haenszel (CMH) test; stratified by ECOG and Investigator's preferred platinum therapy. In addition, 95% confidence interval will be constructed for the estimated proportion.

8.1.5.5 Objective Response Rate in Current Plus Former Smokers

For current smokers plus former smokers, the ORR will be estimated and compared between the two treatment groups using Cochran-Mantel-Haenszel (CMH) test; stratified by ECOG, smoking history (current versus former smokers), and Investigator's preferred platinum therapy. In addition, 95% confidence interval will be constructed for the estimated proportion.

Has been changed to read:

8.1.5 Secondary Analysis of Efficacy

8.1.5.1 Progression Free Survival in LSP + Subgroup

For the LSP+ subgroup, the distribution of PFS will be estimated for each treatment group using Kaplan-Meier methodology and compared between the two treatment groups (HR and 95% CI) using Cox proportional hazard model with treatment group, important prognostic factors (e.g., ECOG, Investigator's choice of platinum therapy and smoking status) as covariates.

8.1.5.2 Objective Response Rate in LSP+ Subgroup

For the LSP+ subgroup, the ORR (proportion of subjects with a complete or partial response based on RECIST (version 1.1) will be estimated and compared between the two treatment groups using Fisher's exact test. In addition, 95% confidence interval will be constructed for the estimated proportion.

8.1.5.3 Overall Survival in All Subjects

For all subjects, the distribution of OS will be estimated for each treatment group using Kaplan-Meier methodology and compared between the two treatment groups (HR and 95% CI) using the Cox Proportional hazard model with treatment group, important prognostic factors (e.g., ECOG, smoking history (current versus former smokers), and Investigator's choice of platinum therapy) as the covariates.

8.1.5.4 Progression Free Survival in All Subjects

For all subjects, the distribution of PFS will be estimated for each treatment group using Kaplan-Meier methodology and compared between the two treatment groups (HR and 95%CI) using Cox proportional hazard model with treatment group, important prognostic factors (e.g., ECOG, and Investigator's choice of platinum therapy, smoking status) as the covariates.

8.1.5.5 Objective Response Rate in All Subjects

For all subjects, the ORR will be estimated and compared between the two treatment groups using Cochran-Mantel-Haenszel (CMH) test; stratified by ECOG, smoking history (current versus former smokers), and Investigator's preferred platinum therapy. In addition, 95% confidence interval will be constructed for the estimated proportion.

Section 8.1.6.1 Duration of Overall Response
Previously read:

For the current smoker subgroup, the distribution of duration of overall response (DOR) will be estimated for each treatment group using Kaplan-Meier methodology and compared between the two treatment groups using the log-rank test, stratified by ECOG and Investigator's preferred platinum therapy.

For the whole population (including both current smokers and former smokers), the distribution of (DOR) will be estimated for each treatment group using Kaplan-Meier methodology and compared between the two treatment groups using the log-rank test, stratified by ECOG, smoking history (current versus former smokers), and Investigator's preferred platinum therapy.

Has been changed to read:

The distribution of duration of overall response (DOR) will be estimated for each treatment group using Kaplan-Meier methodology for LSP+ as well as for all subjects.

Section 8.1.6.2 General Quality of Life
Subsection <u>Subject Reported Symptoms and QOL (NFLSI-17)</u>
First sentence previously read:

The objective is to compare subject reported symptoms and QOL following treatment with the veliparib treated arm and the comparator arm for both the smoker subgroup and the whole population using the NFLSI-17 questionnaire.

Has been changed to read:

The objective is to compare subject reported symptoms and QOL following treatment with the veliparib treated arm and the comparator arm for both the LSP+ subgroup and the whole population using the NFLSI-17 questionnaire.

Section 8.1.6.3 Performance Status
First sentence previously read:

Changes from baseline in ECOG performance status will be summarized using descriptive statistics for each scheduled post-baseline visit.

Has been changed to read:

Changes from baseline in ECOG performance status will be summarized using descriptive statistics for each scheduled post-baseline visit and for LSP+ as well as all subjects.

Section 8.1.7 Additional Exploratory Efficacy Analyses
First paragraph previously read:

In addition to the stratified log-rank test for the primary and secondary efficacy endpoints, the unstratified log-rank test, Wilcoxon test, and the Cox proportional hazards model may be used for the comparison of OS and PFS between the two treatment groups.

Has been changed to read:

In addition to the covariate-adjusted Cox PH analyses for the primary and secondary efficacy endpoints, the unstratified log-rank test and unstratified and unadjusted Cox proportional hazards model may be used for the comparison of OS and PFS between the two treatment groups.

Section 8.1.7 Additional Exploratory Efficacy Analyses
Last paragraph, first sentence previously read:

For OS and PFS, additional analyses may also be performed, such as 1) including only data and events occurring on treatment or within 30 days of the last dose of study drug,

2) using a Cox proportional hazard model to explore the effect of baseline factors including (but not limited to) the following: tumor stage (locally advanced versus metastatic), smoking history (current smoker versus former smoker), gender, ECOG performance status (0 versus 1), Investigator's preferred platinum doublet therapy, and others, 3) subgroup analysis by smoking history (current smoker versus former smoker), gender, ECOG performance status (0 versus 1), Investigator's preferred platinum doublet therapy and others.

Has been changed to read:

For OS and PFS, additional analyses may also be performed, such as 1) including only data and events occurring on treatment or within 30 days of the last dose of study drug, 2) using a Cox proportional hazard model to explore the effect of baseline factors including (but not limited to) the following: LSP subgroup, LSP status unknown, tumor stage (locally advanced versus metastatic), smoking history (current smoker versus former smoker), gender, ECOG performance status (0 versus 1), Investigator's preferred platinum doublet therapy, and others, 3) subgroup analysis by LSP subgroup, LSP status unknown, smoking history (current smoker versus former smoker), gender, ECOG performance status (0 versus 1), Investigator's preferred platinum doublet therapy, post-study anti-cancer therapy (e.g., anti-PD-1, IO etc.) and others.

Section 8.1.8 Statistical Analysis of Safety
Add: new first sentence

Statistical analyses of safety data described below will be performed for three study population separately: LSP+ subgroup, LSP– subgroup, entire study population.

Section 8.1.8.2 Adverse Events
Last sentence previously read:

The percentages of subjects experiencing an adverse event will be compared between veliparib BID + carboplatin/paclitaxel and Investigators' preferred platinum therapy using Fisher's exact test.

Has been changed to read:

The percentages of subjects experiencing an adverse event will be presented by treatment group.

Section 8.1.8.5 Longitudinal Analyses of Laboratory and Vital Signs Data
First sentence previously read:

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.

Has been changed to read:

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 vital sign parameters.

Section 8.1.8.5 Longitudinal Analyses of Laboratory and Vital Signs Data
Delete: last sentence

Comparisons of the differences in mean changes from baseline between veliparib BID + carboplatin/paclitaxel and Investigators' preferred platinum therapy will be made using ANOVA with treatment group as the factor.

Section 8.1.8.6 Analyses of Laboratory Data Using NCI CTCAE
Third sentence previously read:

The percentage of subjects experiencing a shift from baseline grades of 0 to 2 to maximum post-baseline grades of 3 to 4, and from baseline grades of 0 to 2 to final post-baseline grades of 3 to 4 between veliparib BID + carboplatin/paclitaxel and Investigators' preferred platinum therapy will be compared using Fisher's exact test.

Has been changed to read:

The percentage of subjects experiencing a shift from baseline grades of 0 to 2 to maximum post-baseline grades of 3 to 4, and from baseline grades of 0 to 2 to final post-baseline grades of 3 to 4 between veliparib BID + carboplatin/paclitaxel and Investigators' preferred platinum therapy will be presented.

Section 8.2 Determination of Sample Size
Add: new first paragraph

Sample size calculation for the original protocol:

Section 8.2 Determination of Sample Size
Add: new third and fourth paragraph

Sample size consideration for OS analysis in LSP+ subgroup

Based on 452 subjects having LSP tissue samples (assumed 76% LSP sample availability rate), the below table provides the power and number of events with different assumed LSP+ rate if the treatment allocation ratio is 1:1 in the LSP+ subgroup and true HR of OS is 0.65 in LSP+ subgroup.

Number of LSP+ Subjects (LSP+ rate)	Number of Events in LSP+	Power for OS in LSP+ Subgroup (one-sided alpha = 0.025)
271 (60%)	216	89%
226 (50%)	180	82%
180 (40%)	144	73%

Section 15.0 Reference List
Add: new Reference 6

Mayhew G, Hayes N, Perou C, et al. Survival differences of adenocarcinoma lung tumors with squamous cell carcinoma or neuroendocrine profiles by gene expression subtyping. Abstract #384. Presented at the 16th World Conference on Lung Cancer, September 06-09, 2015; Denver, CO.

Section 15.0 Reference List
Reference 22 previously read:

AbbVie. Veliparib (ABT-888) Investigator Brochure, Edition 9. 12 June 2015.

Has been changed to read:

AbbVie. Veliparib (ABT-888) Investigator Brochure, Edition 11. 22 June 2017.

Appendix B. List of Protocol Signatories
Previously read:

Name	Title	Functional Area
[redacted]		Clinical Operations
		GDSM
		Clinical
		Clinical
		Statistics
		Pharmacokinetics

Has been changed to read:

Name	Title	Functional Area
[redacted]		Clinical Program Development
		Oncology Development
		Oncology Development
		Statistics
		Pharmacokinetics