1.0 Title Page

Clinical Study Protocol M14-361

A Phase 1 Dose Escalation and Phase 2 Randomized Double-Blind Study of Veliparib in Combination with Carboplatin and Etoposide as a Therapy of Treatment-Naïve Extensive Stage Disease Small Cell Lung Cancer

Incorporating Administrative Changes 1 and 2, and Amendments 1, 2, 3, 4 and 5

AbbVie Investigational Product:	Veliparib
Date:	22 November 2016
Development Phase:	1/2
Study Design:	This is a Phase 1 3 + 3 dose-escalation/Phase 2 randomized double-blind study of veliparib in combination with carboplatin and etoposide and followed by maintenance veliparib monotherapy. Subjects in Phase 2 will be randomized in a 1:1:1 ratio to carboplatin, etoposide, placebo followed by placebo maintenance or carboplatin, etoposide, veliparib followed by either veliparib or placebo maintenance.
EudraCT Number:	2014-001764-35
Investigator:	Multicenter Trial: Investigator information is on file at AbbVie
Sponsor:	AbbVie Inc.* (AbbVie)

Sponsor/Emergency Contact:	[redacted] Medical Director Oncology [redacted] AbbVie FNC 200 Sidney Street Cambridge, MA 02139	Phone: [redacted] Fax: Email: [redacted]

* The specific contract details of the AbbVie legal/regulatory entity (person) within the relevant country and 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	23 June 2014
Amendment 1	04 May 2015
Administrative Change 1	17 June 2015
Amendment 2	30 July 2015
Amendment 3	18 December 2015
Amendment 4	14 June 2016
Administrative Change 2	28 June 2016

- Added veliparib/placebo Recommended Phase 2 Dose (RPTD) of 240 mg BID in a 14-day schedule as the veliparib/placebo dose and schedule for Phase 2 combination therapy.

  Rationale: *To define the veliparib RPTD and schedule per Phase 1 study data.*

- Added Post-Treatment Follow-Up in Table 8, Study Activities in Phase 2, and clarified Post-Treatment Follow-Up vs. Survival Follow-Up periods throughout.

  Rationale: *To clarify tumor assessment data collection after Phase 2 study drug discontinuation.*

- Modified tumor assessment procedure timing to Q6W for the first 30 weeks in Phase 2.

  Rationale: *To improve resolution of progression free endpoint analysis.*

- Added Section 5.2.4, Contraception Recommendations.

  Rationale: *To include the current protocol template contraception language.*

- Updated Inclusion Criterion 9 to reference new Section 5.2.4, Contraception Recommendations.

  Rationale: *To simplify the Inclusion criteria.*

- Included HBsAg, HCV RNA and Urinalysis to Table 7, Study Activities Phase 1 Dose Escalation, and Table 8, Study Activities in Phase 2.

Rationale: *To clarify collection requirements for each.*

- Clarified that Vital Signs collection on Cycle Day 2 and Cycle Day 3 are for C1 only.

  Rationale: *To simplify the study procedures.*

- Clarified the 30-Day Follow-Up visit timing.

  Rationale: *To ensure safety follow up after drug discontinuation.*

- Clarified anatomy to be scanned during CT scan performance.

  Rationale: *To ensure proper and consistent imaging across the study sites.*

- Updated Physical Examination procedure to include a hearing assessment if recommended per local label for carboplatin.

  Rationale: *To address comments from ethics committee.*

- Updated Section 5.4.1, Discontinuation of Individual Subjects, with the requirement to notify AbbVie of lost progression free survival endpoints.

  Rationale: *To ensure resolution of progression free endpoint analysis.*

- Updated Table 13, Identity of Investigational Products, with a footnote.

  Rationale: *To clarify that 20 mg veliparib capsules will be used in Phase 1 only.*

- Updated Table 16, Guidelines for Veliparib, Carboplatin, and Etoposide Dose Reduction Levels During Combination Therapy, with a footnote.

  Rationale: *To clarify that etoposide drug reduction guidelines due to bilirubin values prevail.*

- Updated survival data collection requirements.

  Rationale: *To clarify that all deaths are to be reported in eCRF, regardless of causality.*

- Updated safety wording.

  Rationale: *To include the current protocol template safety language.*

- Updated Primary Contact for protocol deviations.

  Rationale: *To reflect current team.*

- Updated Section 8.1.1.1, Demographics

  Rationale: *To provide smoking history definitions.*

- Added a paragraph to define the process for transition from Phase 1 to Phase 2.

  Rationale: *To clarify actions after RPTD is determined.*

- Updated requirement to collect HBsAg and HCV RNA laboratory tests at Screening for subjects with unknown history of HBsAg and HCV RNA for Phase 2.

  Rationale: *To ensure subjects positive to hepatitis B and hepatitis C are not enrolled.*

- Replaced "medical monitor" with "Therapeutic Area Medical Director" throughout the document.

  Rationale: *To align the content with the company role name.*

- Replaced "Interactive Voice/Web Response Technology (IVRS)" with "Interactive Response Technology (IRT)" throughout the document.

  Rationale: *To align the content with the company system name.*

- Added new wording to radiation in Concomitant Therapy section.

  Rationale: *To clarify radiation to non-target lesions during the study.*

- Removed coagulation sample collection at odd numbered cycles in Table 8, Study Activities in Phase 2.

  Rationale: *To simplify the laboratory sample collections*.

- Clarified collection window for clinical laboratory tests is 48 hours.

  Rationale: *To allow for flexibility in the laboratory sample collection.*

- Added the requirement for sites to electronically transfer copies of all CT or MRI scans used for radiographic tumor assessments in Phase 2 at the request of AbbVie.

  Rationale: *To facilitate the collection of scans for central review, if necessary.*

- Removed the requirement of survival data collection for up to 2 years in Phase 2.

  Rationale: *To improve resolution of overall survival analysis.*

- Clarified disease progression definition per protocol is radiographic progression.

Rationale: *To clearly define disease progression per protocol to minimize the amount of lost endpoints.*

- Include the language in the Administrative Change 2.

  Rationale: *Include the administrative change language.*

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

An itemized list of all changes made to the protocol under this amendment can be found in Appendix G.

1.2 Synopsis

AbbVie Inc.	**Protocol Number:** M14-361
Name of Study Drug: Veliparib	**Phase of Development:** 1 – 2
Name of Active Ingredient: Veliparib	**Date of Protocol Synopsis:** 22 November 2016

Protocol Title:

A Phase 1 Dose Escalation and Phase 2 Randomized Double-Blind Study of Veliparib in Combination with Carboplatin and Etoposide as a Therapy of Treatment-Naïve Extensive Stage Disease Small Cell Lung Cancer

Objectives:

Phase 1 Dose Escalation:

Primary Objectives:

- To establish the Maximum Tolerated Dose (MTD) and to establish the Recommended Phase 2 Dose (RPTD) and schedule for veliparib in combination with carboplatin and etoposide.
- To evaluate the pharmacokinetic interaction between veliparib and etoposide.

Secondary Objective:

- To evaluate the safety of maintenance veliparib monotherapy at 400 mg twice daily (BID) in subjects completing 4 cycles of carboplatin, etoposide and veliparib without evidence of disease progression.

Phase 2 Randomized Double-Blind:

Primary Objective:

- To evaluate if veliparib in combination with carboplatin and etoposide followed by veliparib maintenance monotherapy results in improved progression free survival (PFS) versus placebo in combination with carboplatin and etoposide followed by placebo monotherapy in subjects with treatment-naïve ED SCLC.

Secondary Objectives:

- To evaluate if veliparib in combination with carboplatin and etoposide followed by placebo monotherapy results in improved progression free survival (PFS) versus placebo in combination with carboplatin and etoposide followed by placebo monotherapy in subjects with treatment-naïve ED SCLC.
- To evaluate if veliparib in combination with carboplatin and etoposide results in improved objective response rate (ORR) versus placebo in combination with carboplatin and etoposide at the time of completion of combination therapy.
- To evaluate if veliparib in combination with carboplatin and etoposide followed by veliparib maintenance monotherapy results in improved overall survival (OS) versus placebo in combination with carboplatin and etoposide followed by placebo monotherapy.
- To evaluate if veliparib in combination with carboplatin and etoposide followed by placebo monotherapy results in improved overall survival (OS) versus placebo in combination with carboplatin and etoposide followed by placebo monotherapy.
- To further evaluate the safety of veliparib in combination with carboplatin and etoposide followed by veliparib maintenance monotherapy.

Objectives (Continued):

Tertiary Objectives:

- To evaluate if veliparib in combination with carboplatin and etoposide followed by veliparib maintenance monotherapy results in improved duration of overall response (DOR) versus placebo in combination with carboplatin and etoposide followed by placebo monotherapy.
- To evaluate if veliparib in combination with carboplatin and etoposide followed by placebo monotherapy results in improved duration of overall response (DOR) versus placebo in combination with carboplatin and etoposide followed by placebo monotherapy.
- To compare PFS and OS of subjects treated with veliparib in combination with carboplatin and etoposide followed by veliparib maintenance to PFS and OS of subjects treated with veliparib in combination with carboplatin and etoposide followed by placebo maintenance.
- To evaluate performance status.

Investigators:

Multicenter

Study Sites:

Approximately 65 globally

Study Population:

Phase 1: Histologically or cytologically confirmed extensive stage disease SCLC or any other advanced/metastatic solid tumor for which carboplatin/etoposide treatment is considered appropriate.

Phase 2: Histologically or cytologically confirmed treatment-naïve extensive stage disease SCLC.

Number of Subjects to be Enrolled:

Phase 1 Dose Escalation portion: Approximately: 35

Phase 2 Randomized Double-Blind portion: Approximately: 180

Methodology:

This is a Phase 1 dose escalation and Phase 2 randomized double-blind study.

Screening Procedures:

Screening procedures should be performed within 28 days of Cycle 1 Day –2. If the screening visit is performed greater than 7 days prior to Cycle 1 Day –2, the physical exam, laboratory tests, and pregnancy test (for female subjects of childbearing potential) must be repeated on Cycle 1 Day –2. Vital signs and performance status assessments will be performed on Cycle 1 Day –2 for all subjects. Baseline radiographic tumor assessments per computed tomography (CT) with IV contrast/magnetic resonance imaging (MRI) of the chest, abdomen, and pelvis will be conducted within 21 days prior to Cycle 1 Day –2. If CNS metastases are suspected, a head CT must also be performed at screening. 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.

Phase 1 Dose Escalation:

For subjects in the dose escalation portion of the study, each subject will participate in only 1 dose group and there is no provision for intra-subject dose-escalation. Study procedures will be provided in the Schedule of Assessments and Pharmacokinetic and Pharmacodynamic tables.

Methodology (Continued):

Phase 1 Dose Escalation (Continued):

The Phase 1 portion of this study will evaluate the safety, tolerability, dose limiting toxicities (DLTs), RPTD, pharmacokinetics (PK), and pharmacodynamics (PD), of veliparib/carboplatin/etoposide combination in subjects diagnosed with Extensive Stage Disease Small Cell Lung Cancer or, other advanced/metastatic solid tumor for which carboplatin/etoposide treatment is considered appropriate. Veliparib will be administered on Days –2 to 5 (7-day schedule), and, if the MTD of the 7-day schedule is not reached at ≤ 200 mg BID veliparib dose level, may be administered on Days –2 to 12 (14-day schedule) and/or Days –2 to 19 (continuous schedule) orally BID, in combination with carboplatin area under the curve 5 mg/mL*min administered on Day 1 and etoposide 100 mg/m^2 administered on Days 1 to 3 via intravenous (IV) infusion in 21-day cycles. An exception would be for the Phase 1 Cycle 2: In the 7-day schedule, veliparib in Cycle 2 will be administered on Days 2 to 5 and for the 14-day schedule, Days 2 to 12 (veliparib dose on Cycle 2 Days –2 and –1 and Cycle 2 Day 1 will be omitted to allow for the evaluation of drug-drug interaction of veliparib with etoposide).

Upon completion of 4 cycles of combination therapy, subjects without evidence of disease progression will continue on veliparib 400 mg BID until disease progression or unacceptable toxicity. Subjects who will be receiving prophylactic cranial irradiation (PCI) will have maintenance veliparib interrupted for the duration of radiotherapy.

All subjects will be monitored for DLTs during the DLT observation period (Cycle 1 Day –2 to pre-dose Cycle 2 Day 1), and treatment-related adverse events (AEs) will be evaluated throughout the course of the study for evidence of acute, delayed, or cumulative toxicities.

The dose levels of veliparib to be evaluated in the dose-escalation portion of this study were determined based on the outcome of prior clinical studies of veliparib as well as on pre-clinical toxicology, toxicokinetic, and nonclinical anti-tumor efficacy studies. The following dose levels may be evaluated in the dose-escalation portion of the study: 80, 120, 160, 200, and 240 mg BID. Reduced dose levels may be evaluated based upon review of subject safety and PK data. Intermediate dose levels may be evaluated based upon review of subject safety including, but not limited to, Grade 2 study-drug related AEs. If the MTD is not reached at veliparib 200 mg BID dose level, higher dose levels (with no more than 25% veliparib dose increments, and not exceeding single agent veliparib RPTD of 400 mg BID) may be evaluated at the discretion of the sponsor. The alternative dosing schedules can include dosing veliparib Day –2 to 12 (14-day schedule) and/or Day –2 to 19 (continuous schedule) of 21 day Cycle. The initial dose for these schedules will be 200 mg BID or the maximum administered dose (MAD), not exceeding the MTD, in the 7-day schedule. The 14-day schedule will be explored prior to continuous dosing schedule. Reduced or interim dose levels may be evaluated based on review of the safety and PK.

A "3 + 3" escalation rule will be used for the dose-escalation portion of this study, with a condition applied for the Dose Level 1, which will allow 3 additional subjects to be entered in Dose Level 1 if 2 of 6 initial subjects experience DLTs. Enrollment of the 3 additional subjects at all dose levels will depend on a review of the specific DLTs observed and discussion with the Investigators.

Dose-Escalation Criteria:

AEs, clinical laboratory results, and vital signs will be assessed throughout the study in each dose-escalation cohort.

Methodology (Continued):

Dose-Escalation Criteria (Continued):

DLTs will be assessed in each dose-escalation cohort during the DLT observation period (Cycle 1 Day –2 to pre-dose on Cycle 2 Day 1). Based on the safety and tolerability of study drugs after the first cycle of treatment has been completed in at least 3 subjects, escalation to a subsequent dose level or expansion of the current dose level will occur based upon the following criteria:

Number of Subjects with DLT in the First Cycle	Escalation Decision Rule
0 out of 3	Enter 3 subjects at the next dose level.
1 out of 3	Add 3 more subjects at current dose level. If AbbVie or the investigator considers the DLT(s) clinically significant, AbbVie will determine if it is appropriate to add more patients at this dose level. • If < 2 of 6 subjects (or < 33% of subjects) experience DLT, dose escalation will proceed to the next dose level. • If ≥ 2 of total 6 subjects (or ≥ 33% of subjects) experience DLTs, then dose escalation will be stopped.*
≥ 2 out of 3 or 6	Dose escalation will be stopped. *Additional subjects will be enrolled at the previous lower dose level as needed. The following exceptions apply to Dose Level 1: • If 2 of 6 initial subjects at Dose Level 1 experience DLTs, 3 additional subjects may be entered and the cohort will be expanded up to 9 subjects for further DLT assessment. o Enrollment of the 3 additional subjects will depend on a review of the specific DLTs observed and discussion with the Investigators. • If 2 of 9 subjects at Dose Level 1 experience DLTs, then escalation to the next dose level may proceed. • If > 2 of 9 subjects in Dose Level 1 experience drug-related DLTs, dose-escalation will stop.

* If 2 out of 6 subjects experience different DLTs, for example nausea and neutropenia, the data will be reviewed by the investigator and AbbVie to determine if 3 additional subjects should be added at that dose level. If 3 subjects will be added and none experience DLTs, this dose level will be declared the MTD.

An MTD and/or maximum administered dose (MAD), and RPTD, will be determined. The MTD is defined as the maximum dose at which < 2 of 6 or ≤ 2 of 9 subjects experience a DLT during the DLT observation period. The MAD is defined as the highest dose tested. Both MAD and MTD may be determined independently for each tested dosing schedule of veliparib. The RPTD and schedule will be determined based on the assessment of the observed toxicities, the MTD or MAD, and the overall safety profile of the study drug. The RPTD cannot exceed the lower of MTD or MAD. At the RPTD and schedule, additional subjects will be added as needed so that a total of at least 9 subjects will be treated at the RPTD during the dose escalation part of the study.

Methodology (Continued):

DLT Definition:

DLT is defined as any of the following drug-related toxicities occurring during the DLT observation period in any of the dose-escalation cohorts, with grading according to the National Cancer Institute (NCI) Common Toxicity Criteria for Adverse Events (CTCAE), Version 4.0:

1. Cycle 1 events associated with treatment delay > 14 days in initiating Cycle 2:
   a. Grade 4 thrombocytopenia (platelets < 25.0×10^9/L)
   b. Grade 4 neutropenia (absolute neutrophil count (ANC) < 0.5×10^9/L)
   c. Grade 3 febrile neutropenia with fever lasting for > 7 days
   d. Grade 4 febrile neutropenia of any duration

   NOTE: Delay of more than 14 days in initiating Cycle 2 due to factors not directly related to treatment-emergent toxicity will not be considered a DLT.
2. Grade ≥ 3 non-hematologic toxicity that represents at least 2 grade increase from baseline and is attributed to veliparib treatment:
   a. Exclusion: nausea and vomiting lasting ≤ 48 hours or inadequately treated
   b. Exclusion: electrolyte abnormalities resolving within ≤ 24 hours
   c. Exclusion: hypersensitivity reactions
   d. Exclusion: alopecia
3. Grade 2 non-hematologic toxicity that represents at least 2 grade increase from baseline, is attributed to veliparib treatment and requires a treatment delay of > 14 days in initiation of Cycle 2
4. Any toxicity that represents at least 2 grade increase from baseline, is attributed to veliparib treatment and requires at least one of:
   a. Dose modification within Cycle 1
   b. Omission of carboplatin, > 1 daily etoposide dose, or > 30% veliparib doses in Cycle 1

Subjects experiencing DLT(s) during DLT observation period (Cycle 1 Day –2 to pre-dose Cycle 2 Day 1) will require an interruption and possible discontinuation from further participation in the study. Veliparib may be reintroduced at a reduced dose, if the toxicity returns to ≤ Grade 1 or to baseline if Grade 2 at study entry. All decisions regarding continued dosing for individual subjects who experience a DLT will be medically managed by the investigator in conjunction with the AbbVie TA MD.

Pharmacokinetics:

Pharmacokinetics of veliparib and etoposide will be assessed to determine the drug-drug interactions. Further pharmacokinetics of carboplatin will be assessed on Day 1 of Cycle 1.

Phase 2 Randomized Double-Blind

The veliparib dose and schedule for the Phase 2 was determined to be 240 mg BID on a 14 day schedule based on the analysis of Phase 1 data.

Approximately 180 total subjects with treatment-naïve ED SCLC will be enrolled at the 240 mg BID veliparib/placebo dose and 14 day schedule in the Phase 2 double-blinded portion of the study. They will be randomized in a 1:1:1 ratio to one of three treatment arms:

- Arm A: veliparib in combination with carboplatin/etoposide followed by veliparib monotherapy
- Arm B: veliparib in combination with carboplatin/etoposide followed by placebo monotherapy

Methodology (Continued):

Phase 2 Randomized Double-Blind (Continued)

- Arm C: placebo in combination with carboplatin/etoposide followed by placebo monotherapy

Subjects in all Phase 2 study arms will receive a minimum of 4 cycles of combination therapy unless disease progression or unacceptable toxicity warrants earlier discontinuation from the treatment. Additional 2 cycles of combination therapy (e.g., up to a total of 6 cycles) may be administered at the investigators discretion if subject status at the completion of initial 4 cycles warrants continued combination treatment and/or if local SOC guidelines require 6 cycles of platinum-based therapy. In the combination cycles of Arms A and B, subjects will receive veliparib at 240 mg BID on a 14-day schedule, Arm C will receive matching placebo. After completion of the chemotherapy combination cycles (at least 4), subjects without evidence of disease progression will receive veliparib at 400 mg BID continuous dosing (21-day cycles) (Arms A), or matching placebo (Arms B and C) as per treatment arm assignment, until disease progression or unacceptable toxicity occurs.

Subjects who will be receiving prophylactic cranial irradiation (PCI) will have maintenance veliparib interrupted for the duration of radiotherapy.

Subject randomization for Phase 2 will be stratified by baseline LDH level (> ULN versus ≤ ULN), and gender.

Pharmacodynamics (Phase 1 Dose Escalation and Phase 2 Randomized Double-Blind):

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.

Tumor Assessments and Safety Follow-Up

Tumor assessments will be performed until radiographic disease progression. Tumor assessment and assessment of response will occur every 6 weeks (± 1 week) from C1D-2 for the first 24 weeks (Phase 1) or 30 weeks (Phase 2), then every 9 weeks (± 1 week) thereafter. Tumor response will be determined according to the Response Evaluation Criteria in Solid Tumors (RECIST), Version 1.1. Subjects will continue on study until they meet defined discontinuation criteria. When the investigator has determined that a subject should discontinue the study, a Final Visit will be conducted. Subjects will have a 30-Day Follow-Up Visit following the last dose of study drugs or placebo (Phase 2, dependent on treatment arm). If the subject begins another treatment regimen directly following protocol treatment and if a 30-Day Follow-Up Visit is not possible, all adverse events ongoing as of the end of study must be followed to a satisfactory conclusion.

Diagnosis and Main Criteria for Inclusion/Exclusion:

Inclusion:

1. Subject has histologically or cytologically confirmed ED SCLC which is newly diagnosed and chemotherapy naïve.
2. Phase 1 ONLY: histologically or cytologically confirmed advanced/metastatic solid tumors for which carboplatin/etoposide treatment is considered appropriate.
3. Subject in Phase 2 ONLY: must have measureable disease per RECIST 1.1.
4. Subjects with ED SCLC must consent to provide <u>available</u> archived formalin fixed paraffin embedded (FFPE) tissue sample of SCLC lesion (primary or metastatic) for central review and biomarker analysis. NOTE: If sufficient tissue is unavailable for analysis, subjects will still be allowed to enroll.

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

Inclusion (Continued):

5. Subject has an Eastern Cooperative Oncology Group (ECOG) performance score of 0 to 1.
6. Subject must be ≥ 18 years of age.
7. Subject must have adequate hematologic, renal and hepatic function as follows:
   - Bone Marrow: Absolute neutrophil count ANC ≥ 1,500/mm^3 (1.5×10^9/L); White blood cells ≥ 3,000/mm^3 (3×10^9/L); Platelets ≥ 100,000/mm^3 (100×10^9/L); Hemoglobin ≥ 9 g/dL (5.58 mmol/L)
   - Renal function: creatinine ≤ ULN or if creatinine > ULN calculated creatinine clearance via the Cockroft Gault formula of ≥ 50 mL/min
   - Hepatic function:
     - Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 × upper limits of normal (ULN). For subjects with liver metastases, AST and ALT ≤ 5 × ULN;
     - Bilirubin: ≤ 1.5 × ULN; for subjects with Gilbert's syndrome bilirubin > 1.5 × ULN is allowed if no symptoms of compromised liver function are present.
8. Subject must be able to swallow pills.
9. Female and male patients of fertile age, and/or their partners should use contraception. If male, subject and subject's female partner(s) of childbearing potential must follow the contraception recommendations as described in Section 5.2.4. If female, subject must be either postmenopausal for at least 1 year, surgically sterile (bilateral tubal ligation, bilateral oophorectomy or hysterectomy), or the subject and the subject's male partner(s) must follow the contraception recommendations as described in Section 5.2.4.

   Female subjects must have negative results for pregnancy tests performed:
   - Screening on a serum specimen obtained within 7 days prior to initial study drug administration, and
   - prior to dosing on a urine sample obtained C1D-2 unless the serum pregnancy test was collected within 7 days of C1D-2.
10. Must voluntarily sign and date each informed consent, approved by an Independent Ethics Committee (IEC)/Institutional Review Board (IRB), prior to the initiation of any screening or study specific procedures.

Exclusion:

1. Phase 1 ONLY: Subject has had any prior anti-cancer therapy other than:
   - Hormonal, non-myelosuppressive, biologic, targeted, or immune therapy (must be completed ≥ 4 weeks prior to Cycle 1 Day –2).
   - One line of cytotoxic chemotherapy (must be completed ≥ 4 weeks prior to Cycle 1 Day –2).
   - Adjuvant/neoaduvant radiotherapy (must be completed ≥ 12 months prior to Cycle 1 Day –2, with field not involving > 10% of bone marrow reserve).
   - Tumor lesion irradiation with intent of symptom palliation ≥ 4 weeks prior Cycle 1 Day –2.

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

Exclusion (Continued):

2. Phase 2 ONLY: Subject has had any prior chemotherapy, radiotherapy, investigational anti-cancer agents or biologic therapy for the disease under study. Single non-target lesion irradiation with intent of symptom palliation is allowed if ≥ 2 weeks prior Cycle 1 Day –2.
3. Subject has known hypersensitivity to etoposide, platinum compounds or veliparib.
4. Phase 1 ONLY: Subject has received prior myelopoietic growth factors.
5. Subject has current central nervous system (CNS) or leptomeningeal metastases or history of CNS or leptomeningeal metastases. If CNS metastasis is suspected, a head CT should be performed at screening.
6. Subject has a history of seizures within 12 months of Cycle 1 Day –2 or diagnosed neurological condition placing subject at the increased risk of seizures.
7. Subject has received traditional herbal anti-cancer medicine (e.g., Chinese, Asian etc.) within 14 days prior to Cycle 1 Day –2.
8. Subject has had major surgery within 6 weeks prior to Cycle 1 Day –2 (subjects must have completely recovered from any previous surgery prior to Cycle 1 Day –2).
9. Subject has clinically significant and uncontrolled major medical condition(s) including but not limited to:
   - Uncontrolled nausea/vomiting/diarrhea;
   - Active uncontrolled infection;
   - History of hepatitis B (HBV) with surface antigen (HBsAg) positivity within 3 months prior to the date of informed consent for this study (if HBsAg status is unknown it must be tested at screening);
   - History of hepatitis C (HCV) with HCV RNA positivity within 3 months prior to the date of informed consent for this study (if HCV RNA status is unknown it must be tested at screening);
   - Symptomatic congestive heart failure (New York Heart Association [NYHA] class ≥ II);
   - Unstable angina pectoris or cardiac arrhythmia;
   - Psychiatric illness/social situation that would limit compliance with study requirements;
   - Any other medical condition, which in the opinion of the Investigator, places the subject at an unacceptably high risk for toxicities.
10. Subject is pregnant or lactating.
11. The subject has a history of another active 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, breast ductal carcinoma in situ [DCIS]).

Questions regarding the eligibility of individual subjects should be directed to the AbbVie TA MD.

Investigational Products:	Veliparib
Doses:	Phase 1 Dose Escalation cohorts: 80, 120, 160, 200 and 240 mg BID (higher doses up to 400 mg BID may be tested) Phase 2 Randomized Double-Blind arms: 240 mg BID Continuous monotherapy maintenance: 400 mg BID
Mode of Administration:	Oral
Investigational Products:	Placebo – BID Phase 2 ONLY
Doses:	Combination therapy: matching capsules for 240 mg BID Continuous monotherapy maintenance: matching capsules for 400 mg BID
Mode of Administration:	Oral
Reference Therapy:	Carboplatin
Doses:	AUC 5 mg/mL*min
Mode of Administration:	Intravenous infusion
Reference Therapy:	Etoposide
Doses:	100 mg/m^2
Mode of Administration:	Intravenous infusion

Duration of Treatment:

Subject will remain on study drug until disease progression or unacceptable toxicity.

Criteria for Evaluation:

Efficacy:

Progression-free survival (PFS) will be derived according to disease progression (radiographic progression per RECIST version 1.1) or death. Radiographic tumor assessments for response will be conducted by CT scanning at baseline, every 6 weeks from C1D-2 for the first 24 weeks (Phase 1) or 30 weeks (Phase 2), then every 9 weeks until disease progression.

Objective response rate (ORR) will be derived per RECIST version 1.1. Radiographic tumor assessments for response will be conducted by CT scanning at baseline, every 6 weeks from C1D-2 for the first 24 weeks (Phase 1) or 30 weeks (Phase 2), then every 9 weeks until disease progression.

Duration of overall response (DOR) will be derived according to disease progression (radiographic progression per RECIST version 1.1).

Overall survival will be determined by the Investigator at assessments throughout therapy. After the final visit, survival information will be collected via electronic data capture (EDC) at 2 month intervals (or as requested by sponsor to support data analysis).

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

Pharmacokinetic:

Blood samples for pharmacokinetics of veliparib, carboplatin (Phase 1 Dose Escalation only) and etoposide (Phase 1 Dose Escalation only) will be collected at designated time points throughout the study. Pharmacokinetics of veliparib and etoposide will be assessed to determine the drug-drug interactions. In addition, pharmacokinetics of carboplatin will be determined.

Criteria for Evaluation (Continued):

Pharmacodynamic:

Research to find biomarkers that may be predictive of veliparib activity will be conducted. Serum, plasma, blood and archived tissue samples will be collected at designated time points throughout the study.

Pharmacogenetic:

DNA samples may be analyzed for genetic factors contributing to the subject's response to veliparib, or other study treatment, in terms of pharmacokinetics, efficacy, tolerability and safety**.**

Safety:

Adverse events, laboratory profiles, physical examinations, vital signs and neurological assessments will be evaluated and recorded throughout the study.

Statistical Methods:

Efficacy:

The following end point will be analyzed using data obtained from subjects in Phase 1 and Phase 2 separately:

Objective Response Rate

The proportion of subjects with objective response (CR or PR) as assessed by the investigator using RECIST 1.1 will be calculated for all dosed subjects.

The following end point will be analyzed using data obtained from subjects in Phase 2:

Progression-Free Survival

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

Overall Survival

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

Duration of Overall Response

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

Performance Status

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

Statistical Methods (Continued):

Pharmacokinetic:

Plasma concentrations of veliparib, etoposide, and carboplatin and pharmacokinetic parameter values will be tabulated for each subject and each dose level, and summary statistics will be computed for each sampling time and each parameter.

The effects of co-administration of veliparib on etoposide pharmacokinetics will be addressed by analyzing the Cycle 1 Day 1 (veliparib with carboplatin and etoposide) and Cycle 2 Day 1 (carboplatin and etoposide alone) etoposide pharmacokinetic variables, including T_{max}, dose normalized C_{max} and dose normalized AUC.

Pharmacodynamic:

Biomarker results will be tabulated for each subject and each regimen, and summary statistics will be computed for each sampling time and each parameter. The relationship between biomarker status and clinical outcome or drug exposure may be examined.

Safety:

- The safety of veliparib in combination with carboplatin/etoposide will be assessed by evaluating the study drugs exposure, adverse events, serious adverse events, all deaths, as well as changes in laboratory determinations and vital sign parameters. Safety will be summarized per dose level using descriptive statistics for the dose escalation cohorts and per treatment arm in Phase 2.
- RPTD was determined based on the rate of DLTs and overall tolerability of the combination of veliparib, carboplatin and etoposide with at least 9 subjects treated at the RPTD in Phase 1 and will be further evaluated in Phase 2.

1.3 List of Abbreviations and Definition of Terms

Abbreviations

AE	Adverse Event
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
AUC	Area Under the Plasma Concentration-time Curve
ASCO	American Society of Clinical Oncology
AST	Aspartate Aminotransferase
aPTT	Activated Partial Thromboplastin Time
BID	Twice Daily
BRCA	Breast Cancer Gene (susceptibility)
BUN	Blood Urea Nitrogen
CS	Clinically Significant
CTEP	Cancer Therapy Evaluation Program
CNS	Central Nervous System
CR	Complete Response
CRF or eCRF	Case Report Form or Electronic Case Report Form
CT	Computed Tomography
CTCAE	Common Toxicity Criteria for Adverse Events
DCIS	Ductal Carcinoma in situ
DICOM	Digital Imaging and Communications in Medicine
DLT	Dose Limiting Toxicity
DNA	Deoxyribonucleic acid
DOR	Duration of Overall Response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
ED	Extensive Disease
EDC	Electronic Data Capture
EDTA	Edetic acid (ethylenediaminetetraacetic acid)
eGFR	Estimated Glomerular Filtration Rate
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
G-CSF	Granulocyte Colony Stimulating Factor
GFR	Glomerular Filtration Rate
GM-CSF	Granulocyte Macrophage-Colony Stimulating Factor
GOG	Gynecologic Oncology Group
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C Virus
Hgb	Hemoglobin
HIV	Human Immunodeficiency Virus
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IIS	Investigator initiated studies
IRB	Institutional Review Board
IRT	Interactive Response Technology
IUD	Intrauterine Device
IUS	Intrauterine hormone-releasing system
IV	Intravenous
LD	Limited Disease
MAD	Maximum Administered Dose
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NCS	Not Clinically Significant
NSCLC	Non-small Cell Lung Cancer
NYHA	New York Heart Association
ORR	Objective Response Rate
OS	Overall Survival
PARP	Poly(ADP-ribose)-polymerase
Pd	Pharmacodynamics
PD	Progressive Disease

PFS	Progression Free Survival
PK	Pharmacokinetics
PLTs	Platelets
PoR	Proof of Receipt
PR	Partial Response
PT	Prothrombin Time
QA	Quality Assurance
QC	Quality Control
QTc	QT interval corrected for heart rate
RBC	Red Blood Cells
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	Ribonucleic acid
RPTD	Recommended Phase Two Dose
SCLC	Small Cell Lung Cancer
SAE	Serious Adverse Event
SD	Stable Disease
SGOT	Serum Glutamic-oxaloacetic Transaminase
SGPT	Serum Glutamic-pyruvic Transaminase
SmPC	Summary of Product Characterizations
SOC	Standard of Care
SOD	Sum of Diameter
SUSAR	Suspected Unexpected Serious Adverse Reactions
TA MD	Therapeutic Area Medical Director
TMZ	Temozolomide
TTP	Time to Progression
ULN	Upper Limit of Normal
US	Ultrasound
WOCBP	Women of Childbearing Potential
WBC	White Blood Cell

2.0 Table of Contents

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3.0 Introduction

3.1 Small Cell Lung Cancer (SCLC)

Small cell lung cancer (SCLC) is a neuroendocrine carcinoma that exhibits aggressive behavior, rapid growth, and early spread to distant sites. It constitutes approximately 15% of lung carcinomas. SCLC is staged as limited or extensive stage disease (LD and ED SCLC, respectively). LD SCLC is defined herein as a disease confined to the hemithorax of origin, with or without the involvement of regional lymph nodes, including ipsilateral and contralateral hilar, ipsilateral and contralateral mediastinal, and ipsilateral supraclavicular nodes. ED SCLC is defined as all other SCLC. At presentation, 60% to 70% of SCLC cases in the United States are diagnosed as extensive-stage disease, for which at present there is no curative treatment. There has been no significant improvement in the clinical outcome for subjects with ED SCLC in the last 2 decades, and it remains one of the most fatal cancers. The National Comprehensive Cancer Network (NCCN) recommended management approach for ED SCLC is platinum-based doublet systemic chemotherapy, and platinum-etoposide is the most common regimen in the North America and Europe. This regimen achieves a response rate of 50% to 70%, median survival of 9 – 11 months and median 5-year survival of less than 5%.[1-3] While SCLC is very sensitive to frontline platinum based doublet chemotherapy, most patients relapse and die of their disease. Previous strategy to improve the outcome of the disease was the use of high intensity chemotherapy which led to an improvement in the response rate; however this did not translate into survival benefit due to heightened toxicities.[4-6] The incorporation of novel targeted agents with excellent safety profile and limited additive toxicity in combination with standard chemotherapy agents as a strategy for improved efficacy has a great potential for improved clinical outcome in this disease.

3.2 Poly (ADP) Ribose Polymerase (PARP)

Poly (ADP) ribose polymerases (PARPs) are a family of enzymes that catalyze the addition of ADP-ribose to a variety of cellular molecules. Several members of PARP family are involved in DNA damage repair, primarily through base excision repair

mechanism.[7-9] 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. Veliparib potently inhibits PARP-1 and -2 enzymes at clinically relevant concentrations.

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.[8] 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.[10] In particular, tumor cells with BRCA1 or BRCA2 deficiencies are exquisitely sensitive to PARP inhibition, even in the absence of any other insults.[11-14]

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.

3.3 Veliparib

Veliparib is a potent oral PARP inhibitor that delays the repair of DNA damage induced by chemotherapeutic agents, including alkylating agents, platinums, and topoisomerase inhibitors, and radiation. Nonclinical efficacy with veliparib in combination with these agents has been demonstrated across an array of tumor types, including melanoma, glioma, prostate, breast, and colon.

A detailed discussion of the preclinical toxicology, metabolism, and pharmacology can be found in the Investigator's Brochure.[15]

3.3.1 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 in several xenograft tumor models. [redacted]

[redacted]

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.

3.3.2 Veliparib Pharmacokinetics/Pharmacodynamics

In humans, at least 90% of the dose is absorbed after oral administration of veliparib. Veliparib is primarily cleared in the urine as intact parent drug (73% of administered dose), with a small fraction of clearance from metabolism. Preliminary clinical pharmacokinetic (PK) data available from 6 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.

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. In study subjects, there was no significant pharmacokinetic interaction between veliparib and TMZ, and preliminary results indicate the absence of 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.

3.3.3 Veliparib Clinical Studies

Veliparib is being 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 temozolomide (TMZ), with radiotherapy, and with carboplatin + paclitaxel.[17] Data from non-AbbVie sponsored studies show veliparib has activity as monotherapy for treatment of ovarian cancer[18] and activity in combination with carboplatin + paclitaxel for treatment of early breast cancer.[19] Veliparib is currently in Phase 2 and Phase 3 clinical development in combination with several DNA-damaging agents across a variety of cancer indications.

Several clinical studies explored combinations of veliparib with carboplatin-based combination chemotherapies and one study is evaluating cisplatin/etoposide/veliparib combination.

Phase 1 data from subjects treated with veliparib, carboplatin, and paclitaxel for advanced non-small cell lung cancer (NSCLC) are available from Cancer Therapy Evaluation Program (CTEP) Study 7967.[20] Veliparib was given orally BID on Days 1 to 7 of each 21-day cycle, and paclitaxel and carboplatin were administered on Day 3. Two DLTs

(febrile neutropenia and hyponatremia) were observed in 2 of 7 evaluable subjects treated at the maximum tolerated dose of veliparib 120 mg BID, paclitaxel 200 mg/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 (Study M10-898) of carboplatin and paclitaxel with veliparib or placebo for subjects with advanced NSCLC is complete. Therapy was 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. Seventy-six squamous NSCLC subjects were treated with veliparib combination. All subjects have completed therapy. 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. The efficacy data are summarized in Investigator Brochure, version 9.

An ongoing ECOG study E2511 is a Phase 1 and randomized Phase 2 double-blind clinical study of cisplatin and etoposide in combination with veliparib or placebo as frontline therapy for ED SCLC.[21] In the Phase 1 part of the study the maximum administered dose of veliparib in combination with 75 mg/m^2 cisplatin and 100 mg/m^2 etoposide was 100 mg BID. This dose was selected as the recommended Phase 2 dose for the randomized part of the study, which is currently ongoing. The Phase 1 part of the study enrolled 9 patients with ED SCLC. Veliparib was well tolerated at the 60 mg dose (0 of 3 patients with DLT). DLT was seen in 1 of 6 patients treated at the 100 mg dose (grade 5 cardiac failure; Takotsubo cardiomyopathy). The same subject experienced G4 respiratory failure prior to G5 cardiac failure. The maximum administered dose of veliparib of 100 mg BID on D1-7 in combination with standard doses of cisplatin and etoposide was defined as the RPTD. Other Grades 3 – 4 adverse events irrespective of

attribution included: neutropenia (6), leukopenia (5), nausea (3), thrombocytopenia (2), fatigue (2), hyponatremia (2), dehydration (1), febrile neutropenia (1), and diarrhea (1). Unconfirmed investigator-assessed efficacy outcome in 7 evaluable patients were stable disease in 2/7 (28.6%), partial response in 4/7 (57.1%) and complete response in 1/7 (14.3%) patients.[21]

Overall, approximately 3,700 cancer patients have been exposed to veliparib in AbbVie and CTEP clinical trials with veliparib administered as monotherapy and as combination therapy to study subjects with various solid and hematological tumors. Based upon mechanism of action, nonclinical, and clinical data, hematological cytopenias (thrombocytopenia, anemia, neutropenia, and lymphopenia) are toxicities that may result from veliparib therapy. When veliparib is administered as single-agent therapy, these toxicities are predominantly Grade 1 or Grade 2 toxicities. In combination with cytotoxic chemotherapy, Grade 3 or Grade 4 cytopenias may be observed. These toxicities are commonly associated with cancer therapies, and standard clinical practices to manage these toxicities are well-established.

Nausea and vomiting have been commonly observed in clinical trials with veliparib, including in subjects receiving single-agent therapy with veliparib. 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.[15]

3.4 Carboplatin and Etoposide

Carboplatin is a commonly used platinum compound that acts by binding to Deoxyribonucleic Acid (DNA) and interrupting cell division. It is approved by the Food and Drug Administration (FDA) for the treatment of patients 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 more recently in breast cancer. Carboplatin is eliminated by renal excretion. 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.[22,23]

Etoposide, commonly known as VP-16, is a semi-synthetic derivative of podophyllotoxin. Etoposide in combination with other approved chemotherapeutic agents is FDA approved as first-line treatment in subjects with small cell lung cancer. The predominant macromolecular effect of etoposide appears to be the induction of DNA strand breaks by an interaction with DNA-topoisomerase II or the formation of free radicals. Its main effect appears to be at the G2 portion of the cell cycle in mammalian cells. Hematologic toxicity (myelosuppression) is the most frequently observed toxicity of etoposide. Other frequent toxicities include nausea and vomiting, anorexia and alopecia.[24]

Carboplatin in combination with etoposide (both IV and oral formulations) has been extensively tested in randomized clinical trials in SCLC as well as in other tumor types.[24-27] Most frequently reported adverse events in subjects treated with carboplatin and etoposide combination were myelosuppression (leukopenia and thrombocytopenia), nausea, vomiting and alopecia.

The recommended dose of carboplatin for this combination is AUC of 5 – 6 mg/mL*min on Day 1 and the dose for etoposide 100 mg/m^2 on Days 1 – 3 of 21-day cycles per NCCN 2014 guidelines for the treatment of ED SCLC.

3.5 Study Rationale

The proposed study has the potential to advance the management of SCLC if it results in improved clinical outcome as anticipated, based on preclinical evaluation.

DNA damaging agents constitute the mainstay of therapy for SCLC. The combination of DNA damaging cytotoxic chemotherapy (e.g., cisplatin and etoposide) and a

pharmacologic inhibitor of DNA damage repair enzyme, poly (ADP) Ribose polymerase (PARP), may result in greater cytotoxicity and antitumor efficacy of the cytotoxic agents. It is postulated that enhanced efficacy may translate into improved disease progression without concomitant increased toxicity in subjects with extensive stage SCLC.

The in vitro and in vivo studies of veliparib and standard cytotoxic agents for SCLC including cisplatin, carboplatin and etoposide, discussed in the preceding sections provide specific supporting evidence for the clinical evaluation of veliparib as an agent that can further potentiate currently available therapies for the treatment of SCLC. Similar strategies are currently in clinical translation for various types of cancer including melanoma, breast and ovarian cancers.[4-6] This clinical protocol represents the first attempt to translate the same concept into the treatment of SCLC where DNA damage-inducing agents form the cornerstone of therapy. If successful, the proposed trial is able to provide additional clinical proof for the biologic principle that DNA damage repair enzyme inhibition through pharmacological agents will enhance the efficacy of classic cytotoxic agents that act by inducing DNA damage.

A positive outcome in this Phase 2 evaluation, in conjunction with such outcome from ECOG E2511 study, will provide a strong rationale to conduct a large definitive registration study of veliparib in combination with platinums and etoposide in ED SCLC.

3.6 Differences Statement

This study is designed to evaluate the safety and tolerability of veliparib in combination with carboplatin and etoposide in subjects with small cell lung cancer or advanced/metastatic solid tumors. This is the first study being conducted with this combination of treatment. Previous early phase studies have been designed to test the safety and tolerability of veliparib as monotherapy or in combination with chemotherapy.

3.7 Benefits and Risks

The Phase 1 Dose Escalation portion of this study proposed to establish the recommended Phase 2 dose and veliparib schedule. These were determined to be veliparib 240 mg BID

on Days –2 – 12 (14-Day schedule) in combination with carboplatin AUC 5 mg/ml*hr on Day 1 and etoposide 100 mg/m^2 on Days 1 – 3 of 21-Day cycle. The Phase 2 portion of this study proposes to evaluate clinical outcomes for subjects with ED SCLC treated with veliparib added to standard therapy with carboplatin and etoposide. Preclinical data demonstrate that veliparib potentiates the anti-tumor activity of platinums, and that platinum sensitivity often correlates with the sensitivity to PARP inhibitors. The current study, Study M14-361, is the first to test veliparib in combination with carboplatin and etoposide in human subjects.

Risks in this study include toxicity from the addition of veliparib to standard therapy. Preliminary safety data from several Phase 1 and Phase 2 studies indicate that veliparib is tolerated in combination with carboplatin and paclitaxel at doses of up to 120 – 200 mg BID, and with cisplatin and etoposide at the maximum tested dose of 100 mg BID. Standard clinical practices to manage the toxicity of carboplatin + etoposide are well established. Toxicity will be closely monitored at all study visits. Toxicities of veliparib expected to overlap with the toxicity of carboplatin + etoposide regimen include nausea/vomiting and myelosuppression. 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. Addition of veliparib resulted in no compromise to the delivery of carboplatin. Drug-drug interaction with etoposide is not anticipated, but will be monitored.

4.0 Study Objectives

The objectives of the Phase 1 dose escalation are:

Primary Objectives:

- To establish the Maximum Tolerated Dose (MTD) and to establish the Recommended Phase 2 Dose (RPTD) and schedule for veliparib in combination with carboplatin and etoposide.
- To evaluate the pharmacokinetic interaction between veliparib and etoposide.

Secondary Objective:

- To evaluate the safety of maintenance veliparib monotherapy at 400 mg BID in subjects completing 4 cycles of carboplatin, etoposide and veliparib without evidence of disease progression.

The objectives of Phase 2 are:

Primary Objective:

- To evaluate if veliparib in combination with carboplatin and etoposide followed by veliparib maintenance monotherapy results in improved progression free survival (PFS) versus placebo in combination with carboplatin and etoposide followed by placebo monotherapy in subjects with treatment-naïve ED SCLC.

Secondary Objectives:

- To evaluate if veliparib in combination with carboplatin and etoposide followed by placebo monotherapy results in improved progression free survival (PFS) versus placebo in combination with carboplatin and etoposide followed by placebo monotherapy in subjects with treatment-naïve ED SCLC.
- To evaluate if veliparib in combination with carboplatin and etoposide results in improved objective response rate (ORR) versus placebo in combination with carboplatin and etoposide, at the time of completion of combination therapy.
- To evaluate if veliparib in combination with carboplatin and etoposide followed by veliparib maintenance monotherapy results in improved overall survival (OS) versus placebo in combination with carboplatin and etoposide followed by placebo monotherapy.
- To evaluate if veliparib in combination with carboplatin and etoposide followed by placebo monotherapy results in improved overall survival (OS) versus placebo in combination with carboplatin and etoposide followed by placebo monotherapy.

- To further evaluate the safety of veliparib in combination with carboplatin and etoposide followed by veliparib maintenance monotherapy.

Tertiary Objectives are:

- To evaluate if veliparib in combination with carboplatin and etoposide followed by veliparib maintenance monotherapy results in improved duration of overall response (DOR) versus placebo in combination with carboplatin and etoposide followed by placebo monotherapy.
- To evaluate if veliparib in combination with carboplatin and etoposide followed by placebo monotherapy results in improved duration of overall response (DOR) versus placebo in combination with carboplatin and etoposide followed by placebo monotherapy.
- To compare PFS and OS of subjects treated with veliparib in combination with carboplatin and etoposide followed by veliparib maintenance to PFS and OS of subjects treated with veliparib in combination with carboplatin and etoposide followed by placebo maintenance.
- To evaluate performance status.

5.0 Investigational Plan

5.1 Overall Study Design and Plan: Description

This is a Phase 1, open-label, dose escalation/Phase 2 randomized double-blind study of veliparib in combination with carboplatin and etoposide and maintenance veliparib monotherapy. Subjects in Phase 1 will be group sequentially assigned to the ascending dose levels of veliparib in combination with standard carboplatin/etoposide regimen based on the observed toxicities. Subjects in Phase 2 will be randomized in a 1:1:1 ratio to carboplatin, etoposide, placebo followed by placebo maintenance, or carboplatin, etoposide, veliparib followed by either veliparib or placebo maintenance. Approximately 215 adult male or female subjects diagnosed with extensive stage disease SCLC or other advanced/metastatic solid tumors will be selected to participate in the study according to the inclusion/exclusion criteria.

The study was designed to enroll approximately 35 subjects in Phase 1 and approximately 180 subjects in Phase 2 to meet scientific and regulatory objectives without enrolling an undue number of subjects in alignment with ethical considerations. Possible dose levels to be evaluated are as shown in Table 4.

Phase 1 Dose Escalation

The Phase 1 portion of this study will evaluate the safety, tolerability, dose limiting toxicities (DLTs), RPTD, pharmacokinetics (PK), and pharmacodynamics (PD) of veliparib in combination with carboplatin and etoposide in 21-day cycles in subjects with small cell lung cancer or advanced/metastatic solid tumors with possible schedules outlined in Table 1, Table 2 and Table 3. For the Phase 1 subjects receiving non-continuous dosing, veliparib in Cycle 2 will be administered on Days 2 – 5 or Days 2 – 12 dependent on the dosing schedule to allow for evaluation of drug-drug interaction of veliparib with etoposide (Table 2). Details on drug administration and cycle schedules are described in Section 5.5.1.2.

Table 1. Treatment Schema for Combination Therapy Cycles 1, 3, 4 in Phase 1 Dose Escalation (Non-Continuous Veliparib Dosing Schedules)

Days	–2	–1	1	2	3	4 – 5 or 4 – 12	6 – 19 or 13 – 19
Veliparib	Twice a day	Twice a day	Twice a day	Twice a day	Twice a day	Twice a day	
Carboplatin			Once				
Etoposide			Once	Once	Once		

Note: Starting at Cycle 5 Day 1 veliparib dosed at 400 mg BID monotherapy continuous dosing for 21 days per cycle.

Table 2. Treatment Schema for Combination Therapy Cycle 2 in Phase 1 Dose Escalation (Non-Continuous Veliparib Dosing Schedules)

Days	–2	–1	1	2	3	4 – 5 or 4 – 12	6 – 19 or 13 – 19
Veliparib				Twice a day	Twice a day	Twice a day	
Carboplatin			Once				
Etoposide			Once	Once	Once		

Table 3. Treatment Schema for Combination Therapy Cycles in Phase 1 Dose Escalation (Continuous Veliparib Dosing Schedule)

Days	–2	–1	1	2	3	4 – 19
Veliparib	Twice a day	Twice a day	Twice a day	Twice a day	Twice a day	Twice a day
Carboplatin			Once			
Etoposide			Once	Once	Once	

Note: Starting at Cycle 5 Day 1 veliparib dosed at 400 mg BID monotherapy continuous dosing for 21 days per cycle.

Upon completion of 4 cycles of combination therapy, subjects without evidence of disease progression will continue on maintenance monotherapy veliparib 400 mg BID until disease progression or unacceptable toxicity. Subjects who will be receiving prophylactic cranial irradiation (PCI) will have maintenance veliparib interrupted for the duration of radiotherapy as described in Section 5.2.3.2.

For subjects in the Phase 1 dose escalation portion of the study, each subject will participate in only 1 dose group and there is no provision for intra-subject dose-escalation. Study procedures are provided in the Schedule of Assessments and Pharmacokinetic and Pharmacodynamic tables (Section 5.3.1).

All subjects will be monitored for DLTs during DLT observation period (Cycle 1 Day –2 to pre-dose on Cycle 2 Day 1), and treatment-related adverse events (AEs) will be evaluated throughout the course of the study for evidence of acute, delayed, or cumulative toxicities.

Subjects who do not complete the DLT observation period for reasons other than DLT (e.g., withdraw consent, non-compliance, etc.) will be replaced to ensure appropriate number of subjects are evaluated.

The dose levels of veliparib to be evaluated in the dose-escalation portion of this study were determined based on the outcome of prior clinical studies of veliparib as well as on pre-clinical toxicology, toxicokinetic, and nonclinical anti-tumor efficacy studies. The following dose levels may be evaluated in the dose-escalation portion of the study: 80, 120, 160, 200 and 240 mg BID (Table 4). Reduced dose levels may be evaluated based upon review of subject safety and PK data. Intermediate dose levels may be evaluated based upon review of subject safety including, but not limited to, Grade 2 study-drug related AEs. If the MTD is not reached at veliparib 200 mg BID dose level, higher dose levels (with no more than 25% veliparib dose increments, and not exceeding single agent veliparib RPTD of 400 mg BID (Table 4, Levels V – VIII) or alternative veliparib dosing schedules may be evaluated at the discretion of the sponsor. The alternative dosing schedules can include dosing veliparib for Day –2 to Day 12 (14-day schedule) and/or Day –2 to Day 19 (continuous schedule) of the 21 day cycle (Table 1, Table 2 and Table 3). The initial dose for these schedules will be 200 mg BID or the maximum administered dose (MAD), not exceeding the MTD in the 7 day schedule. The 14-day schedule will be explored prior to continuous dosing schedule. Reduced or interim dose levels may be evaluated based on review of the safety and PK.

Table 4. Phase 1 Dose Escalation

		Doses		
Dose Level	**Number of Subjects**	**Veliparib mg**	**Carboplatin AUC, mg/mL*min**	**Etoposide mg/m^2**
I	3 – 9	80	5	100
II	3 – 6	120	5	100
III	3 – 6	160	5	100
IV	3 – 6	200	5	100
V	3 – 6	240	5	100
VI	3 – 6	300	5	100
VII	3 – 6	340	5	100
VIII	3 – 6	400	5	100

A "3 + 3" escalation rule will be used for the dose-escalation portion of this study, with a condition applied for the Dose Level 1, which will allow 3 additional subjects to be entered in Dose Level 1 if 2 of 6 initial subjects experience DLTs. Enrollment of the 3 additional subjects at all dose levels will depend on a review of the specific DLTs observed and discussion with the Investigators.

A minimum of 3 evaluable subjects will be enrolled at each dose level. Additional eligible subjects may be enrolled at the current dose level at the discretion of the Investigators and the AbbVie TA MD. The dose escalation decisions will be made following the completion of the DLT observation period for the evaluable subjects in the intended cohort size. If a cohort is over-enrolled, reported toxicities in additional subjects will be taken into consideration.

Dose-Escalation Criteria:

AEs, clinical laboratory results and vital signs will be assessed throughout the study in each dose-escalation cohort.

DLTs will be assessed in each dose-escalation cohort during DLT observation period (Cycle 1 Day –2 to pre-dose Cycle 2 Day 1). Based on the safety and tolerability of study

drugs after the first cycle of treatment has been completed in at least 3 subjects, escalation to a subsequent dose level or expansion of the current dose level will occur based upon the following criteria (Table 5):

Table 5. Dose Escalation Guidelines

Number of Subjects with DLT in the First Cycle	Escalation Decision Rule
0 out of 3	Enter 3 subjects at the next dose level.
1 out of 3	Add 3 more subjects at current dose level. If AbbVie or the investigator considers the DLT(s) is clinically significant, AbbVie will determine if it is appropriate to add more patients at this dose level. ● If < 2 of 6 subjects (or < 33% of subjects) experience DLT, dose escalation will proceed to the next dose level. ● If ≥ 2 of total 6 subjects (or ≥ 33% of subjects) experience DLTs, then dose escalation will be stopped.*
≥ 2 out of 3 or 6	Dose escalation will be stopped. *Additional subjects will be enrolled at the previous lower dose level as needed. The following exceptions apply to Dose Level 1: ● If 2 of 6 initial subjects at Dose Level 1 experience DLTs, 3 additional subjects may be entered and the cohort will be expanded up to 9 subjects for further DLT assessment. ○ Enrollment of the 3 additional subjects will depend on a review of the specific DLTs observed and discussion with the Investigators. ● If 2 of 9 subjects at Dose Level 1 experience DLTs, then escalation to the next dose level may proceed. ● If > 2 of 9 subjects in Dose Level 1 experience DLTs, dose-escalation will stop.

* If 2 out of 6 subjects experience different DLTs, for example nausea and neutropenia, the data will be reviewed by the investigators and AbbVie to determine if 3 additional subjects should be added at that dose level. If 3 subjects will be added and none experience DLTs, this dose level will be declared the MTD.

An MTD and/or maximum administered dose (MAD), and RPTD, will be determined. The MTD is defined as the maximum dose at which < 2 of 6 or ≤ 2 of 9 subjects experience a DLT during the DLT observational period C1D-2 to C2D1. The MAD is defined as the highest dose tested. Both MAD and MTD may be determined independently for each tested dosing schedule of veliparib. The RPTD and schedule will be determined based on the assessment of the observed toxicities, the MTD or MAD, and

the overall safety profile of the study drug. The RPTD cannot exceed the lower of the MTD or MAD. At the RPTD and schedule additional subjects will be added as needed so that a total of at least 9 subjects will be treated at the RPTD.

DLT Definition: DLT is defined as any of the following drug-related toxicities occurring during the DLT observation period (Cycle 1 Day –2 to Cycle 2 Day 1) in any of the dose-escalation cohorts, with grading according to the National Cancer Institute (NCI) Common Toxicity Criteria for Adverse Events (CTCAE), version 4.0[20]:

1. Cycle 1 events associated with treatment delay > 14 days in initiating Cycle 2 chemotherapy:
   a. Grade 4 thrombocytopenia (platelets < 25.0×10^9/L)
   b. Grade 4 neutropenia (absolute neutrophil count (ANC) < 0.5×10^9/L)
   c. Grade 3 febrile neutropenia with fever lasting for > 7 days
   d. Grade 4 febrile neutropenia of any duration

   NOTE: Delay of more than 14 days in initiating Cycle 2 due to factors not directly related to treatment emergent toxicity will not be considered a DLT.
2. Grade ≥ 3 non-hematologic toxicity that represents at least 2 grade increase from baseline and is attributed to veliparib treatment:
   a. Exclusion: nausea and vomiting lasting ≤ 48 hours or inadequately treated
   b. Exclusion: electrolyte abnormalities resolving within ≤ 24 hours
   c. Exclusion: hypersensitivity reactions
   d. Exclusion: alopecia
3. Grade 2 non-hematologic toxicity that represents at least 2 grade increase from baseline, is attributed to veliparib treatment and requires a treatment delay of > 14 days in initiation of Cycle 2
4. Any toxicity that represents at least 2 grade increase from baseline, is attributed to veliparib treatment and requires at least one of:

a. Dose modification within Cycle 1
b. Omission of carboplatin, > 1 daily etoposide dose, or > 30% veliparib doses in Cycle 1

Subjects experiencing DLT(s) during the DLT observation period will require an interruption of study drugs and possible discontinuation from further participation in the study. Veliparib may be reintroduced at a reduced dose, if the toxicity returns to ≤ Grade 1 or to baseline if Grade 2 at study entry. All decisions regarding continued dosing for individual subjects experiencing a DLT will be medically managed by the investigator in conjunction with the AbbVie TA MD.

A subject will be considered evaluable for DLT if he/she has completed the DLT evaluation period with the assigned regimen (full dose carboplatin, at least two doses of etoposide, with ≥ 80% compliance of veliparib) or discontinued Cycle 1 due to a DLT. All cohort sizes and numbers of subjects in the Phase 1 dose escalation criteria section above refer to evaluable subjects. Any subjects who discontinue from study prior to the completion of the DLT evaluation period for any reason other than a DLT will be replaced.

Phase 1 Pharmacokinetics

Pharmacokinetics of veliparib and etoposide will be assessed to determine the drug-drug interactions. Further pharmacokinetics of carboplatin will be assessed on Day 1 of Cycle 1 (please reference Table 10 and Table 11.)

Transition from Phase 1 to Phase 2

Once the veliparib RPTD and schedule is determined, the veliparib RPTD and schedule will be communicated to all participating research sites prior to the start of enrollment into the Phase 2. Subjects from the Phase 1 Dose Escalation portion are not eligible for enrollment into the Phase 2 portion, but may continue to receive veliparib, carboplatin and etoposide at the assigned dose and schedule as long as they tolerate the study drug, show

no evidence of disease progression, and do not meet any of the criteria for subject discontinuation (Section 5.4.1).

Phase 2 Randomized Double-Blind

The veliparib dose and schedule for the Phase 2 was determined to be 240 mg BID on a 14 day schedule based on the analysis of Phase 1 data.

Approximately 180 total subjects with treatment-naïve ED SCLC will be enrolled at the 240 mg BID veliparib/placebo dose and 14 day schedule in the Phase 2 double-blinded portion of the study. They will be randomized in a 1:1:1 ratio to one of three treatment arms:

Arm A: veliparib 240 mg in combination with carboplatin/etoposide followed by veliparib 400 mg BID monotherapy

Arm B: veliparib 240 mg in combination with carboplatin/etoposide followed by placebo monotherapy

Arm C: placebo in combination with carboplatin/etoposide followed by placebo monotherapy

Subjects in all Phase 2 study arms will receive a minimum of 4 cycles of combination therapy unless disease progression or unacceptable toxicity warrants earlier discontinuation from the treatment. Additional 2 cycles of combination therapy (e.g., up to a total of 6 cycles) may be administered at the investigators discretion if subject status at the completion of initial 4 cycles warrants continued combination treatment and/or if local SOC guidelines require 6 cycles of platinum-based therapy. In the combination cycles of Arms A and B, subjects will receive veliparib at 240 mg BID on a 14-day schedule, Arm C will receive matching placebo. After completion of the chemotherapy combination cycles (at least 4), subjects without evidence of disease progression will receive veliparib at 400 mg BID continuous dosing (21-day cycles) (Arms A), or

matching placebo (Arms B and C) as per treatment arm assignment, until disease progression or unacceptable toxicity occurs (Figure 2).

Subject randomization for Phase 2 will be stratified by baseline LDH level (> ULN versus ≤ ULN), and gender.

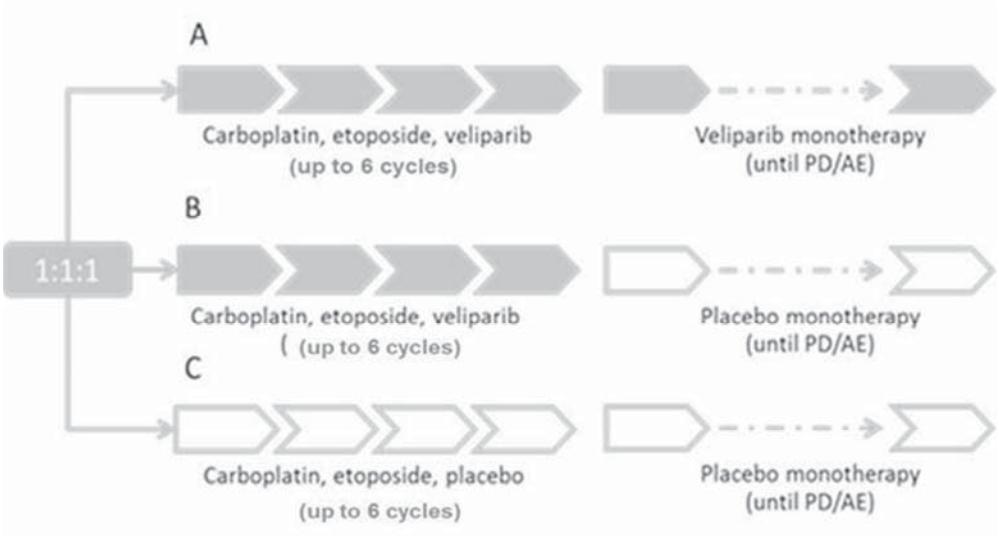
Table 6. Treatment Schematic for Combination Cycles in Phase 2

Days	–2	–1	1	2	3	4 – 12
Veliparib/Placebo	240 mg BID	240 mg BID	240 mg BID	240 mg BID	240 mg BID	240 mg BID
Carboplatin			Once			
Etoposide			Once	Once	Once	

Notes: Starting at Maintenance Day 1 veliparib will be dosed at 400 mg BID monotherapy continuous dosing for 21 days per cycle.

A minimum of 4 cycles of combination treatment are to be administered. If subject/disease status at the completion of Cycle 4 warrants continued combination treatment, up to 2 additional combination cycles (e.g., up to a total of 6) may be administered at investigators discretion.

Figure 2. Phase 2 Treatment and Randomization Schematics



For subjects who experience toxicities due to veliparib or carboplatin/etoposide, appropriate dose modifications or dosing delays should be managed according to Section 5.7. Subsequent cycles of therapy will be administered if there is no evidence of disease progression and observed toxicities have recovered adequately as described in Section 5.7.

5.2 Selection of Study Population

Subjects will undergo screening procedures within 28 days (tumor assessments within 21 days) prior to initial study drug administration. Adult male and female subjects with histologically or cytologically confirmed diagnosis of extensive disease SCLC who meet the inclusion criteria and who do not meet any of the exclusion criteria will be eligible for enrollment into the study.

5.2.1 Inclusion Criteria

A subject will be eligible for study participation if he/she meets the following criteria:

1. Subject with histologically or cytologically confirmed extensive-stage disease small cell lung cancer (ED SCLC), which is newly diagnosed and chemotherapy naïve.

   Notes:

   - ED SCLC is defined herein as any SCLC except a disease confined to the hemithorax of origin, with or without the involvement of regional lymph nodes, including ipsilateral and contralateral hilar, ipsilateral and contralateral mediastinal, and ipsilateral supraclavicular nodes.

2. Phase 1 ONLY: subject with advanced/metastatic solid tumors for which carboplatin/etoposide treatment is considered appropriate.
3. Subject in Phase 2 ONLY: must have measureable disease per RECIST 1.1.

4. Subjects with SCLC must consent to provide available archived FFPE tissue sample of SCLC lesion (primary or metastatic) for central review and biomarker analysis.
5. Subject has an Eastern Cooperative Oncology Group (ECOG) performance score of 0 to 1.
6. Subject must be ≥ 18 years of age.
7. Subject must have adequate hematologic, renal and hepatic function as follows:
   - Bone Marrow: Absolute neutrophil count ANC ≥ 1,500/mm^3 (1.5×10^9/L); White blood cells ≥ 3,000/mm^3 (3×10^9/L); Platelets ≥ 100,000/mm^3 (100×10^9/L); Hemoglobin ≥ 9 g/dL (5.58 mmol/L);
   - Renal function: creatinine ≤ ULN or, if > ULN, calculated creatinine clearance via the Cockroft Gault formula of ≥ 50 mL/min;
   - Hepatic function:
     - AST and ALT ≤ 2.5 × ULN. For subjects with liver metastases, AST and ALT ≤ 5 × ULN;
     - Bilirubin: ≤ 1.5 × ULN; for subjects with Gilbert's syndrome bilirubin > 1.5 × ULN is allowed if no symptoms of compromised liver function are present.
8. Subject must be able to swallow pills.
9. Female and male patients of fertile age, and/or their partners should use contraception. If male, subject and subject's female partner(s) of childbearing potential must follow the contraception recommendations as described in Section 5.2.4. If female, subject must be either postmenopausal for at least 1 year, surgically sterile (bilateral tubal ligation, bilateral oophorectomy or hysterectomy), or the subject and the subject's male partner(s) must follow the contraception recommendations as described in Section 5.2.4.

   Female subjects must have negative results for pregnancy tests performed:

   - Screening on a serum specimen obtained within 7 days prior to initial study drug administration, and

- prior to dosing on a urine sample obtained C1D-2 unless the serum pregnancy test was collected within 7 days of C1D-2.

10. Must voluntarily sign and date each 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 – 4) These criteria were selected to ensure the appropriate subject population with sufficient disease severity for evaluation.

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

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

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

5.2.2 Exclusion Criteria

A subject will not be eligible for study participation if he/she meets any of the following criteria:

1. Phase 1 ONLY: Subject has had any prior anti-cancer therapy other than:
   - Hormonal, non-myelosuppressive, biologic, targeted, or immune therapy (must be completed ≥ 4 weeks prior to Cycle 1 Day –2). See Section 5.2.3.1 for details.
   - One line of cytotoxic chemotherapy (must be completed ≥ 4 weeks prior to Cycle 1 Day –2). See Section 5.2.3.1 for details.
   - Adjuvant/neoadjuvant radiotherapy completed ≥ 12 months prior to Cycle 1 Day –2, with field not involving > 10% of bone marrow reserve.
   - Tumor lesion irradiation with intent of symptom palliation ≥ 4 weeks prior Cycle 1 Day –2.

2. Phase 2 ONLY: Subject has had any prior chemotherapy, radiotherapy, investigational anti-cancer agents or biologic therapy for the disease under study. Single non-target lesion irradiation with intent of symptom palliation is allowed if completed ≥ 2 weeks prior Cycle 1 Day –2.
3. Subject has known hypersensitivity to etoposide, platinum compounds or veliparib.
4. Phase 1 ONLY: Subject has received prior myelopoietic growth factors.
5. Subject has current or history of central nervous system (CNS) or leptomeningeal metastases. If CNS metastasis is suspected, a head CT should be performed at screening.
6. Subject has a history of seizures within 12 months of Cycle 1 Day–2 or diagnosed neurological condition placing subject at the increased risk of seizures.
7. Subject has received traditional herbal anti-cancer medicine (e.g., Chinese, other Asian, etc.) within 14 days prior to Cycle 1 Day –2.
8. Subject has had major surgery within 6 weeks prior to Cycle 1 Day –2 (subjects must have completely recovered from any previous surgery prior Cycle 1 Day –2).
9. Subject has clinically significant and uncontrolled major medical condition(s) including but not limited to:
    - Uncontrolled nausea/vomiting/diarrhea;
    - Active uncontrolled infection;
    - History of hepatitis B (HBV) with surface antigen (HBsAg) positivity within 3 months prior to the date of informed consent for this study (if HBsAg status is unknown it must be tested at screening);
    - History of hepatitis C (HCV) with HCV RNA positivity within 3 months prior to the date of informed consent for this study (if HCV RNA status is unknown it must be tested at screening);
    - Symptomatic congestive heart failure (NYHA class ≥ II);
    - Unstable angina pectoris or cardiac arrhythmia;

- Psychiatric illness/social situation that would limit compliance with study requirements;
- Any other medical condition, which in the opinion of the Investigator, places the subject at an unacceptably high risk for toxicities.

10. Subject is pregnant or lactating.

11. The subject has a history of another active 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, breast DCIS).

Questions regarding the eligibility of individual subjects should be directed to the AbbVie TA MD.

Rationale for Exclusion Criteria

(1 – 3, 11) To select the adequate subject population with the appropriate disease severity for evaluation.

(4 – 10) For the safety of the subject.

5.2.3 Prior and Concomitant Therapy

If a subject reports taking any over-the-counter or prescription medications, vitamins and/or herbal supplements or if administration of any medication becomes necessary from 2 weeks prior to study drug administration through the end of the study, the name of the medication, dosage information including dose, route and frequency, date(s) of administration including start and end dates, and reason for use must be recorded.

The AbbVie TA MD should be contacted if there are any questions regarding concomitant or prior therapy(ies).

5.2.3.1 Prior Therapy

Phase 1 Dose Escalation

For Phase 1 subjects, prior hormonal, non-myelosuppressive, biologic, immune, and targeted therapy is allowed if completed ≥ 4 weeks prior to Cycle 1 Day –2. Allowed biologic and targeted agents are listed below (List 1). Other prior biologic, immune or targeted agents may be permitted upon review by AbbVie TA MD.

List 1. Allowable Prior Therapies

Afatinib	Cetuximab	Ficlatuzumab	Lapatinib	Provenge	Sunitinib
Axitinib	Dacomitinib	Gefitinib	Pazopanib	Rilotimumab	Tivozanib
Bevacizumab	Erlotinib	Ipilimumab	Pembrolizumab	Sorafenib	Trastuzumab

For Phase 1 subjects one line of prior cytotoxic chemotherapy is allowed, however regimens known to cause significant myelosuppression will not be permitted. Specific prior regimen received must be reviewed and approved by AbbVie TA MD.

For Phase 1 subjects, adjuvant/neoadjuvant radiotherapy is allowed if completed ≥ 12 months prior to Cycle 1 Day –2 and the field did not involve > 10% of bone marrow reserve.

Phase 2 Randomized Double-Blind

Subjects in the Phase 2 portion of the study are not allowed to have any prior antitumor treatment for the disease under study. For the purposes of this protocol, antitumor treatment is defined as systemic anticancer agents (cytotoxic chemotherapy, hormonal therapy, immunotherapy, biologic therapy), radiotherapy, and investigational anti-cancer agents. For subjects in Phase 2, radiotherapy to a single lesion with the intent of symptom palliation (irradiated lesion will not be used as a target lesion for RECIST evaluations) is allowed, if completed at least 2 weeks prior to Cycle 1 Day –2.

5.2.3.2 Concomitant Therapy

The locally approved product label, institutional guidelines, local practice, or applicable Summary of Product Characterizations (SmPC) for carboplatin and etoposide should be referenced for any concomitant therapy guidelines.

Premedication:	The prophylactic antiemetics, including 5-HT3 antagonists, according to institution, National Comprehensive Cancer Network (NCCN), European Society for Medical Oncology (ESMO) or American Society of Clinical Oncology (ASCO) guidelines should be given, prior to administration of carboplatin and etoposide. Prophylaxis with anti-emetics (e.g., 5-HT3 antagonists such as ondansetron) is strongly recommended when initiating single agent veliparib/placebo maintenance monotherapy.
Anticancer Agents:	Other anticancer agents are not permitted during the treatment portion of the study. All subjects will receive carboplatin + etoposide with veliparib/placebo at specified timepoints during the treatment portion of the study. The locally approved carboplatin and etoposide product labels or SmPCs should be referenced to determine if there are any contraindications associated with concomitant medications (e.g., phenytoin, etc.).
Supportive Care:	Best supportive care and treatment will be given as appropriate to each subject (antiemetics, antibiotics, transfusions, nutritional support, palliative treatment for pain, bisphosphonates or denosumab) according to institutional or clinical practice guidelines (e.g., ASCO, ESMO, or NCCN).
Growth Factors:	Biologic response modifiers administered for erythropoiesis (e.g., erythropoietin, darbepoetin alpha) and colony stimulating factors (e.g., neulasta, G-CSF, GM CSF, etc.) may be administered according to institutional or clinical practice guidelines (e.g., ASCO, ESMO, or NCCN). Growth factors prophylaxis will not be allowed in Cycle 1 (Day –2 through Day 21) of the dose escalation cohorts. Growth factors prophylaxis is acceptable in Phase 2.

Radiation:	Prophylactic cranial irradiation (PCI) is allowed during the study in the Maintenance phase of treatment at Investigators discretion. The dose of PCI should be 24 Gy in 8 fractions of 3 Gy each, or per local treatment standards. Veliparib or placebo maintenance monotherapy will be held starting 2 days prior to the initiation of radiation therapy, throughout the radiation therapy and for 4 days following radiation therapy. Palliative radiation to a non-target lesion with the intent of symptom control is allowed; non-progressing status of lesion to be irradiated must be documented prior to the procedure. Radiation to non-target lesions for other reasons will not be allowed during combination treatment cycles and generally will not be allowed during maintenance; exceptional circumstances that may arise during maintenance must be discussed with AbbVie TA MD and non-progressing status of such lesions using the same modality as study tumor assessments will have to be documented prior to procedure.
Surgery:	If the subject requires surgery during the study, then this needs to be discussed with the AbbVie TA MD.
Alternate Therapy:	No traditional herbal anti-cancer medicine (e.g., Chinese, Asian, etc.) may be taken concurrently with veliparib (a 14-day washout period must be documented).

5.2.4 Contraception Recommendations

If female, subject must be either postmenopausal or permanently surgically sterile (refer to inclusion criteria for definitions of both) OR a Women of Childbearing Potential, practicing at least one of the following methods of birth control, on C1D-2 (or earlier) through at least 6 months after the last dose of study drug.

- Combined (estrogen and progestogen containing) hormonal contraception (oral, intravaginal, transdermal) associated with the inhibition of ovulation, initiated at least 1 month prior to C1D-2.
- Progestogen-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation, initiated at least 1 month prior to C1D-2.
- Bilateral tubal occlusion/ligation.
- Bilateral tubal occlusion via hysteroscopy (i.e., Essure), provided a hysterosalpingogram confirms success of the procedure.

- Vasectomized partner(s), provided the vasectomized partner verbally confirms receipt of medical assessment of the surgical success, and is the sole sexual partner of the WOCBP trial participant.
- Intrauterine device (IUD).
- Intrauterine hormone-releasing system (IUS).
- True abstinence: Refraining from heterosexual intercourse when this is in line with the preferred and usual lifestyle of the subject [periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable].

If required per local practices, male or female condom with or without spermicide OR cap, diaphragm or sponge with spermicide should be used in addition to one of the birth control methods listed above (excluding true abstinence).

If the subject or subject's female partner(s) is currently using a hormonal contraceptive, she should also use a barrier method during this study and for 6 months (or per local label) after study completion.

Male subjects who are sexually active with a WOCBP, even if the male subject has undergone a successful vasectomy, must agree from C1D-2 through at least 6 months after the last dose of study drug to use condoms and his female partner(s) must use at least one of the contraceptive measures (as defined in the protocol for female study subjects of childbearing potential).

Male subject agrees not to donate sperm from C1D-2 through at least 6 months after the last dose of study drug.

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 7 and Table 8. Pharmacodynamic (PD) and Pharmacogenetic (PG) assessments will be performed as summarized in Table 9 Pharmacokinetic (PK) assessment will be performed as summarized in Table 10 and Table 11.

Table 7. Study Activities Phase 1 Dose Escalation

Activity	SCR[a]	C1 D-2	D1 through D3 Combination Cycles	C1 D8 and D15	C2 Through C4 D1	C2 Through C4 D8	C2 Through C4 D15	Maintenance Veliparib D1 of Each Cycle Starting in C5	Tumor Assessments Every 6 Weeks First 24 Weeks	Tumor Assessments Every 9 Weeks Thereafter	Final Visit	30-Day Follow-Up Visit
Informed Consent[b]	X											
Medical and Oncology History[c]	X											
Physical Exam (including weight)[d]	X	X		X	X		X	X			X	X
Performance Status (ECOG)	X	X			X		X	X			X	X
12-Lead ECG	X										X	
Vital Signs	X	X	X Cycle 1 only	X	X		X	X			X	X
Pregnancy Test Serum (s), Urine (u)[e]	X[e] (s)	X[e] (u)										
Hematology[f]	X	X		X	X	X	X	X			X	X
Chemistry[g]	X	X		X	X		X	X			X	X
Coagulation Tests	X				X C3 D1			X Odd cycles			X	
HBsAg, HCV RNA[n]	X											

Table 7. Study Activities Phase 1 Dose Escalation (Continued)

Activity	SCR[a]	C1 D-2	D1 through D3 Combination Cycles	C1 D8 and D15	C2 Through C4 D1	C2 Through C4 D8	C2 Through C4 D15	Maintenance Veliparib D1 of Each Cycle Starting in C5	Tumor Assessments Every 6 Weeks First 24 Weeks	Tumor Assessments Every 9 Weeks Thereafter	Final Visit	30-Day Follow-Up Visit
Urinalysis	X										X	
Clinical Disease Progression[h]					X			X			X	
Tumor Assessments[i]	X								X[i]	X[i]	X[i]	
Monitor Adverse Events/ Concomitant Medication	X	X	X	X	X	X	X	X			X	X
Monitor Compliance		X			X			X				
Enrollment	X											
Dispense Veliparib[k,m]		X			X			X[k]				
Administer Premedication[l]			X									
Administer Etoposide[j]			X									
Administer Carboplatin[j]			X Day 1 only		X							

C = Cycle; D = Day; SCR = Screening

Table 7. Study Activities Phase 1 Dose Escalation (Continued)

a. Screening visit must be performed within 28 days of Cycle 1 Day–2. If the screening visit is performed > 7 days prior to Cycle 1 Day –2 the physical exam, laboratory tests (hematology and chemistry) and pregnancy test must be repeated on Cycle 1 Day –2. Tumor assessments must be performed within 21 Days of Cycle 1 Day –2. The scanned areas will include chest and abdomen (with image of liver and adrenal glands) at all radiographic assessments and head CT at screening visit (if clinical suspicion of CNS metastases).

b. The informed consent must be signed and dated prior to the initiation of any screening or study specific procedure is performed.

c. A subject's medical history will be reviewed at each visit. Any changes from baseline will be recorded on the adverse event eCRF.

d. Height will be assessed at Screening only.

e. A serum pregnancy test must be performed at Screening, a urine pregnancy test on Cycle 1 Day –2 prior to dosing if > 7 days since obtaining the serum pregnancy test for women of childbearing potential. Pregnancy tests may be repeated at any time during the study at the discretion of the investigator.

f. Hematology labs do not need to be repeated if screening is within 7 days of Cycle 1 Day –2. A central laboratory will be used for the study; however, sites may use a certified local laboratory to collect a sample to dose the subject.

g. Chemistry panels do not need to be repeated if screening is within 7 days of Cycle 1 Day –2. A central laboratory will be used for the study; however, sites may use a certified local laboratory to collect a sample to dose the subject.

h. Clinical progression will include, but not limited to an evaluation of worsening performance status due to progressive disease, requirement for non-palliative radiation therapy, chemotherapy or surgery due to progressive disease or death due to progressive disease.

i. Tumor assessments will be performed until disease progression. Tumor assessment and assessment of response will occur every 6 weeks (± 1 week) from C1D-2 for the first 24 weeks, then every 9 weeks (± 1 week) thereafter. Tumor Assessments at the end of Cycle 4 should be performed 1 week prior to the conclusion of Cycle 4 with radiographic results determined and reported to ensure subjects eligibility prior to subject starting continuous monotherapy veliparib dosing at Cycle 5. A tumor assessment will 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. The scanned areas will include chest, abdomen and pelvis at all tumor assessments. A head CT will be performed if there is clinical suspicion of CNS metastases.

j. Etoposide on Days 1, 2 and 3 and carboplatin on Day 1 of Cycles 1 – 4 will be administered IV by site staff after veliparib administration (exception: veliparib will not be administered on Cycle 2 Day 1 of non-continuous dosing schedules). Etoposide will be given prior to carboplatin, unless institutional guidelines require inverse sequence of administration.

k. Starting at Cycle 5 Day 1 and all subsequent monotherapy cycles, veliparib will be dispensed on Day 1. See Section 5.0.

l. Pre-medication will be given as per institutional guidelines.

Table 7. Study Activities Phase 1 Dose Escalation (Continued)

m. As per cohort and dosing schedule assignment veliparib will be dosed orally on Days –2 to 5 (7-day schedule), or Day –2 to 12 (14-day schedule) or Day –2 – 19 (continuous schedule) of each 21-day cycle for up to 4 cycles. Veliparib will be administered after the pre-medications on all days when given with chemotherapy. Veliparib will be given approximately every 12 hours with a glass of water (approximately 240 mL). Subjects in Phase 1 dose escalation on non-continuous dosing schedules will receive veliparib on Days 2 to 5 during Cycle 2 (for 7-day schedule) or on Days 2 to 12 (for 14-day schedule). After completing 4 Cycles of combination therapy subjects may receive veliparib continuous dosing at 400 mg BID (each cycle will be 21 days) until disease progression or unacceptable toxicity occurs.

n. If no HBsAg/HCV RNA test has been performed within 3 months prior to the date of informed consent for this study.

Table 8. Study Activities in Phase 2

Activity	SCR[a]	C1 D-2	D1 through D3 Combination Cycles	C1 D8	C2 Through Last Combination Cycle D1	C2 Through Last Combination Cycle D8	Monotherapy Veliparib/ PBO D1 of Each Cycle Starting in Maintenance	Tumor Assessments Every 6 Weeks First 30 Weeks	Tumor Assessments Every 9 Weeks Thereafter	Post-Treatment Follow-Up	Final Visit[o]	30-Day Follow-Up Visit[p]	Survival Follow-Up
Informed Consent[b]	X												
Medical and History[c]	X												
Physical Exam (including weight)[d]	X	X		X	X		X				X	X	
Performance Status (ECOG)	X	X			X		X				X	X	
12-Lead ECG	X										X		
Vital Signs	X	X	X C1 only	X	X		X				X	X	
Pregnancy Test Serum (s), Urine (u)[e]	X (s)	X (u)											
Hematology[f]	X	X		X	X	X	X				X	X	
Chemistry[f]	X	X			X		X				X	X	
Coagulation Tests	X										X		
HBsAg, HCV RNA[g]	X												
Urinalysis	X										X		

Table 8. Study Activities in Phase 2 (Continued)

Activity	SCR[a]	C1 D-2	D1 through D3 Combination Cycles	C1 D8	C2 Through Last Combination Cycle D1	C2 Through Last Combination Cycle D8	Monotherapy Veliparib/ PBO D1 of Each Cycle Starting in Maintenance	Tumor Assessments Every 6 Weeks First 30 Weeks	Tumor Assessments Every 9 Weeks Thereafter	Post-Treatment Follow-Up	Final Visit[o]	30-Day Follow-Up Visit[p]	Survival Follow-Up
Clinical Disease Progression[h]					X			X			X		
Tumor Assessments[i]	X							X[i]	X[i]	X[i]	X		
Monitor Adverse Events/Concomitant Medications		X	X	X	X	X	X				X	X	
Monitor Compliance		X		X	X		X						
Randomization		X											
Dispense Veliparib		X			X[j]		X[l]						
Administer Premedication[k]			X		X								
Administer Etoposide[m]			X		X								
Administer Carboplatin[m]			X Day 1 only		X								
Survival Follow-Up[n]													X

C = Cycle; D = Day, SCR = Screening; RND = Randomization; PBO = Placebo; TA = Tumor Assessments; FV = Final Visit; PT = Post-treatment; F/U = Follow-up

Table 8. Study Activities in Phase 2 (Continued)

a. Screening visit must be performed within 28 days of Cycle 1 Day –2. If the screening visit is performed > 7 days prior to Day –2 the physical exam, laboratory tests (hematology and chemistry) and pregnancy test must be repeated on Cycle 1 Day –2. Tumor assessments must be performed within 21 Days of Cycle 1 Day –2.

b. The informed consent must be signed and dated prior to the initiation of any screening or study specific procedure being performed.

c. A subject's medical history will be reviewed at each visit. Any changes from baseline will be recorded on the adverse event eCRF.

d. Physical exam does not need to be repeated at Cycle 1 Day –2 if screening physical exam was completed within 7 days of Cycle 1 Day –2. Physical exams during combination cycles must include assessment of hearing if required by the local SmPC for carboplatin. The Cycle 1 Day 8 physical exam may be symptom directed. Height will be assessed at Screening only.

e. A serum pregnancy test must be performed at Screening, a urine pregnancy test on Cycle 1 Day –2 prior to dosing if > 7 days since obtaining the serum pregnancy test for women of childbearing potential. Pregnancy tests may be repeated at any time during the study at the discretion of the investigator.

f. Hematology and Chemistry panels do not need to be repeated at Cycle 1 Day –2 if screening labs were completed within 7 days of Cycle 1 Day –2. A central laboratory will be used for the study; however, sites may use a certified local laboratory to collect a sample to dose the subject. If local labs are drawn the sample MUST be split and also sent to central lab.

g. Only for subjects with known history of HBV or HCV without prior evidence of active disease-free status and if HBsAg/HCV RNA status within 3 months of the study entry is unknown.

h. If clinical disease progression is suspected, progression must be confirmed radiographically per RECIST 1.1. Clinical disease progression will include, but will not be limited to worsening performance status due to progressive disease, requirement for non-palliative radiation therapy, alternative chemotherapy or surgery due to progressive disease. At the Final Visit, a clinical disease progression assessment is required only for subjects who discontinue the study for reasons other than progression (clinical or radiographic).

i. Tumor assessment and assessment of response will occur every 6 weeks (± 1 week) from C1D-2 for the first 30 weeks, then every 9 weeks (± 1 week) thereafter. A tumor assessment will 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 in Post-Treatment Follow-Up should continue to receive tumor assessments at the protocol defined time points until an event of radiographic progression.

j. Veliparib will be dosed orally at 240 mg BID and 14-day schedule for up to 6 cycles. Veliparib will be administered after the pre medications on all days when given with chemotherapy. Veliparib will be given approximately every 12 hours with a glass of water (approximately 240 mL).

k. Pre-medication will be given as per institutional guidelines.

l. Starting at Maintenance Day 1 and all subsequent monotherapy cycles, veliparib or placebo will be dosed orally at 400 mg BID and continuous (21-day) dosing schedule. Subjects should remain on veliparib until disease progression or unacceptable toxicity occurs.

Table 8. Study Activities in Phase 2 (Continued)

m. Etoposide on Days 1, 2 and 3 and carboplatin on Day 1 of Combination Cycles will be administered IV by site staff after veliparib administration. Etoposide will be given prior to carboplatin, unless institutional guidelines require inverse sequence of administration.

n. Survival follow-up will be performed at 2 month intervals after the subject discontinues the study and until the endpoint of death, the subject has become lost to follow-up, the subject specifically withdraws consent for survival follow-up or if AbbVie terminates the study.

o. 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.

p. A 30-Day Follow-Up visit must occur when the subject discontinues all study drugs due to toxicity and will transition to Post-Treatment Follow-Up. Subjects who discontinue treatment due to radiographic progression and have a Final Visit within 30 days of last dose of study drug will have one Follow-Up Visit approximately 30 days after the last dose of study drug.

Table 9. Schedule of Pharmacogenetic and Pharmacodynamic Assessments for Phase 1 Dose Escalation and Phase 2

Procedure	Visit Schedule	Before Drug Administration	After Drug Administration	Sampling Plan Specimen Matrix
PG Blood Sampling[a] Genetic (DNA)	Cycle 1 Day –2	Not Dose Dependent	Not Dose Dependent	Whole Blood Frozen –20°C or Colder
Plasma Markers[b]	Cycle 1 Day –2, Cycle 2 Day 1, Cycle 3 Day 1, Cycle 4 Day 1 and Final Visit	Prior to Dose	Prior to Dosing	Blood → Plasma Frozen –70°C or Colder
Serum Markers[b]	Cycle 1 Day –2, Cycle 2 Day 1 and Final Visit	Prior to Dose	NA	Blood → Serum Frozen –70°C or Colder
Archived Tissue Sample Collection[c]	Cycle 1 Day –2	N/A	N/A	FFPE

a. Perform once at Cycle 1 Day –2. If not collected at this visit, it may be collected at any time throughout the study. Subjects must sign a separate informed consent prior to obtaining the PG sample.

b Samples will not be drawn during carboplatin and/or etoposide dose delays.

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

Table 10. Schedule of Pharmacokinetic Assessments for Phase 1 Dose Escalation

Procedure	Visit Schedule	Before Drug Administration	After Drug Administration	Sampling Plan Specimen Matrix
PK Blood Sampling[a] Etoposide	Cycle 1 Day 1		55 min (5 min before the end of infusion), 3 h, 5 h, 8 h, and 24 h post Day 1 dosing (24 hours is prior to dosing on Cycle 1 Day 2)	Blood → Plasma Frozen –20°C or Colder
	Cycle 2 Day 1[b]		55 min (5 min before the end of infusion), 3 h, 5 h, 8 h, and 24 h post Day 1 dosing (24 hours is prior to dosing on Cycle 2 Day 2)	Blood → Plasma Frozen –20°C or Colder
PK Blood Sampling[a] Carboplatin	Cycle 1 Day 1		25 min, 4 h, and 23 h post the start of Day 1 carboplatin infusion	Blood → Plasma Frozen –20°C or Colder
PK Blood Sampling for Veliparib (ABT-888)[a]	Cycle 1 Day 1	Pre-dose	1 h, 2 h, 3 h, 5 h, 8 h, and 24 h	Blood → Plasma Frozen –20°C or Colder

a. Pharmacokinetic sampling is further discussed in Section 5.3.2.1. Samples will not be drawn during carboplatin and/or etoposide dose delays. All timepoints of etoposide and carboplatin samples are referred to the start of the infusion.

b. This sampling will be omitted for subjects receiving continuous veliparib schedule.

Table 11. Schedule of Pharmacokinetic Assessments in Phase 2

Procedure	Visit Schedule	Before Drug Administration	After Drug Administration	Sampling Plan Specimen Matrix
PK Blood Sampling for Veliparib[a]	Cycle 1 Day 1	Pre-dose (0 h)	1 and 2 h	Blood → Plasma Frozen –20°C or Colder
	Cycle 2 Day 1, Cycle 3 Day 1, Cycle 4 Day 1	Pre-dose (0 h)	N/A	Blood → Plasma Frozen –20°C or Colder

a. Pharmacokinetic sampling is further discussed in Section 5.3.2.1. Samples will not be drawn during carboplatin and/or etoposide dose delays.

5.3.1.1 Study Procedures

Unless otherwise stated, the baseline measurement for any given variable will be defined as the last value obtained for the variable prior to the first dose of study drug.

The study procedures outlined in Table 7 and Table 8 are discussed in detail in this section, with the exception of the monitoring of treatment compliance (discussed in Section 5.5.7) and adverse event information (discussed in Section 6.0). All study data will be recorded on eCRFs with supporting source documentation.

Screening procedures should be performed within 28 days prior to Cycle 1 Day –2. If the screening visit is performed greater than 7 days prior to Cycle 1 Day –2, the physical exam, laboratory tests, and pregnancy test (for female subjects of childbearing potential) must be repeated on Cycle 1 Day –2. Vital signs and performance status assessments will be performed on Cycle 1 Day –2 for all subjects. Baseline radiographic tumor assessments per computed tomography (CT) with IV contrast/magnetic resonance imaging (MRI) of the chest, abdomen, pelvis and head (if CNS metastases are suspected) will be conducted within 21 days prior to Cycle 1 Day –2. 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.

For procedures performed at Screening and repeated, the later procedure performed prior to dosing will serve as a baseline for clinical assessment. Subsequent study procedures should be performed approximately within ± 1 day on days of IV infusion of carboplatin and etoposide and ± 2 days for all safety visits and first Maintenance visit. Clinical laboratory tests can be performed up to 48 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 enter into the study. The reason for screen failure will be documented in the source and will be captured in the eCRF.

Medical History

A complete medical history, including alcohol, tobacco and nicotine-containing product use history, will be taken at Screening. The medical history includes complete medical history, including documentation of any clinically significant medical condition; the presence and severity of any symptoms/conditions associated with SCLC; and detailed SCLC oncology history (histology, staging, date of diagnosis, tumor burden, metastatic sites, surgical history).

On Cycle 1 Day –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 7 and Table 8. Physical examination during combination cycles will include hearing assessment if required by carboplatin locally approved product label, local practice, or applicable SmPC. If the Screening physical examination is performed within 7 days of Cycle 1 Day –2, it is not required to repeat the exam on Cycle 1 Day –2 unless clinically indicated. The Cycle 1 Day 8 physical examination may be symptom directed. 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. The subject will wear lightweight clothing and no shoes during weighing.

Vital Signs

Vital signs will be performed per Table 7 and Table 8. 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 single ECG will be performed per as per Table 7 and Table 8. 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 7 and Table 8 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 Cycle 1 Day –2. A urine pregnancy test should also be performed prior to dosing on Cycle 1 Day –2 if > 7 days since obtaining Screening serum test results. The test results must be reviewed and determined to be negative prior to dosing. A positive urine pregnancy test will be confirmed with a serum pregnancy test. Pregnancy tests may also be repeated at the discretion of the investigator at any time during the study.

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

Hepatitis Screen

Subjects with history of hepatitis C (HCV) must be tested for HCV RNA at screening if no documented test result is available from within 3 months from the date of informed consent, and for Phase 2 if status within 3 months of the study entry is unknown. Subjects with history of hepatitis B (HBV) must be tested for HBV surface antigen (HBsAg) at screening if no documented test result is available from within 3 months from the date of informed consent, and for Phase 2 if status within 3 months of the study entry is unknown. Testing will be performed by the sponsor-designated central laboratory.

Clinical Laboratory Tests

Samples for chemistry, hematology and urinalysis will be collected per Table 7 (Phase 1) and Table 8 (Phase 2). Specific laboratory assessments are outlined in Table 12.

All study samples will be shipped to the central laboratory, and central laboratory results will be used for data analysis. A certified local laboratory may be used to perform laboratory analyses for immediate treatment decisions; however, split or concurrent samples must be drawn and sent to the central laboratory for analysis. The central laboratory will provide instructions regarding the collection, processing and shipping of samples.

Sites will obtain the estimated creatinine clearance locally.

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 6.6.

For any laboratory test value outside the reference range that the investigator considers being clinically significant:

- The investigator will follow the out-of-range value to a satisfactory clinical resolution.
- A laboratory test value that requires a subject to be discontinued from the study or requires a subject to receive treatment will be recorded as an adverse event.

Study samples for central laboratory analysis may be performed within 48 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.

Table 12. Clinical Laboratory Tests

Hematology	Clinical Chemistry	Urinalysis
Hematocrit Hemoglobin Red Blood Cell (RBC) count White Blood Cell (WBC) count Neutrophils Bands (if detected) Lymphocytes Monocytes Basophils Eosinophils (if detected) Absolute Platelet count Mean corpuscular hemoglobin (MCH) Mean corpuscular volume (MCV) Mean corpuscular hemoglobin concentration (MCHC) Reticulocyte count **Coagulation** Prothrombin Time (PT) Activated Partial Thromboplastin Time (aPTT) International Normalized Ratio (INR)	Blood Urea Nitrogen (BUN) Serum Creatinine Total bilirubin Serum glutamic-pyruvic transaminase (SGPT/ALT) Serum glutamic-oxaloacetic transaminase (SGOT/AST) Alkaline phosphatase Sodium Potassium Chloride Calcium Inorganic phosphorus Uric acid Total protein Glucose Albumin Magnesium Bicarbonate Lactate dehydrogenase (LDH) Hepatitis C RNA/hepatitis B surface antigen (HBsAG)+	Specific gravity Ketones pH Protein Blood Glucose Leukocyte esterase Microscopic examination (perform only if dipstick results warrant) **Serum Pregnancy Test** Human Chorionic Gonadotropin (hCG)*

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

\+ Subjects with history of hepatitis C (HCV) must be tested for HCV RNA at screening if no documented test result is available from within 3 months from the date of informed consent. Subjects with history of hepatitis B (HBV) must be tested for HBV surface antigen (HBsAg) at screening if no documented test result is available from within 3 months from the date of informed consent. If HBsAg/HCV RNA status is unknown it must be tested at screening for Phase 2 subjects. Testing will be performed by the sponsor-designated central laboratory.

Tumor Assessments (Radiographic)

A CT scan with contrast will be used in the evaluation of tumor responses with RECIST version 1.1. The scanned areas will include chest, abdomen and pelvis at all radiographic assessments, and head CT as warranted by clinical suspicion of CNS metastases.

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.

Subjects will continue to be monitored by the same methodology unless evidence of tumor metastasis warrants otherwise.

Sites may be requested to electronically transfer copies of all CT or MRI scans used for radiographic tumor assessments in the Phase 2 part of the study to AbbVie. Electronic copies of scans in DICOM format should be maintained at the sites until notification from AbbVie or end of study, whichever comes first. Instructions regarding procedures for transferring scans will be provided separately, if the request for scans becomes necessary.

Tumor Assessments Schedule

Tumor assessments will be performed until radiographic disease progression. Tumor assessment and assessment of response will occur every 6 weeks (± 1 week) from C1D-2 for the first 24 weeks (Phase 1) or 30 weeks (Phase 2), then every 9 weeks (± 1 week) thereafter. Tumor response will be determined according to the Response Evaluation Criteria in Solid Tumors (RECIST), Version 1.1. 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.

For Phase 2, the protocol defined tumor assessment schedule should be maintained independent of any treatment delays or changes.

Refer to Appendix C "RECIST (Version 1.1) for Tumor Response (PFS)" for response criteria and guidelines.

Post-Treatment Follow-Up

Subjects who discontinue all study drugs prior to reaching an event of radiographic progression must enter into Post-Treatment Follow-Up. Subjects will remain on study

(off study drug) and will continue to receive tumor assessments according to the protocol defined tumor assessment schedule until reaching an event of radiographic progression.

Subjects who discontinue all study drugs due to toxicity should have a 30-day Follow-up visit prior to entering into Post-Treatment Follow-Up to ensure all toxicities have resolved. Subjects will have a Final Visit and be discontinued from the study upon reaching an event of radiographic progression, if the Investigator determines they should be discontinued for any other reason or if the subject withdraws consent.

Survival Follow-Up (Phase 2 Only)

All discontinued subjects will have survival information collected via electronic data capture (EDC) at two month intervals (or as requested by sponsor to support data analysis) after the subject discontinues the study and continuing until the endpoint of death, the subject has become lost to follow-up, or AbbVie terminates the study.

All subjects will be followed for survival information (i.e., the date and cause of death or last known alive date if not deceased) unless the subject requests to be withdrawn specifically from study survival follow-up; this request must be documented in the subject's medical record and signed by the Investigator.

If known, post treatment anti-cancer therapies, dates of initiation, and end dates will be collected.

If the subject withdraws from survival 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.

Randomization and Subject Number Assignment

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

The site will access the IRT system at Screening, after the subject signs informed consent and a unique subject number will be provided. Subjects who complete all Screening

procedures and meet the eligibility criteria will proceed to dosing. Subjects who sign consent and do not meet the eligibility criteria will be considered a screen failure and the reason for screen failure will be documented in the source and in the eCRF. Subjects will also be registered as a screen failure in the IRT system.

Subjects in Phase 2 who complete all Screening procedures and meet the eligibility criteria will be randomized in a 1:1:1 ratio to one of three treatment arms:

Arm A: veliparib 240 mg in combination with carboplatin/etoposide followed by veliparib 400 mg BID monotherapy

Arm B: veliparib 240 mg in combination with carboplatin/etoposide followed by placebo monotherapy

Arm C: placebo in combination with carboplatin/etoposide followed by placebo monotherapy

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

5.3.1.2 Confinement

Subjects will not be confined in this study.

5.3.1.3 Meals and Dietary Requirements

There are no meal and dietary requirements for this study.

5.3.1.4 Blood Samples for Pharmacogenetic Analysis

One 4 mL whole blood sample for DNA isolation will be collected on Cycle 1 Day –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 Cycle 1 Day –2, it may be collected at any time throughout the study.

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

If pharmacogenetic (PG) testing is performed, results from individual subjects will be kept coded and confidential and will not be given to anyone not directly involved with this research study. AbbVie will store the DNA samples in a secure storage space with adequate measures to protect confidentiality. Samples will be coded so that subject identities will not be available to the scientists conducting the genotyping analyses. Individual subject results will not be provided to the Investigator so that neither the subject nor the Investigator will have knowledge of specific subject genotypes. AbbVie will keep the DNA samples until destroyed by AbbVie when this research is completed. These samples will not be stored longer than 20 years or per country requirement.

5.3.1.5 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

Twelve (12) mL (Cycle 1 Day –2 or Final Visit) or 6 mL (all other time points) of blood will be collected pre-dose by venipuncture at time points outlined in Table 9 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 at time points as outlined in Table 9. The collection, processing and storage 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 for IHC, ELISA and FISH DNA Mutational/Methylation Analysis

Archived Tissue Specimens:

Subjects must consent to provide available archived tissue for analysis. It is recognized that samples suitable for analysis will not be available from all consenting subjects. The most recent archived biopsy is preferred and should be obtained at Cycle 1 Day –2, if possible. While sending FFPE blocks is preferred, slides prepared by the local pathology laboratory are acceptable and should be prepared as described in the study specific laboratory manual. Study specific biopsies are not required for subject participation.

5.3.1.6 Shipment of Pharmacodynamic Samples

All samples 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 Analysis

Blood Samples for Veliparib Assay

Blood samples for veliparib assay will be collected by venipuncture at the designated time points outlined in Table 10 (Phase 1) and Table 11 (Phase 2). The timing of blood collection is fundamental to the success of the study. The timing of blood collections will take priority over all other scheduled study activities except for dosing. The order of blood collections will be maintained to the minute such that the time intervals relative to

the preceding dose will be the same for all subjects. The time that each blood sample is collected will be recorded to the minute.

The date and time of the morning dose of veliparib on PK sampling day will be recorded. In Phase 2 portion, the date and time of the two doses of veliparib prior to PK sampling on C1D1, C2D1, C3D1 and C4D1 will also be recorded.

The collection, processing and storage should be performed as described in the study specific laboratory manual.

Approximately 7 blood samples are planned to be collected per subject in Phase 1 and 6 samples per subject in Phase 2 for pharmacokinetic analysis. The approximate number of blood samples planned for pharmacokinetic analysis is approximately 1325 for the entire study.

Blood Samples for Etoposide Assay

Blood samples for etoposide assay will be collected at the time points specified in Table 10. The date and time of the dose of etoposide on PK sampling day will be recorded. The collection, processing and storage should be performed as described in the study specific laboratory manual. A total of 10 samples per subject will be collected for etoposide analysis in Phase 1 Cycles 1 and 2. Blood samples for etoposide assay will not be collected for Phase 2 subjects.

Blood Samples for Unbound Carboplatin Assay

Plasma concentration-time course of carboplatin will be determined on Cycle 1 Day 1. Blood samples will be collected at the time points outlined in Table 10. The date and time of the dose of carboplatin on PK sampling day will be recorded. The collection, processing and storage should be performed as described in the study specific laboratory manual. A total of 3 samples per subject will be collected for carboplatin assay in Phase 1 Cycle 1 Day 1. Blood samples for carboplatin assay will not be collected for Phase 2 subjects.

Pharmacokinetic variable are discussed in Section 5.3.5.

5.3.2.2 Handling/Processing of Samples

The processing and storage of the PK samples for veliparib, carboplatin and etoposide should be performed as described in the study specific laboratory manual.

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. The placebo samples may not be analyzed to confirm the absence of veliparib. Upon completion of this research, AbbVie or a designated laboratory will destroy the samples.

5.3.2.3 Disposition of Samples

The frozen plasma samples for veliparib, carboplatin and etoposide assays will be packed in dry ice sufficient to last during transport and shipped from the study site to the central laboratory according to instructions in the central laboratory manual.

5.3.2.4 Measurement Methods

Analysis of Plasma Samples

Plasma concentrations of veliparib will be determined under the supervision of the Drug Analysis Department at AbbVie. Placebo samples may or may not be analyzed to confirm the absence of veliparib (ABT-888). Plasma concentrations of etoposide and carboplatin will be determined at external laboratories using validated assays under the supervision of the Drug Analysis Department at AbbVie.

5.3.3 Efficacy Variables

Efficacy variables are not primary endpoints in the Phase 1 Dose Escalation portion of the study.

The primary efficacy endpoint in Phase 2 is progression free survival (PFS) from the time of subject randomization. The secondary endpoints are objective response rate (ORR), overall survival (OS). The tertiary endpoints are duration of response (DOR) and ECOG performance status.

5.3.3.1 RECIST 1.1 for Tumor Response

Response criteria will be assessed using RECIST (Version 1.1).[28] Changes in the measurable lesions over the course of therapy must be evaluated using the criteria presented in Appendix C. Tumor assessments will be performed until disease progression. See tumor assessment schedule in Section 5.3.1.1.

5.3.3.2 Definition of Disease Progression

Disease progression will be defined as radiographic progression of disease as determined by the investigator by RECIST (Version 1.1) Appendix C.

Clinical progression as determined by the investigator, which may be characterized as, but not limited to:

- Increase in at least two points of ECOG performance status attributable to cancer progression;
- Subject requires non-palliative radiation, chemotherapy or surgery due to progressive disease;
- Death from progressive disease.

In cases where an Investigator determines that a subject has met the criteria for clinical disease progression, every effort should be made to confirm the progression radiographically.

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.[21]

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

Values for pharmacokinetic parameters of veliparib, including the maximum observed plasma concentration (C_{max}), the time to C_{max} (peak time, T_{max}), the area under the plasma concentration-time curve from time 0 to time of last measurable concentration (AUC_t) will be determined for veliparib doses on Day 1 of Cycle 1 using non-compartmental methods.

Values for pharmacokinetic parameters of etoposide including C_{max}, AUC from time 0 to the last measurable concentration (AUC_t) and from time 0 to time infinity (AUC_∞), clearance and terminal half-life will be determined on Day 1 of Cycle 1 and Day 1 of Cycle 2 using noncompartmental methods.

Values for compartmental pharmacokinetic parameters of carboplatin in the dose escalation cohorts (such as volume of distribution and clearance) and of veliparib in the Phase 2 part of the study such as rate of absorption (K_a), apparent volume of distribution (V/F) and oral clearance (CL/F) may be estimated using a nonlinear mixed-effect population modeling approach with NONMEM software and reported in a separate pharmacokinetic report.

5.3.6 Pharmacogenetic Variables

DNA samples may be sequenced and data analyzed for genetic factors contributing to the disease or to the subject's response to veliparib, (or other study treatment) in terms of pharmacokinetics, efficacy, tolerability, and safety. Such genetic factors may include

genes for drug metabolizing enzymes, drug transport proteins, genes within the target pathway, 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 will not be reported to subjects and 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, analysis of proteins, including but not limited to proteins involved in DNA repair, such as ERCC1 and XPF, may be performed on tumor tissue obtained from each consented subject and associated with response.

Samples collected during the course of this study may be banked and used in the future 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

5.4.1 Discontinuation of Individual Subjects

Each subject has the right to withdraw from the study at any time. In addition, the investigator may discontinue a subject from the study at any time if the investigator considers it necessary for any reason, including the occurrence of an adverse event or noncompliance with the protocol. Subjects who withdraw or are discontinued from the study will not be replaced except as described in Section 5.1, unless it is mutually agreed upon, in writing, by the investigator and AbbVie.

When a subject discontinuation from the study (without reaching a protocol-defined endpoint) is planned, the Investigator is to notify the AbbVie TA MD 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 TA MD may contact the site to discuss the reason for withdrawal from the study.

If a subject is discontinued from the study with an ongoing adverse event or an unresolved laboratory result that is significantly outside of the reference range, the investigator will attempt to provide follow-up until a satisfactory clinical resolution of the laboratory result or adverse event is achieved.

In the event that a positive result is obtained on a pregnancy test for a subject or a subject reports becoming pregnant during the study, the administration of study drug to that subject must be discontinued immediately. The investigator must report a pregnancy within 1 working day of the site being aware to one of the AbbVie representatives listed in Section 6.6 or Section 7.0.

Post-Treatment Follow-Up

Phase 2 subjects who discontinue treatment for reasons other than radiographic progression will be monitored in the Post-Treatment Follow-Up period of the study by the same imaging method (unless medical contraindication is noted) until disease progression (Table 8).

Final Visit

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 7 and Table 8. 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.

30-Day Follow-Up Visit

Subjects who discontinue treatment for reasons other than radiographic progression will have a Follow-Up Visit approximately 30 days after the last dose of study drug and will transition to Post-Treatment Follow-Up.

Subjects who discontinue treatment due to radiographic progression and have a Final Visit within 30 days of last dose of study drug will have one Follow-Up Visit approximately 30 days after the last dose of study drug.

Survival Follow-Up

All discontinued subjects will have survival information collected via electronic data capture (EDC) at 2 month intervals (or as requested by sponsor to support data analysis) after the subject discontinues the study and continuing until the endpoint of death, the subject has become lost to follow-up, or AbbVie terminates the study.

5.4.1.1 Discontinuation of Combination and Maintenance Therapies in Phase 2

Subjects will receive veliparib, carboplatin and etoposide up to a maximum of 4 – 6 combination cycles or until reaching a protocol defined event of disease progression or experiencing unmanageable toxicity. Dose reductions of carboplatin and etoposide will occur on the basis of the toxicity observed and may result in discontinuation of either agent. The subject may continue on therapy with the remaining agent in combination with veliparib. At the Investigator's discretion, carboplatin and/or etoposide administration may continue after veliparib has been discontinued. Suitable subjects will receive veliparib/placebo maintenance monotherapy as per treatment arm assignment 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. 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

Phase 1 subjects will receive the following:

- Designated doses of veliparib BID on Days –2 through 5 or Day –2 through 12 (14-day schedule) or Day –2 to 19 (continuous schedule) + Carboplatin AUC

5 mg/mL*min administered on Day 1 and Etoposide 100 mg/m^2 administered on Days 1 through 3 of each 21-day cycle for up to 4 cycles.

  - Exception: Phase 1 subjects receiving non-continuous veliparib will have their Cycle 2 dosing schedule altered as follows to allow for the evaluation of veliparib effect on etoposide exposure: veliparib BID on Days 2 through 5 or Days 2 through 12 + Carboplatin AUC 5 mg/mL*min administered on Day 1 and Etoposide 100 mg/m^2 administered on Days 1 through 3 of a 21-day cycle.

- Phase 1 subjects with SD, PR or CR at the completion of all scheduled combination therapy cycles will receive veliparib (400 mg) monotherapy, BID continuously in 21-day cycles starting on Day 1 of each cycle starting at Cycle 5.

Phase 2 subjects will receive the following:

- Veliparib/Placebo 240 mg BID on Day –2 through 12 (14-day schedule) + Carboplatin AUC 5 mg/mL*min administered on Day 1 and Etoposide 100 mg/m^2 administered on Days 1 through 3 of each 21-day cycle for up to 6 cycles.
- Phase 2 subjects with SD, PR or CR at the completion of combination therapy cycles will receive veliparib (400 mg) or placebo monotherapy, BID continuously in 21-day cycles starting on Maintenance Day 1 of each cycle.

The sequence of administration is as follows on days when veliparib is dosed in combination with chemotherapy as described in Figure 3:

Figure 3. Sequence of Administration*

Pre Medication Administration → Veliparib/Placebo → etoposide (60 min infusion) → carboplatin (30 min infusion)

* If institutional guidelines mandate inverse sequence of etoposide and carboplatin administration, they may be followed. Infusion times are approximate.

5.5.1.1 Administration of Veliparib/Placebo

Subjects will self-administer the morning dose of veliparib/placebo and the evening doses of veliparib/placebo approximately 12 hours after the morning dose with or without food in the same calendar day. Veliparib dose should be followed by a glass of water (approx. 240 mL).

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

If the subject vomits within 15 minutes of taking veliparib, 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 the remainder 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 Table 15 in Section 5.5.2.3. Subjects should return bottles of veliparib (empty, partially filled or full) and the completed dosing card to the study site prior to each cycle and at the Final Visit.

5.5.1.2 Administration of Carboplatin and Etoposide

Carboplatin will be administered intravenously on Day 1 of every 21-day cycle. Etoposide will be administered intravenously on Days 1, 2 and 3 of every 21-day cycle. Carboplatin and Etoposide are to be given only after veliparib/placebo dosing on Cycle Day –2 and Day –1 are confirmed. If veliparib/placebo 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, if needed. Etoposide will be administered

prior to carboplatin, unless institutional guidelines require inverse sequence of administration. On the days of chemotherapy, veliparib will be administered after the premedications are given for etoposide, prior to the infusion of etoposide.

Investigators should evaluate subjects for carboplatin and etoposide treatment per the locally approved product label, local practice, or applicable SmPC. Carboplatin will be administered intravenously over approximately 30 minutes at AUC 5 mg/mL/min. The dose of carboplatin will be calculated using the Calvert formula, with creatinine clearance calculated using the modified Cockroft-Gault equation, as specified in the Appendix E.

The maximum allowed doses of carboplatin are:

AUC_5 = 750 mg

AUC_4 = 600 mg

Etoposide will be administered intravenously over approximately 60 minutes at 100 mg/m^2.

5.5.2 Identity of Investigational Products

Information regarding the veliparib/placebo formulation to be used in this study is presented in Table 13.

Table 13. Identity of Investigational Products

Study Drug	Dosage Form	Strength	Route of Administration	Manufacturer
Veliparib (ABT-888)	Capsule	40 mg or placebo*	Oral	AbbVie
Veliparib (ABT-888)	Capsule	100 mg or placebo*	Oral	AbbVie
Veliparib (ABT-888)	Capsule	20 mg*	Oral	AbbVie

* Placebo for Phase 2 ONLY. 20 mg capsule strength for Phase 1 ONLY.

5.5.2.1 Standard of Care Medicinal Products for Study Treatment

Information regarding carboplatin and etoposide to be used in this study is presented in Table 14.

Table 14. Standard of Care Medicinal Products for Study Treatment

Study Treatment	Dosage Form	Route of Administration
Carboplatin (commercially available)*	Vial	Intravenously
Etoposide (commercially available)*	Vial	Intravenously

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

Carboplatin and etoposide are commercially available marketed products and will be obtained by the clinical site pharmacy. Each site will be responsible for tracking the lot numbers for all carboplatin and etoposide dispensed.

5.5.2.2 Packaging and Labeling

Phase 1 Dose Escalation

Veliparib (ABT-888) will be supplied by AbbVie in HDPE bottles containing either 20 mg, 40 mg, 100 mg active capsules. Bottles will contain either 15, 24 or 50 capsules per bottle. This will allow for the 2, 5, 14, 21, or monotherapy days of administration (with one additional dose to cover loss, spillage or replacement due to vomiting within 15 minutes). Each bottle will be labelled per country requirements including at a minimum the information required by local regulations. The label is to remain affixed to the bottle. All blank spaces on the label will be completed by site staff prior to dispensing to the subject.

Phase 2 Randomized Double-Blind

Veliparib (ABT-888)/placebo will be supplied by AbbVie in HDPE bottles containing either 40 mg, 100 mg active or their placebo capsules. Bottles will contain either 15, 24 or 50 capsules per bottle. This will allow for the 14 days combination or continuous monotherapy days of administration (with additional doses to cover loss, spillage or

replacement due to vomiting within 15 minutes). Each bottle will be labelled per country requirements including at a minimum the information required by local regulations. The label is to remain affixed to the bottle. All blank spaces on the label will be completed by site staff prior to dispensing to the subject.

AbbVie will provide study sites with instructions and training for the proper handling, storage and documentation related to all investigational supplies.

5.5.2.3 Storage and Disposition of Study Drug

All sponsor supplied investigational products are for investigational use only and are to be used only within the context of this study. The study drug supplied for this study must be maintained under adequate security and stored under the conditions specified on the label until dispensed for subject use or returned to the destruction facility. Veliparib in Phase 1 and veliparib/placebo in Phase 2 will be designated through the IRT system. Resupplies of veliparib/placebo will be automatically generated through the IRT system based on sites active enrollment.

Veliparib or Placebo

Table 15. Study Drug Storage Conditions

Study Drug	Country	Storage Conditions
Veliparib or Placebo	All countries	Store at 15° to 25°C (59° to 77°F).

Veliparib or Placebo bottles must be stored as presented in Table 15. A storage temperature log is to be maintained to document proper storage conditions. The storage temperature must be recorded on a daily basis. All Temperature Excursions must be reported to the Sponsor immediately. Investigational product should be quarantined and not dispensed until AbbVie GPRD or Abbott Temperature Excursion System (ATEMS) deems the medication as acceptable.

Storage and Use of Carboplatin and Etoposide

Carboplatin and etoposide are commercially available marketed products and will be obtained by the clinical site pharmacy.

Both carboplatin and etoposide are to be used, stored, and disposed of in accordance with their approved commercial product labeling Product Package Insert or Summary of Product Characteristics (SmPC) and/or local institutional guidelines.

5.5.3 Method of Assigning Subjects to Treatment Groups (Phase 1 Dose Escalation)

In the Phase 1 dose escalation portion of the study, there is no randomization schedule; however, an IRT system will still be utilized to assign subject numbers. Subject numbers will be assigned by the IRT as subjects are enrolled in the study.

5.5.4 Method of Assigning Subjects to Treatment Groups (Phase 2 Randomized Double-Blind)

All subjects will be randomized using an IRT system. Before the study is initiated, the IRT user manual, which provides instruction on how to use the system via the web or phone, will be provided to each site.

Subjects who complete all Screening procedures and meet eligibility criteria may proceed to randomization. Subject randomization will be stratified by: LDH (≤ ULN versus > ULN), and gender; therefore a subject's baseline LDH value must be known prior to randomization and when accessing the IRT to perform the randomization transaction.

The site will contact the IRT to obtain a Screening (subject) number once the subject has signed the informed consent and a study-specific procedure has been performed (i.e., central laboratory samples drawn). Once the subject number is assigned, if the subject is not enrolled/randomized the reason for screen failure will be documented in the source document and in the eCRF. If the subject meets all inclusion and none of the

exclusion criteria, the site will access the system to randomize the subject. The IRT will randomize subjects in a 1:1:1 ratio to one of the three treatment arms as follows:

- Arm A: veliparib in combination with carboplatin/etoposide followed by veliparib monotherapy
- Arm B: veliparib in combination with carboplatin/etoposide followed by placebo monotherapy
- Arm C: placebo in combination with carboplatin/etoposide followed by placebo monotherapy

Subject randomization will be stratified by: LDH (≤ ULN versus > ULN), and gender

5.5.5 Selection and Timing of Dose for Each Subject

Phase 1 Dose Escalation

All Phase 1 subjects will receive veliparib orally. Depending on the dosing schedule assigned, veliparib will be dosed twice a day on Days –2 through 5 (7-day schedule) or Days –2 through 12 (14-day schedule) of 1st, 3rd and 4th 21-day cycles and on Days 2 through 5 or Days 2 through 12 (14-day schedule) of the 2nd 21-day cycle, or on Days –2 through 19 (continuous schedule) of the 21 day Cycles 1 – 4 at a dose level based on the dose escalation cohort assignment. One dose will be taken in the morning and the second dose will be taken in the evening (approximately 12 hours after the morning dose). The morning dose of veliparib should be administered in the clinic prior to etoposide and carboplatin, but after chemotherapy premedications on days when administered with chemotherapy. Premedications may be administered per individual institutional standards.

After the end of Cycle 4, subjects without evidence of disease progression by radiographic assessment (CT) will receive veliparib at 400 mg BID continuous schedule 21 day cycle, until disease progression or unacceptable toxicity.

A "3 + 3" escalation rule will be used for the Phase 1 dose escalation portion of this study, with a condition applied for the Dose Level 1, which will allow 3 additional subjects to be entered in Dose Level 1 if 2 of 6 initial subjects experience DLTs. Enrollment of the 3 additional subjects at all dose levels will depend on a review of the specific DLTs observed and discussion with the Investigators. At the RPTD and schedule, additional subjects will be added as needed so that a total of at least 9 subjects will be treated at the RPTD.

Phase 2 Randomized Double-Blind

Subjects will complete at least 4 cycles of combination therapy, unless disease progression or unacceptable toxicity warrants earlier discontinuation from the combination treatment. Subject whose status at the completion of the 4th cycle of combination therapy warrants, in the opinion of the investigator, continued combination treatment may receive up to two additional combination therapy cycles (e.g., up to a total of 6 cycles) if required by local standard of care. After the completion of combination therapy, subjects without evidence of disease progression by most recent scheduled radiographic assessment (CT) will receive veliparib at 400 mg BID or placebo continuous schedule in 21-day cycles, until disease progression or unacceptable toxicity.

5.5.6 Blinding

All study site personnel, including the investigator, study coordinator, as well as the subjects, will remain blinded to the treatment throughout the course of the Phase 2 portion of the study. The IRT system will provide access to blinded subject treatment information during the double-blind period, if needed.

AbbVie must be notified before breaking the blind, unless identification of the study drug is required for a medical emergency, i.e., situation in which the knowledge or the specific blinded treatment will affect the immediate management of the subject's conditions (e.g., antidote is available). AbbVie must then be notified within 24 hours of the blind being broken. The date and reason that the blind was broken must be recorded in the source documentation and on the CRF or eCRF, as applicable.

5.5.7 Treatment Compliance

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

Subjects will be instructed to return all veliparib/placebo bottles (empty, partially filled or full) and the completed dosing card to the study site personnel at each combination cycle Day 1, each Maintenance cycle Day 1, 30-Day Follow-Up Visit and/or at the Final Visit. The Investigator or his/her designated and qualified representatives will document the bottles returned and the number of capsules returned per bottle in the IRT system.

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

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

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. The Investigator or his/her designated and qualified representatives will document compliance on the appropriate eCRF.

5.5.8 Drug Accountability

Upon receipt of a shipment of veliparib, the representative at each site will verify that study drug supplies are received intact and in the correct amounts. This will be documented by signing and dating the Proof of Receipt (PoR) or similar document respectively via direct recording in the IRT. The shipment receipt must be acknowledged in the IRT in order to become available for dispensation to subjects. All veliparib/placebo must be retained in the designated secure area under proper storage conditions. The study site will record the kit number of veliparib/placebo given to each subject in the source documents and on the eCRF.

The IRT will maintain a current and accurate inventory of study drug, accountability, reconciliation, returns, and destruction for each site. The IRT will also include the lot number, the bottle/kit numbers, and the date veliparib/placebo was dispensed for each subject.

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

The Investigator or designee will document the bottles of veliparib/placebo returned and the number of capsules on the appropriate form in the IRT. If the number of capsules taken and the number of capsules returned do not add up to the number of capsules dispensed, an explanation is required and should be documented in the IRT.

An overall accountability of the study drug will be performed and verified by the AbbVie monitor throughout the study and at the site close-out visit. All study drug unit doses must be inventoried, accounted for, and returned to the destruction facility or to AbbVie or destroyed per instructions from AbbVie and according to local regulations.

The investigator and/or named the sub-investigators agree not to supply study medication to any persons not enrolled in the study.

The site will record the dose of carboplatin and etoposide given to each subject in the source documents and on the eCRF. As the investigator will obtain both carboplatin and etoposide commercially, site inventory and accountability of carboplatin and etoposide will not be performed, and drug accountability for carboplatin and etoposide will not be performed in the IRT. However, each site will be responsible for tracking the lot numbers for all carboplatin and etoposide dispensed.

5.6 Discussion and Justification of Study Design

5.6.1 Discussion of Study Design and Choice of Control Groups

The carboplatin and etoposide combination chemotherapy is standard first-line treatment for ED SCLC. Veliparib may have a potential benefit for subjects with ED SCLC. This Phase 1 dose escalation/Phase 2 randomized double-blind study will determine the recommended Phase 2 dose of veliparib in combination with carboplatin and etoposide (Phase 1 portion), and will evaluate the treatment effect due to the addition of veliparib to carboplatin/etoposide chemotherapy followed by veliparib monotherapy maintenance in subjects with ED SCLC (Phase 2 portion).

5.6.2 Appropriateness of Measurements

The Phase 1 dose escalation portion of the study is a standard 3 + 3 design. Standard pharmacokinetic, statistical, clinical, and laboratory procedures will be utilized in this study.

The randomized double-blind Phase 2 portion will utilize a well-established surrogate ED SCLC and other solid tumor endpoint of progression free survival using RECIST 1.1 as a guideline for the measurement of responses in subjects with advanced or metastatic solid tumors.[28] Secondary and tertiary endpoints of objective response rate, duration of overall response and overall survival of subjects receiving veliparib maintenance monotherapy will also be evaluated.

5.6.3 Suitability of Subject Population

Subjects with ED SCLC and advanced/metastatic solid tumors (Phase 1) and with treatment-naïve ED SCLC (Phase 2) and meeting inclusion and exclusion selection criteria as outlined in the Section 5.2.1 and Section 5.2.2 are appropriate for this study. Subjects with advanced/metastatic solid tumors will allow defining the recommended Phase 2 dose as the tolerability of the study regimen in this population should be similar to the target population with ED-SCLC. Subjects with treatment-naïve ED SCLC are appropriate to define efficacy and safety of the study regimen since carboplatin/etoposide is the first line standard of care in this tumor type and SCLC is the intended indication for further clinical evaluation of veliparib/carboplatin/etoposide combination.

5.6.4 Selection of Doses in the Study

Phase 1 Dose Escalation

The initial starting dose of 80 mg BID veliparib in the Phase 1 portion of the study was derived from the results obtained in the ECOG E2511, GOG 9923 and AbbVie M10-898 clinical studies, as well as from the non-clinical studies.

Doses for carboplatin in combination with etoposide will be given as per standard of care in first line treatment for extensive stage SCLC as per NCCN guideline 2014.[3]

The dose for veliparib monotherapy is 400 mg BID. This dose is well characterized for safety and tolerability based on the experience from multiple clinical trials.

Phase 2 Randomized Double-Blind

The RPTD has been defined in the Phase 1 portion of the study as veliparib 240 mg BID administered on Days –2 – 12 (14-Day schedule), carboplatin AUC 5 mg/ml*hr administered on Day 1, etoposide 100 mg/m^2 administered on Days 1 – 3 of 21-Day cycles.

The dose for veliparib/placebo monotherapy is 400 mg BID administered continuously in 21-Day cycles.

5.7 Dose Reductions or Delays

If a subject experiences an adverse event that results in a delay in starting a cycle or requires that study regimen is delayed or interrupted during a cycle, the subject will complete the planned activities per Section 5.7.1 until resuming treatment.

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 timing of dose resumption should be at the discretion of the Investigator. Study treatment may be delayed for up to 21 days due to toxicity. Toxicity-related delays greater than 21 days will result in study treatment discontinuation.

Table 16. Guidelines for Veliparib, Carboplatin, and Etoposide Dose Reduction Levels During Combination Therapy

Dose Reductions	Carboplatin	Etoposide[a]	Veliparib[b]
Starting Dose	AUC 5	100 mg/m^2	Phase 1: As assigned Phase 2: 240 mg BID
Dose Reduction 1	AUC 4	75 mg/m^2	Phase 1: Next lower DL (assigned –1) Phase 2: 200 mg BID
Dose Reduction 2	No Additional Reductions Allowed	55 mg/m^2	Phase 1: Next lower DL (assigned –2) Phase 2: 160 BID

a. Refer to Section 5.7.2.1.2 for etoposide dose reduction guidelines related to bilirubin.

b. Refer to Section 5.7.1 for veliparib dose reduction guidelines for maintenance therapy. "Next lower DL" refers to the daily dose levels tested in the dose escalation part of the study. The dose of each drug can be reduced independently based on the observed toxicities. For veliparib dose level of 80 mg (Phase 1 only), Dose Reduction 1 is to 60 mg, Dose Reduction 2 is to 40 mg.

5.7.1 Veliparib/Placebo Dose Reductions and Interruptions

The following are guidelines for dose reduction, interruption and discontinuation of veliparib/placebo during combination therapy:

1. Veliparib/placebo will be discontinued if both carboplatin and etoposide are discontinued prior to the completion of the planned number of combination therapy cycles.
2. For any subject who experiences Grade 3/4 toxicity which is not attributable to carboplatin/etoposide or the underlying disease, refer to Table 17 for dosing guidelines.
3. Two dose reductions are prospectively allowed during combination therapy for subjects who experience toxicity attributable to veliparib/placebo. Refer to Table 16 for dose reduction guidelines.
    a. Veliparib dose reduction at C1D1 is allowed in case of nausea and vomiting attributable to C1D-2 and C1D-1 veliparib doses
    b. All veliparib/placebo dose reductions within combination therapy cycles are permanent.
    c. If further dose reductions (beyond prospectively allowed two) are required, sites must contact the AbbVie TA MD.
4. Any ≥ Grade 2 event of seizure attributed to veliparib/placebo requires discontinuation of veliparib/placebo.
5. Veliparib/placebo interruptions will not affect the schedule of planned study procedures and will not be replaced. If veliparib/placebo-related toxicity necessitates the delay in veliparib/placebo re-initiation beyond the scheduled start of the next combination therapy cycle, the start of the cycle should be delayed until veliparib/placebo can be restarted. The AbbVie TA MD may be contacted (Section 6.6) for subjects who require more than a 2-week delay in the re-initiation of the next cycle.

The following are guidelines for dose reduction, interruption and discontinuation of veliparib/placebo during Maintenance Therapy:

1. Dose Reduction 1: 300 mg BID.

2. Dose Reduction 2: 200 mg BID.
3. Subjects requiring dose reduction of veliparib/placebo to below 200 mg BID will be discontinued from treatment.
4. For subjects who experience any Grade 3/4 toxicity during maintenance therapy which is attributable to veliparib, refer to Table 18 for dosing guidelines.

Table 17. Dose Interruption or Reduction Due to Toxicity Attributable to Veliparib in the Combination Therapy Cycles

Adverse Event	Veliparib
Any Grade 3 or 4 toxicity attributable to veliparib which is not attributable to carboplatin/etoposide or underlying disease	1. Interrupt dosing in the current cycle until Grade 1 (or Grade 2 if present at baseline) and 2. Reduce veliparib dose to next lower dose level upon dosing re-initiation

Table 18. Veliparib Dose Interruption or Reduction Due to Toxicity Attributable to Veliparib in the Maintenance Therapy Cycles

Adverse Event	Veliparib
Any Grade 3 or 4 toxicity attributable to veliparib	1. Interrupt dosing in the current cycle until Grade 1 (or Grade 2 if present at baseline) and 2. At resumption reduce veliparib dose to next lower monotherapy dose level

5.7.2 Carboplatin/Etoposide Dose Reductions and Delays

If a subject experiences an adverse event attributable to carboplatin or etoposide, carboplatin or etoposide may either be interrupted or the dose reduced.

If a dose reduction or delay is required for carboplatin and/or etoposide, the Investigator should follow procedures as defined in the locally approved product label or applicable Summary of Product Characteristics (SmPC). Section 5.7.2.1 outlines suggested dose

reductions for carboplatin/etoposide if above information is not available. PD and/or PK samples will not be drawn during carboplatin and/or etoposide dose delays.

5.7.2.1 Guidelines for Carboplatin and Etoposide Dose Reductions and Delays

The below guidelines are suggested, unless described as mandatory. If a dose reduction or delay is required for carboplatin and/or etoposide, the Investigator should follow procedures according to institutional guidelines, the locally approved product label, local practice, or applicable SmPC. If the Investigator considers an event attributable to carboplatin and/or etoposide, the Investigator may consider reducing carboplatin and/or etoposide, but not veliparib/placebo. Suggested guidelines for dose reduction, delay, and discontinuation are included in Table 16 and Table 19 (if locally approved product label, local standard of care guideline or applicable SmPC for carboplatin/etoposide combination chemotherapy are not available).

All carboplatin and/or etoposide dose reductions are permanent. Re-escalation of the dose of therapy is not allowed. All toxicities should have 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 toxicity precludes the initiation of the dosing of carboplatin/etoposide in the cycle, and veliparib doses on Days –2 and –1 of the cycle have already been administered, veliparib should be administered again once the toxicity resolves for 2 days prior to carboplatin/etoposide dosing. In such a case, a new supply of veliparib/placebo is to be dispensed, and Day –2 and Day –1 are to be repeated for that cycle.

For Phase 1 ONLY: PD and/or PK samples will not be drawn during carboplatin and/or etoposide dose delays. If the Investigator considers an event attributable to carboplatin and/or etoposide and not veliparib, the Investigator may consider reducing the dose of both agents.

5.7.2.1.1 Hematologic Toxicity

If chemotherapy must be withheld due to hematologic toxicity, CBC and platelet counts should be obtained weekly via central labs (if done locally, sample MUST be split for central lab) until the counts reach the lower limits for treatment as outlined. The treatment schedule will then proceed in the usual sequence.

Neutropenia or Febrile Neutropenia

For febrile neutropenia with absolute neutrophil count (ANC) < 500/mm^3 and a single temperature of > 38.3°C (101°F) or a sustained temperature of ≥ 38°C (100.4°F) for more than one hour, requiring intravenous antibiotics:

a. Doses of both carboplatin and etoposide drugs should be reduced to the next lower dose level for all subsequent cycles of chemotherapy. Suggested dose reduction levels are outlined in Table 14.
b. Implement dose reductions, as outlined in Table 19.
c. Initiate prophylactic neutrophil growth factors (e.g., G-CSF) after the first episode and in accordance with local SOC practices, ASCO or NCCN guidelines.
d. If ANC counts do not recover within 3 weeks, discontinue all protocol therapy.

For treatment delays of more than 7 days due to neutropenia, carboplatin and etoposide should be dose-reduced to next lower dose level for all subsequent cycles of chemotherapy, as outlined in Table 19.

For nadir neutropenia in the absence of fever or with fever that is successfully treated by oral antibiotics, there will be no dose adjustment.

ANC must be ≥ 1,500/mm^3 on Day 1 of each cycle (mandatory). If the ANC is lower than 1,500/mm^3, then dosing of all drugs (carboplatin, etoposide and veliparib) will be delayed until recovery to the required ANC.

Platelets

For Grade 4 nadir platelet count decrease (thrombocytopenia) (platelets < 25,000 mm^3), the dose of both carboplatin and etoposide should be reduced to next lower dose level from the previous dose for all subsequent cycles of chemotherapy. Implement dose reductions 1 and 2 for the first and second episodes, respectively as outlined in Table 19. If counts do not recover within 3 weeks, discontinue all protocol therapy.

Platelet count must be > 100,000/mm^3 on Day 1 of each cycle (mandatory). Doses or all drugs (carboplatin, etoposide and veliparib) should be delayed until platelet count recovers to > 100,000/mm^3.

Anemia

No dose reductions will be made for anemia. Subjects should be supported per the treating physician's discretion. The use of RBC transfusions for anemia will be allowed as clinically indicated and as per local standard of care or current NCCN guidelines. The use of growth factors for anemia is not permitted during Phase 1 Cycle 1.

If more than two dose modifications of carboplatin and etoposide are required for hematologic toxicity, e.g., in cases where an additional dose modification is needed for a toxicity which was not observed earlier, please consult the AbbVie TA MD.

5.7.2.1.2 Non-Hematological Toxicity

Gastrointestinal Toxicity: Nausea and Vomiting

All subjects should receive antiemetics* to prevent nausea and vomiting. Specific antiemetic therapy is left to the discretion of the treating physician (steroids and 5-HT3 antagonists should be used). For vomiting Grade ≥ 3, consider hospital admission and/or use of aprepitant, if possible. Nausea/vomiting should have resolved to Grade 1 or less prior to initiation of next treatment cycle. Do not modify carboplatin and/or etoposide doses due to nausea/vomiting.

* Aprepitant, when given once daily for 14 days as a 100 mg capsule with an oral contraceptive containing 35 mcg of ethinyl estradiol and 1 mg of norethindrone, decreased the AUC of ethinyl estradiol by 43% and decreased the AUC of norethindrone by 8%. Women of childbearing potential using pregnancy contraception that includes ethinyl estradiol should not receive Aprepitant for the treatment of nausea/delayed emesis. Subjects may change to a different method of contraception if they wish to use Aprepitant.

Hepatic Toxicity

For bilirubin > 1.5 – 3.0 × ULN, not attributable to underlying disease, reduce the dose of etoposide to 50 mg/m^2. For bilirubin > 3 – 5 × ULN reduce the dose of etoposide to 30 mg/m^2. For bilirubin > 5 × ULN hold etoposide or hold all treatment if starting the next treatment cycle. When bilirubin resolves to ≤ 5 × ULN, treatment can be resumed, with etoposide dose to 30 mg/m^2. If bilirubin does not improve to ≤ 5 × ULN within 3 weeks of first occurrence, discontinue protocol therapy.

5.7.2.1.3 Other Grade 3/4 Non-Hematologic Toxicity

Other non-hematologic Grade 3/4 toxicity should be managed as per local SmPC guidelines and institutional standard practices.

Table 19. Suggested Guidelines for Carboplatin/Etoposide Dose Delay or Reduction

Adverse Event	Carboplatin Dose	Etoposide Dose
ANC < 1,500/mm^3 Day 1 of Cycle	Hold next cycle until ANC ≥ 1,500/mm^3.	Hold next cycle until ANC ≥ 1,500/mm^3.
Treatment delays of > 7 days due to neutropenia	Implement Dose Reduction 1 for 1st episode.	Implement Dose Reduction 1 for 1st episode and Dose Reduction 2 for 2nd episode.
Grade 3/4 febrile neutropenia with ANC < 500/mm^3, requiring IV antibiotics	Implement Dose Reduction 1 for 1st episode. Initiate Prophylactic G-CSF after 1st episode.	Implement Dose Reduction 1 for 1st episode and Dose Reduction 2 for 2nd episode. Initiate Prophylactic G-CSF after 1st episode.
Grade 3 nausea, vomiting or Grade 4 vomiting	Hold next cycle until resolution to Grade 1 or better. If more than 2 weeks dose delay is required consult with AbbVie TA MD.	Hold next cycle until resolution to Grade 1 or better. If more than 2 weeks dose delay is required consult with AbbVie TA MD.
Platelets < 100,000/mm^3 Day 1 of Cycle	Hold next cycle until platelets ≥ 100,000/mm^3.	Hold next cycle until platelets ≥ 100,000/mm^3.
Grade 4 thrombocytopenia	Implement Dose Reduction 1 for 1st episode.	Implement Dose Reduction 1 for 1st episode and Dose Reduction 2 for 2nd episode.
Bilirubin > 1.5 – 3.0 × ULN	No Change	Reduce dose to 50 mg/m^2
Bilirubin > 3 – 5 × ULN	No Change	Reduce dose to 30 mg/m^2
Bilirubin > 5 × ULN	Hold if bilirubin does not improve to ≤ 5 × ULN within 3 weeks of first occurrence, discontinue protocol therapy	Hold if bilirubin does not improve to ≤ 5 × ULN within 3 weeks of first occurrence, discontinue protocol therapy
Any other Grade 3/4 toxicity	Per local SmPC/institution guidelines	Per local SmPC/institution guidelines

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 another cause of the event. For adverse events to be considered

intermittent, the events must be of similar nature and severity. Adverse events, whether in response to a query, observed by site personnel, or reported spontaneously by the subject will be recorded.

All adverse events will be followed to a satisfactory conclusion.

6.1 Definitions

6.1.1 Adverse Event

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

Such an event can result from use of the drug as stipulated in the protocol or labeling, as well as from accidental or intentional overdose, drug abuse, or drug withdrawal. Any worsening of a pre-existing condition or illness is considered an adverse event. Worsening in severity of a reported adverse event should be reported as a new adverse event. Laboratory abnormalities and changes in vital signs are considered to be adverse events only if they result in discontinuation from the study, necessitate therapeutic medical intervention, (meets protocol specific criteria [see Section 6.8 regarding toxicity management]) 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 is 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 Deaths

For this protocol, mortality is an efficacy endpoint. Deaths that occur during the protocol specified adverse event reporting period (Section 6.5) that are attributed by the investigator solely to progression of disease under study should be recorded only on the Study Completion/Early Discontinuation eCRF. All other on-study deaths, regardless of relationship to study drug, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (Section 6.1.4).

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

During survival follow-up, deaths should be recorded on Survival eCRF.

6.1.3 Lack of Efficacy or Worsening of Disease Under Study

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. These data will be captured as efficacy assessment data only. Refer to Appendix F for listing of events expected with progression of ED SCLC.

6.1.4 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 SCLC or Progression of SCLC

Adverse events that may be expected from primary SCLC 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 SCLC subjects but will not be subject to expedited reporting. These data will be captured as efficacy assessment data only.

6.3 Adverse Event Severity

The 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).[21]

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 3/4)	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 SAE supplemental eCRFs also need to be updated and need to include the new AE serial number.

6.4 Relationship to Study Drug

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

Reasonable Possibility	After consideration of factors including timing of the event, biologic plausibility, clinical judgment, and potential alternative causes, there is **sufficient** evidence (information to suggest a causal relationship.
No Reasonable Possibility	After consideration of factors including timing of the event, biologic plausibility, clinical judgment and potential alternative causes there is **insufficient** evidence (information to suggest a causal relationship.

For causality assessments, events assessed as having a reasonable possibility of being related to the study drug will be considered "associated." Events assessed as having no reasonable possibility of being related to study drug 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. For the purposes of this study, causality assessments will be attributed to veliparib/placebo or carboplatin or etoposide separately.

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

6.5 Adverse Event Collection Period

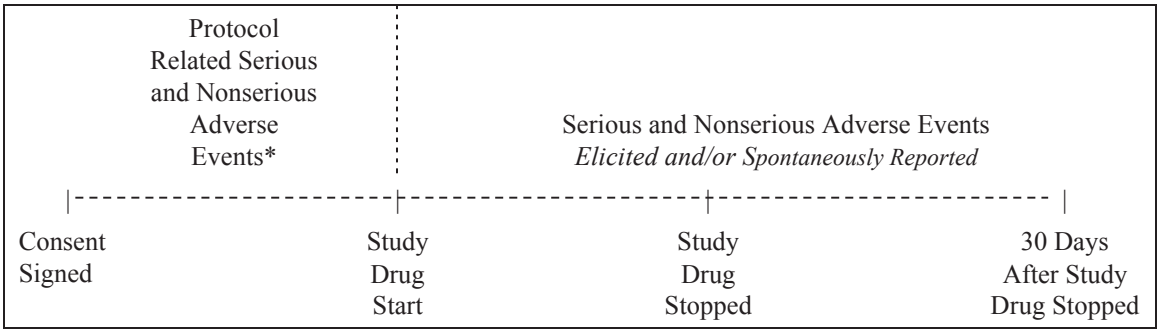
All protocol related serious adverse events and nonserious adverse events must be collected from the signing of the study specific informed consent until study drug administration.

In addition, all adverse events reported from the time of study drug administration until 30 days following discontinuation of study drug administration have elapsed will be collected, whether solicited or spontaneously reported by the subject.

Serious and nonserious adverse events occurring after the study specific informed consent is signed but prior to the initial dose of study drugs will be collected only if they are considered by the Investigator to be causally related to the study-required procedures.

Adverse event information will be collected as shown in Figure 4.

Figure 4. Adverse Event Collection



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

6.6 Adverse Event Reporting

In the event of a serious adverse event, whether associated with study drug or not, the Investigator will notify Clinical Pharmacovigilance within 24 hours of the site being made aware of the serious adverse event by entering the serious adverse event data into the electronic data capture (EDC) system. Serious adverse events that occur prior to the site having access to the RAVE® system or if RAVE is not operable should be sent to Clinical Pharmacovigilance within 24 hours of being made aware of the serious adverse event using the paper CRF (pCRF).

Serious adverse events which are considered expected due to the underlying disease of SCLC would not be expedited as individual safety case reports to regulatory authorities.

FAX to:	[redacted]
Email to:	

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

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

Office: [redacted]
Fax:
Email:

Or the physician through the operator at:

Phone: [redacted]

For any subject safety concerns, please contact the physician listed below:

Primary TA MD:

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

Phone: [redacted]
Fax:
Email:

Alternate Contact:

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

Office:
Cell:
Fax:
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 and etoposide.

6.7 Pregnancy

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

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

Male subjects should be informed that contraceptive measures should be taken by their female partners. If the subject's partner should become pregnant during the study, this

should also be reported and data may be collected. In the event of pregnancy occurring in the partner of an enrolled subject, written informed consent for release of medical information from the partner must be obtained prior to the collection of any pregnancy-specific information and the pregnancy will be followed to outcome.

Pregnancy in a study subject is not considered an adverse event. However, the medical outcome of an elective or spontaneous abortion, stillbirth or congenital anomaly is considered a serious adverse event and must be reported to AbbVie within 24 hours of the site becoming aware of the event.

6.8 Dose Limiting Toxicities

Dose limiting toxicities for Phase 1 dose escalation purposes will be determined during DLT observational period C1D-2 to pre-dose C2D1 in any of the dose-escalation cohorts, with grading according to the National Cancer Institute (NCI) Common Toxicity Criteria for Adverse Events (CTCAE), version 4.0. Any of the events described in Section 5.1 considered to have a reasonable possibility of being related to veliparib will be considered a dose limiting toxicity (DLT).

Subjects experiencing DLTs during the DLT observational period C1D-2 to pre-dose C2D1 will generally be discontinued from further participation in the study, but may continue at the same or a reduced dose with written approval by the Sponsor if there is evidence of clinical benefit.

6.8.1 Determination of the MTD

If a single subject within a cohort experiences a DLT, a total of 6 subjects will be enrolled and dosed at the same dose level. If these additional subjects do not exhibit a DLT, dose escalation may proceed. If any of the additional subjects exhibits a dose limiting toxicity, then dose de-escalation may occur to interrogate lower dose levels. MTD, if identified, will be defined at the highest dose level at which less than 2 of 6 subjects or < 33% of (if cohort is expanded beyond 6) subjects experience a DLT. MTD may be determined independently for each veliparib dosing schedule.

6.8.2 Determination of the RPTD

If an MTD is reached, the RPTD will not be a dose higher than the MTD and will be selected based on the types of DLTs which occur and the MTD identified. If an MTD is not reached, then the RPTD will be defined based on the safety and available PK data.

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 Field Monitor or the following AbbVie Clinical Monitor(s):

Primary Contact:

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

Office:
Fax:
Email: [redacted]

Alternate Contact:

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

Office:
Cell:
Fax:
Email: [redacted]

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

8.0 Statistical Methods and Determination of Sample Size

8.1 Statistical and Analysis Plans

For subjects in the Phase 1 portion, the date of enrollment is defined as the first day of study drug administration. For subjects in the randomized Phase 2 portion, the date of randomization (enrollment) is defined as the date that the IRT issued a subject number.

ORR will be performed on all dosed subjects in the Phase 1 portion of the study.

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

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

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

8.1.1 Baseline Characteristics

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

8.1.1.1 Demographics

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

Smoking history can be defined as current smoker (subject who has smoked within the last 12 months and has more than 100 smoking events [for example, cigarettes] in their lifetime), never smoked (subject with a lifetime smoking history of ≤ 100 smoking events [for example, cigarettes] in lifetime) and past smoker (subject who has not smoked in past 12 months and has more than 100 smoking events [for example, cigarettes] in their lifetime).

8.1.1.2 Medical History

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

8.1.2 Efficacy Endpoints

8.1.2.1 Primary Efficacy Endpoint

The primary efficacy endpoint is progression-free survival (PFS).

Progression-free survival will be defined as the number of days from the date of randomization to the date of earliest disease progression (radiographic progression per RECIST version 1.1) or death. 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. 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 available radiographic disease progression assessment.

8.1.2.2 Secondary Efficacy Endpoints

Secondary efficacy endpoints include objective response rate and overall survival.

Objective Response Rate

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

Overall Survival

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

8.1.2.3 Tertiary Efficacy Endpoints

In addition to the primary and secondary efficacy analyses, tertiary efficacy analyses of duration of overall response and performance status will be performed.

Duration of Overall Response

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

Performance Status

ECOG performance status will be determined by the investigator at assessment throughout therapy and at the final visit.

8.1.3 Primary Analysis of Efficacy

PFS will be analyzed by Kaplan-Meier methodology and compared between Arm A (veliparib in combination with carboplatin/etoposide followed by veliparib monotherapy) and Arm C (placebo in combination with carboplatin/etoposide followed by placebo monotherapy), using a log-rank test stratified by LDH level. A two-sided, stratified log-rank test *P* value will be provided. Median PFS time will be calculated and 95% confidence interval for median PFS time will be presented. A hazard ratio estimate (Arm A versus Arm C) and the corresponding 95% confidence interval will be obtained from a Cox proportional hazards model.

8.1.4 Secondary Analysis of Efficacy

8.1.4.1 Progression-Free Survival (Arm B Versus Arm C)

PFS will be analyzed by Kaplan-Meier methodology and compared between Arm B (veliparib in combination with carboplatin/etoposide followed by placebo monotherapy) and Arm C, using a log-rank test stratified by LDH level. A two-sided, stratified log-rank test *P* value will be provided. Median PFS time will be calculated and 95% confidence interval for median PFS time will be presented. A hazard ratio estimate (Arm B versus Arm C) and the corresponding 95% confidence interval will be obtained from a Cox proportional hazards model.

8.1.4.2 Objective Response Rate

The objective response rate at the time of completion of combination therapy will be estimated and compared between Arm A + B combined and Arm C, using a Cochran-Mantel-Haenszel test stratified by LDH level. A two-sided, stratified CMH test

P value will be provided. In addition, a 95% confidence interval will be constructed for the estimated proportions.

8.1.4.3 Overall Survival

OS will be analyzed by Kaplan-Meier methodology and compared between Arm A and Arm C as well as between Arm B and Arm C, using a log-rank test stratified by LDH level. A two-sided, stratified log-rank test *P* value will be provided. Median OS time will be calculated and 95% confidence interval for median OS time will be presented. Hazard ratio estimates (Arm A versus Arm C, Arm B versus Arm C) and the corresponding 95% confidence intervals will be obtained from a Cox proportional hazards model.

8.1.5 Tertiary Analysis of Efficacy

8.1.5.1 Duration of Overall Response

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

8.1.5.2 Progression-Free Survival (Arm A Versus Arm B)

PFS will be analyzed by Kaplan-Meier methodology and compared between Arm A and Arm B, using a log-rank test stratified by LDH level. A two-sided, stratified log-rank test *P* value will be provided. Median PFS time will be calculated and 95% confidence interval for median PFS time will be presented. A hazard ratio estimate (Arm A versus Arm B) and the corresponding 95% confidence interval will be obtained from a Cox proportional hazards model.

8.1.5.3 Overall Survival (Arm A Versus Arm B)

OS will be analyzed by Kaplan Meier methodology and compared between Arm A and Arm B, using a log-rank test stratified by LDH level. A two-sided, stratified log-rank test *P* value will be provided. Median OS time will be calculated and 95% confidence interval for median OS time will be presented. A hazard ratio estimate (Arm A versus Arm B)

and the corresponding 95% confidence interval will be obtained from a Cox proportional hazards model.

8.1.5.4 ECOG Performance Status

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

8.1.6 Pharmacokinetics

8.1.6.1 Tabulations and Summary Statistics

Plasma concentrations and pharmacokinetic parameter values of veliparib, carboplatin, and etoposide will be tabulated for each subject by dose level, and summary statistics will be computed for each sampling time and each parameter by dose level.

8.1.6.2 Model and Tests

Dose Proportionality of Veliparib on Phase 1 Cycle 1 Day 1

To address the issue of dose proportionality for designated veliparib doses, a linear mixed effects model analysis will be performed for dose-normalized C_{max} and AUC_{0-8} and other pharmacokinetic parameters provided that they can be adequately determined from the data. The natural logarithmic transformation will be employed for C_{max} and the AUC's unless the data clearly indicate that other transformation or the untransformed variable provides more nearly symmetric probability distributions and/or more nearly homogenous variances across dose levels. The model will include dose level, this may be done by classifying subjects by dose level or, if appropriate, using dose level as a continuous

variable. Some variables such as age, body weight, gender, and perhaps others that might explain some of the variability in the population will be included in the model initially as covariates. A necessary condition for a variable to be included in the final model is that the regression coefficient be significant at level 0.10. The dependence among explanatory variable candidates will also be considered when selecting the final model.

Within the framework of the final model, the null hypothesis of no difference between the means of the highest and lowest veliparib doses will be tested. Assuming that at least four veliparib dose levels are indeed studied, a test will also be performed on a contrast in the dose level, with the contrast chosen to be sensitive to an approximately linear function of dose or the logarithm of dose.

Veliparib Effect on Etoposide Pharmacokinetics Parameters

For the dose escalation subjects, a linear mixed effects model analysis will be performed for dose normalized C_{max}, AUC_{0-24} and AUC_{∞}, to compare etoposide pharmacokinetics parameters when co-administered with veliparib (Cycle 1 Day 1) relative to etoposide administered alone (Cycle 2 Day 1). For C_{max} and AUC, the logarithmic transformation will be used unless the data indicate that the logarithm has significant non-normality. The model will include effects for visit (Cycle 1 Day 1, Cycle 2 Day 1). The within-subject variability will be accounted for utilizing the repeated statement for the effect of visit. Within the repeated measure analysis modeling framework, the null hypothesis of no difference between etoposide in combination with veliparib and etoposide alone will be tested with a significance level of 0.05. The relative bioavailability of etoposide co-administered with veliparib relative to etoposide alone will be estimated. Point estimates and corresponding 90% confidence intervals for the ratio of etoposide co-administered relative to etoposide alone will be provided. The point estimates will be obtained by antilogarithm of the estimate of the difference of the logarithmic means. The 90% confidence intervals will be similarly obtained by antilogarithm of the endpoints of the corresponding confidence intervals for the difference of mean logarithms obtained within the framework of the repeated measure analysis model.

8.1.6.3 Missing Values and Model Violations

All available data will be included in the mixed effect analyses. Data exclusion, if any, will be documented and justification provided.

Normally values of pharmacokinetic variables (C_{max}, AUC, etc.) will be determined without replacing missing individual concentration values, simply using the available data, and if necessary doing the analysis with some missing values for a pharmacokinetic variable. However, if a missing individual concentration results in a value of a pharmacokinetic parameter that may be too low or too high to a meaningful degree, the value of the pharmacokinetic parameter will tentatively be considered missing. In this case, a value for the missing individual concentration may be imputed so that an appropriate value of the pharmacokinetic parameter can be included in the analysis. The imputed value will be obtained using appropriate methodology that takes into account the individual characteristics of the subject.

If an outlier is identified and/or a pronounced non-normal probability distribution is observed (after logarithmic transformation for C_{max} and AUC), then a non-parametric analysis may also be performed. Such a model violation may be identified by graphical methods, measures of non-normality (e.g., skewness, kurtosis) or other appropriate methods. If the regimens have unequal variances to the extent that conclusions might be affected, then approximate methods that allow for unequal variances will be used.

8.1.7 Safety

Safety analyses will be performed for Phase 1 and Phase 2 separately.

8.1.7.1 Duration of Study Drug

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

8.1.7.2 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 (veliparib or placebo). Analyses will not include those that have an onset greater than 30 days after the last dose of study drug.

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

8.1.7.3 Serious Adverse Events

Serious adverse events will be summarized using the same methods as adverse events described above in Section 8.1.7.2.

8.1.7.4 Deaths

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

8.1.7.5 Longitudinal Analyses of Laboratory and Vital Signs Data

Changes from baseline will be analyzed for each scheduled post-baseline visit and for the final visit for blood chemistry and hematology parameters, as well as urinalysis and vital sign parameters. If more than one measurement exists for a subject on a particular day, an arithmetic average will be calculated. This average will be considered to be that subject's

measurement for that day. Post-baseline measurements more than 30 days after the last dose of randomized study drug will not be included. Subjects that do not have a baseline measurement or do not have any post-baseline measurements will not be included. For Phase 1, changes from baseline will be analyzed by dose level at each scheduled visit. For Phase 2, comparisons of the differences in mean changes from baseline between Arm A and Arm C as well as between Arm B and Arm C will be made using ANCOVA with treatment group as the factor and baseline as a covariate.

8.1.7.6 Analyses of Laboratory Data Using NCI CTCAE

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

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

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

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

8.1.8 Timing of Efficacy Analyses and Safety Evaluations

When the 126th PFS event is observed, all efficacy and safety data as of this time will be retrieved and entered into the clinical database prior to breaking the study blind. When the data collection is completed and reviewed for completeness and all data management quality assurance (QA) and quality control (QC) procedures are performed, the study blind will be broken and clinical database data will be extracted for documentation and statistical analyses of the efficacy and safety data.

Overall survival will be collected on all subjects. After all survival data have been collected and entered into the clinical database, the clinical database will be extracted again for documentation and a "Final OS Analysis" will be performed on this dataset.

8.1.9 Data Monitoring Committee (DMC)

A safety DMC will be set up for the Phase 2 portion of the study to review the aggregate unblinded safety data. The initial safety DMC review will occur once the first 30 Phase 2 subjects complete combination treatment. Based on this initial safety DMC review, the frequency of subsequent safety DMC reviews will be determined. However, the initial safety DMC review may occur sooner: if the observed rate of DLT-like events in the aggregate blinded safety review of the first 15 Phase 2 subjects exceeds the rate observed in the MTD/RPTD cohort by more than 10%, the safety DMC will convene immediately to review the aggregate unblinded safety data. The details of the safety DMC setup and procedure will be outlined in a separate document.

The DMC will not evaluate efficacy data.

8.2 Determination of Sample Size

Phase 1 Dose Escalation

The number of subjects required for dose escalation portion will depend upon the toxicities observed as the trial progresses.

Phase 2 Randomized Double-Blind

Assuming a median PFS of 5.5 months for placebo in combination with carboplatin and etoposide followed by placebo monotherapy (Arm C) and a hazard ratio of 0.63 for veliparib in combination with carboplatin and etoposide followed by veliparib monotherapy (Arm A) versus Arm C, a total of 85 PFS events will provide an least 80% power to detect a statistically significant difference between Arm A and Arm C at a one-sided $\alpha = 0.1$. Further assuming a hazard ratio of 0.75 for veliparib in combination with carboplatin and etoposide followed by placebo monotherapy (Arm B) versus Arm C, a total of 126 PFS events will be observed across all three arms at the time when 85 PFS events are observed for Arm A and Arm C combined. A total of approximately 180 subjects (60 subjects per treatment arm) will be enrolled into the study to obtain the 126 PFS events.

8.3 Randomization Methods

All subjects in the Phase 2 portion of 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 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 and a unique randomization number will be provided.

The IRT will randomize subjects in a 1:1:1 ratio to one of the treatment arms as follows:

- Arm A: veliparib in combination with carboplatin/etoposide followed by veliparib monotherapy
- Arm B: veliparib in combination with carboplatin/etoposide followed by placebo monotherapy
- Arm C: placebo in combination with carboplatin/etoposide followed by placebo monotherapy

Subject randomization will be stratified by baseline LDH (≤ ULN versus > ULN) and gender. The stratification factors used for the randomization should be the last values on or prior to the date of randomization and should be consistent with those on the eCRF.

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.

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.

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 or 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) GCP guidelines, applicable regulations and guidelines governing clinical study conduct and ethical principles that have their origin in the Declaration of Helsinki. Responsibilities of the clinical investigator are specified in Appendix A.

9.3 Subject Information and Consent

The investigator or his/her representative will explain the nature of the study to the subject, and answer all questions regarding this study. Prior to any study-related screening procedures being performed on the subject, the informed consent statement will be reviewed and signed and dated by the subject, the person who administered the informed consent, and any other signatories according to local requirements. A copy of the informed consent form will be given to the subject and the original will be placed in the subject's medical record. An entry must also be made in the subject's dated source documents to confirm that informed consent was obtained prior to any study-related procedures and that the subject received a signed copy.

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 form, approved by an IRB/IEC, after the nature of the testing has been explained and the subject has had the opportunity to ask questions. The subject must provide consent specific to pharmacogenetic testing 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.

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

All information concerning veliparib and AbbVie operations, such as AbbVie patent applications, formulas, manufacturing processes, basic scientific data, or formulation information, supplied by AbbVie and not previously published is considered confidential information.

The information developed during the conduct of this clinical study is also considered confidential and will be used by AbbVie in connection with the development of veliparib. This information may be disclosed as deemed necessary by AbbVie to other clinical investigators, other pharmaceutical companies, and to governmental agencies. To allow for the use of the information derived from this clinical study and to ensure complete and thorough analysis, the investigator is obligated to provide AbbVie with complete test results and all data developed in this study and to provide direct access to source data/documents for study-related monitoring, audits, IEC/IRB review and regulatory inspection.

This confidential information shall remain the sole property of AbbVie, shall not be disclosed to others without the written consent of AbbVie, and shall not be used except in the performance of this study.

The investigator will maintain a confidential subject identification code list of all subjects enrolled in the study (by name and subject number). This list will be maintained at the site and will not be retrieved by AbbVie.

Any pharmacogenetic research that may be done using DNA samples from this study will be experimental in nature and the results will not be suitable for clinical decision-making or patient management. Hence, neither the investigator, the subject, nor the subject's physician (if different than the investigator) will be informed of individual subject pharmacogenetic results, should analyses be performed, nor will anyone not directly involved in this research. Correspondingly, genetic researchers will have no access to subject identifiers. Individual results will not be reported to anyone not directly involved

in this research other than for regulatory purposes. Aggregate pharmacogenetic information from this study may be used in scientific publications or presented at medical conventions. Pharmacogenetic information will be published or presented only in a way that does not identify any individual subject.

13.0 Completion of the Study

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

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

AbbVie will select the signatory investigator from the investigators who participate in the study. Selection criteria for this investigator will include level of participation as well as significant knowledge of the clinical research, investigational drug and study protocol. The signatory investigator for the study will review and sign the final study report in accordance with the European 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 on-site 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 etoposide.
2. I have read this protocol and agree that the study is ethical.
3. I agree to conduct the study as outlined and in accordance with all applicable regulations and guidelines.
4. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.
5. I agree that all electronic signatures will be considered the equivalent of a handwritten signature and will be legally binding.

Protocol Title: A Phase 1 Dose Escalation and Phase 2 Randomized Double-Blind Study of Veliparib in Combination with Carboplatin and Etoposide as a Therapy of Treatment-Naïve Extensive Stage Disease Small Cell Lung Cancer

Protocol Date: 22 November 2016

Signature of Principal Investigator | Date

Name of Principal Investigator (printed or typed)

15.0 Reference List

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Appendix A. Responsibilities of the Clinical Investigator

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

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

9. Reporting promptly, all changes in the research activity and all unanticipated problems involving risks to human subjects or others, to the appropriate individuals (e.g., coordinating investigator, institution director) and/or directly to the ethics committees and AbbVie.

10. Following the protocol and not make any changes in the research without ethics committee approval, except where necessary to eliminate apparent immediate hazards to human subjects.

Appendix B. List of Protocol Signatories

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

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

Response criteria will be assessed using RECIST (version 1.1).[22] 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 patient, these are preferred for selection as target lesions. Lesions with prior local treatment Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion.

All measurements should be taken and recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as closely as possible to the beginning of treatment and not more than 21 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 with contrast 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 that 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 made. This decision should be guided by the tumor type under investigation and the anatomic location of the disease and the outcome of the decision should be communicated to AbbVie.

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 TA MD.

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 patient who has visceral disease at baseline and while on study has a CT or MRI brain ordered which reveals metastases. The patient's brain metastases are considered evidence of progressive disease even if he/she did not have brain imaging at baseline.

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

Appendix D. NYHA Functional Classification

The NYHA classifies heart failure into classes based on functional limitations and severity.

Class	Patient Symptoms.
Class I (Normal)	Few observable symptoms, no limitation in ordinary physical activity.
Class II (Mild)	Mild observable symptoms and slight limitation during ordinary activity. Comfortable at rest.
Class III (Moderate)	Marked limitation in physical activity due to symptoms even during less-than-ordinary activity. Comfortable only at rest.
Class IV (Severe)	End-stage heart failure. Severe limitations. Experience symptoms even while at rest.

Appendix E. Calculation of Carboplatin Dose

The Cockcroft-Gault formula will be used.

The carboplatin dose will be calculated to reach a target AUC according to the Calvert formula using an estimated glomerular filtration rate (GFR) from the Cockcroft-Gault formula.

The initial dose of carboplatin must be calculated using GFR. In the absence of renal toxicity greater than or equal to CTCAE Grade 2 (serum creatinine > 1.5 × ULN) or toxicity requiring dose modification, the dose of carboplatin will not need to be recalculated for subsequent cycles, but will be subject to dose modification for toxicity as noted in the protocol.

Carboplatin doses will be based on the subject's weight at baseline and will remain the same throughout the study. However, the doses may be recalculated based on the subject's weight at each cycle, and need to be recalculated if the subject has a weight change of greater than or equal to 10% from baseline.

In subjects with an abnormally low serum creatinine (less than 0.7 mg/dL), the creatinine clearance should be estimated using a minimum value of 0.7 mg/dL.

CALVERT FORMULA:

Carboplatin dose (mg) = target AUC × (GFR + 25)

NOTE: the GFR used in the Calvert formula should not exceed 125 mL/min.

Maximum carboplatin dose (mg) = target AUC (mg/ml × min) × 150 mL/min.

The maximum allowed doses of carboplatin are:

- AUC_5 = 750 mg
- AUC_4 = 600 mg

For the purposes of this protocol, the GFR is considered to be equivalent to the estimated creatinine clearance. The estimated creatinine clearance (mL/min) is calculated by the method of Cockcroft-Gault using the following formula:

$$\text{Creatinine Clearance (mL/min)} = [140\text{-Age (years)}] \times \text{Weight (kg)} \times \frac{}{72 \times \text{serum creatinine (mg/dL)}}$$

For female subjects: multiply the result above by 0.85.

Notes:

a. Body mass index (BMI) should be calculated for each subject. A BMI should be calculated using the following formula:

$$\text{BMI} = (\text{Weight in kg}) / (\text{Height in meters})^2$$

b. Actual weight should be used for estimation of GFR for subjects with BMI < 25.
c. Adjusted weight should be used for estimation of GFR for subjects with BMI ≥ 25.
d. Adjusted weight calculation:
    i. Ideal weight (kg) = (((Height (cm)/2.54) – 60) × 2.3) + 45.5
    ii. Adjusted weight (kg) = ((Actual weight – Ideal weight) × 0.40) + Ideal weight
e. If a patient with BMI of ≥ 25 is currently being dosed using actual weight, adjust dose with next planned treatment.

At the time of a dose modification for toxicity:

- If the creatinine at the time of a dose modification is lower than the creatinine used to calculate the previous dose, use the previous (higher) creatinine;
- If the creatinine at the time of a dose modification is higher than the creatinine used to calculate the previous dose, use the current (higher) creatinine. This will ensure that the patient is actually receiving a dose reduction.

Note that carboplatin dose will be recalculated if the subject has weight change of greater than or equal to 10% from baseline.

Appendix F. Adverse Events Expected Due to SCLC or Progression of SCLC

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

Deep vein thrombosis*
Lower respiratory tract infection*
Respiratory tract infection*
Upper respiratory tract infection*
Opportunistic infection*
Viral infection*
Fungal infection*
Bacterial infection*
Pulmonary haemorrhage*
Lung abscess*
Empyema*
Sepsis*
Lymphadenopathy
Decreased appetite
Malaise
Weight decreased
Headache
Pain excluding chest pain
Pyrexia

* Includes life threatening or fatal events.

Appendix G. Protocol Amendment: List of Changes

The summary of changes is listed in Section 1.1.

Global Protocol Changes:

"Medical monitor" and "study designated physician" have been changed to read "TA MD" throughout the document. "Interactive Voice/Web Response Technology (IVRS)" has been changed to read "Interactive Response Technology (IRT)" throughout the document.

Specific Protocol Changes

Section 1.2 Synopsis
Previously read:

AbbVie Inc.	**Protocol Number:** M14-361
Name of Study Drug: Veliparib	**Phase of Development:** 1 – 2
Name of Active Ingredient: Veliparib	**Date of Protocol Synopsis:** 14 June 2016
Protocol Title: A Phase 1 Dose Escalation and Phase 2 Randomized Double-Blind Study of Veliparib in Combination with Carboplatin and Etoposide as a Therapy of Treatment-Naïve Extensive Stage Disease Small Cell Lung Cancer	
Objectives: **Phase 1:** Primary Objectives: ● To establish the Maximum Tolerated Dose (MTD) and to establish the Recommended Phase 2 Dose (RPTD) and schedule for veliparib in combination with carboplatin and etoposide. ● To evaluate the pharmacokinetic interaction between veliparib and etoposide. Secondary Objective: ● To evaluate the safety of maintenance veliparib monotherapy at 400 mg twice daily (BID) in subjects completing 4 cycles of carboplatin, etoposide and veliparib without evidence of disease progression. **Phase 2:** Primary Objective: ● To evaluate if veliparib in combination with carboplatin and etoposide followed by veliparib maintenance monotherapy results in improved progression free survival (PFS) versus placebo in combination with carboplatin and etoposide followed by placebo monotherapy in subjects with treatment-naïve ED SCLC.	

Objectives (Continued):

Secondary Objectives:

- To evaluate if veliparib in combination with carboplatin and etoposide followed by placebo monotherapy results in improved progression free survival (PFS) versus placebo in combination with carboplatin and etoposide followed by placebo monotherapy in subjects with treatment-naïve ED SCLC.
- To evaluate if veliparib in combination with carboplatin and etoposide results in improved objective response rate (ORR) versus placebo in combination with carboplatin and etoposide at the time of completion of combination therapy.
- To evaluate if veliparib in combination with carboplatin and etoposide followed by veliparib maintenance monotherapy results in improved overall survival (OS) versus placebo in combination with carboplatin and etoposide followed by placebo monotherapy.
- To evaluate if veliparib in combination with carboplatin and etoposide followed by placebo monotherapy results in improved overall survival (OS) versus placebo in combination with carboplatin and etoposide followed by placebo monotherapy.

To further evaluate the safety of veliparib in combination with carboplatin and etoposide followed by veliparib maintenance monotherapy.

Tertiary Objectives:

- To evaluate if veliparib in combination with carboplatin and etoposide followed by veliparib maintenance monotherapy results in improved duration of overall response (DOR) versus placebo in combination with carboplatin and etoposide followed by placebo monotherapy.
- To evaluate if veliparib in combination with carboplatin and etoposide followed by placebo monotherapy results in improved duration of overall response (DOR) versus placebo in combination with carboplatin and etoposide followed by placebo monotherapy.
- To compare PFS and OS of subjects treated with veliparib in combination with carboplatin and etoposide followed by veliparib maintenance to PFS and OS of subjects treated with veliparib in combination with carboplatin and etoposide followed by placebo maintenance.
- To evaluate performance status.

Investigators:

Multicenter

Study Sites:

Approximately 65 globally

Study Population:

Phase 1: Histologically or cytologically confirmed extensive stage disease SCLC or any other advanced/metastatic solid tumor for which carboplatin/etoposide treatment is considered appropriate.

Phase 2: Histologically or cytologically confirmed treatment-naïve extensive stage disease SCLC.

Number of Subjects to be Enrolled:

Dose Escalation Cohort: Approximately: 35

Phase 2 Portion Approximately: 180

Methodology:

This is a Phase 1 dose escalation and Phase 2 randomized double-blind study.

Screening Procedures:

Screening procedures should be performed within 28 days of Cycle 1 Day –2. If the screening visit is performed greater than 7 days prior to Cycle 1 Day –2, the physical exam, laboratory tests, and pregnancy test (for female subjects of childbearing potential) must be repeated on Cycle 1 Day –2. Vital signs and performance status assessments will be performed on Cycle 1 Day –2 for all subjects. Baseline radiographic tumor assessments per computed tomography (CT)/magnetic resonance imaging (MRI) of the chest, abdomen, and head will be conducted within 21 days prior to Cycle 1 Day –2. If CNS metastases are suspected, a head CT should also be performed at screening.

Phase 1 Dose Escalation:

For subjects in the dose escalation portion of the study, each subject will participate in only 1 dose group and there is no provision for intra-subject dose-escalation. Study procedures will be provided in the Schedule of Assessments and Pharmacokinetic and Pharmacodynamic tables.

The Phase 1 portion of this study will evaluate the safety, tolerability, dose limiting toxicities (DLTs), RPTD, pharmacokinetics (PK), and pharmacodynamics (PD), of veliparib/carboplatin/etoposide combination in subjects diagnosed with Extensive Stage Disease Small Cell Lung Cancer or, other advanced/metastatic solid tumor for which carboplatin/etoposide treatment is considered appropriate. Veliparib will be administered on Days –2 to 5 (7-day schedule), and, if the MTD of the 7-day schedule is not reached at ≤ 200 mg BID veliparib dose level, may be administered on Days –2 to 12 (14-day schedule) and/or Days –2 to 19 (continuous schedule) orally BID, in combination with carboplatin area under the curve 5 mg/mL*min administered on Day 1 and etoposide 100 mg/m^2 administered on Days 1 to 3 via intravenous (IV) infusion in 21-day cycles. An exception would be for the Phase 1 Cycle 2: In the 7-day schedule, veliparib in Cycle 2 will be administered on Days 2 to 5 and for the 14-day schedule, Days 2 to 12 (veliparib dose on Cycle 2 Days –2 and –1 and Cycle 2 Day 1 will be omitted to allow for the evaluation of drug-drug interaction of veliparib with etoposide).

Upon completion of 4 cycles of combination therapy, subjects without evidence of disease progression will continue on veliparib 400 mg BID until disease progression or unacceptable toxicity. Subjects who will be receiving prophylactic cranial irradiation (PCI) will have maintenance veliparib interrupted for the duration of radiotherapy.

All subjects will be monitored for DLTs during the DLT observation period (Cycle 1 Day –2 to pre-dose Cycle 2 Day 1), and treatment-related adverse events (AEs) will be evaluated throughout the course of the study for evidence of acute, delayed, or cumulative toxicities.

The dose levels of veliparib to be evaluated in the dose-escalation portion of this study were determined based on the outcome of prior clinical studies of veliparib as well as on pre-clinical toxicology, toxicokinetic, and nonclinical anti-tumor efficacy studies. The following dose levels may be evaluated in the dose-escalation portion of the study: 80, 120, 160, 200, and 240 mg BID. Reduced dose levels may be evaluated based upon review of subject safety and PK data. Intermediate dose levels may be evaluated based upon review of subject safety including, but not limited to, Grade 2 study-drug related AEs. If the MTD is not reached at veliparib 200 mg BID dose level, higher dose levels (with no more than 25% veliparib dose increments, and not exceeding single agent veliparib RPTD of 400 mg BID) may be evaluated at the discretion of the sponsor. The alternative dosing schedules can include dosing veliparib Day –2 to 12 (14-day schedule) and/or Day –2 to 19 (continuous schedule) of 21 day Cycle.

Methodology (Continued):

Phase 1 Dose Escalation (Continued):

The initial dose for these schedules will be 200 mg BID or the maximum administered dose (MAD), not exceeding the MTD, in the 7-day schedule. The 14-day schedule will be explored prior to continuous dosing schedule. Reduced or interim dose levels may be evaluated based on review of the safety and PK.

A "3 + 3" escalation rule will be used for the dose-escalation portion of this study, with a condition applied for the Dose Level 1, which will allow 3 additional subjects to be entered in Dose Level 1 if 2 of 6 initial subjects experience DLTs. Enrollment of the 3 additional subjects at all dose levels will depend on a review of the specific DLTs observed and discussion with the Investigators.

Dose-Escalation Criteria:

AEs, clinical laboratory results, and vital signs will be assessed throughout the study in each dose-escalation cohort.

DLTs will be assessed in each dose-escalation cohort during the DLT observation period (Cycle 1 Day –2 to pre-dose on Cycle 2 Day 1). Based on the safety and tolerability of study drugs after the first cycle of treatment has been completed in at least 3 subjects, escalation to a subsequent dose level or expansion of the current dose level will occur based upon the following criteria:

Methodology (Continued):
Dose-Escalation Criteria (Continued):

Number of Subjects with DLT in the First Cycle	Escalation Decision Rule
0 out of 3	Enter 3 subjects at the next dose level.
1 out of 3	Add 3 more subjects at current dose level. If AbbVie or the investigator considers the DLT(s) clinically significant, AbbVie will determine if it is appropriate to add more patients at this dose level. • If < 2 of 6 subjects (or < 33% of subjects) experience DLT, dose escalation will proceed to the next dose level. • If ≥ 2 of total 6 subjects (or ≥ 33% of subjects) experience DLTs, then dose escalation will be stopped.*
≥ 2 out of 3 or 6	Dose escalation will be stopped. *Additional subjects will be enrolled at the previous lower dose level as needed. The following exceptions apply to Dose Level 1: • If 2 of 6 initial subjects at Dose Level 1 experience DLTs, 3 additional subjects may be entered and the cohort will be expanded up to 9 subjects for further DLT assessment. o Enrollment of the 3 additional subjects will depend on a review of the specific DLTs observed and discussion with the Investigators. • If 2 of 9 subjects at Dose Level 1 experience DLTs, then escalation to the next dose level may proceed. • If > 2 of 9 subjects in Dose Level 1 experience drug-related DLTs, dose-escalation will stop.

* If 2 out of 6 subjects experience different DLTs, for example nausea and neutropenia, the data will be reviewed by the investigator and AbbVie to determine if 3 additional subjects should be added at that dose level. If 3 subjects will be added and none experience DLTs, this dose level will be declared the MTD.

An MTD and/or maximum administered dose (MAD), and RPTD, will be determined. The MTD is defined as the maximum dose at which < 2 of 6 or ≤ 2 of 9 subjects experience a DLT during the DLT observation period. The MAD is defined as the highest dose tested. Both MAD and MTD may be determined independently for each tested dosing schedule of veliparib. The RPTD and schedule will be determined based on the assessment of the observed toxicities, the MTD or MAD, and the overall safety profile of the study drug. The RPTD cannot exceed the lower of MTD or MAD. At the RPTD and schedule, additional subjects will be added as needed so that a total of at least 9 subjects will be treated at the RPTD during the dose escalation part of the study.

Methodology (Continued):

DLT Definition:

DLT is defined as any of the following drug-related toxicities occurring during the DLT observation period in any of the dose-escalation cohorts, with grading according to the National Cancer Institute (NCI) Common Toxicity Criteria for Adverse Events (CTCAE), Version 4.0:

1. Cycle 1 events associated with treatment delay > 14 days in initiating Cycle 2:
   a. Grade 4 thrombocytopenia (platelets < 25.0×10^9/L)
   b. Grade 4 neutropenia (absolute neutrophil count (ANC) < 0.5×10^9/L)
   c. Grade 3 febrile neutropenia with fever lasting for > 7 days
   d. Grade 4 febrile neutropenia of any duration

   NOTE: Delay of more than 14 days in initiating Cycle 2 due to factors not directly related to treatment-emergent toxicity will not be considered a DLT.
2. Grade ≥ 3 non-hematologic toxicity that represents at least 2 grade increase from baseline and is attributed to veliparib treatment:
   a. Exclusion: nausea and vomiting lasting ≤ 48 hours or inadequately treated
   b. Exclusion: electrolyte abnormalities resolving within ≤ 24 hours
   c. Exclusion: hypersensitivity reactions
   d. Exclusion: alopecia
3. Grade 2 non-hematologic toxicity that represents at least 2 grade increase from baseline, is attributed to veliparib treatment and requires a treatment delay of > 14 days in initiation of Cycle 2
4. Any toxicity that represents at least 2 grade increase from baseline, is attributed to veliparib treatment and requires at least one of:
   a. Dose modification within Cycle 1
   b. Omission of carboplatin, > 1 daily etoposide dose, or > 30% veliparib doses in Cycle 1

Subjects experiencing DLT(s) during DLT observation period (Cycle 1 Day –2 to pre-dose Cycle 2 Day 1) will require an interruption and possible discontinuation from further participation in the study. Veliparib may be reintroduced at a reduced dose, if the toxicity returns to ≤ Grade 1 or to baseline if Grade 2 at study entry. All decisions regarding continued dosing for individual subjects who experience a DLT will be medically managed by the investigator in conjunction with the AbbVie Medical Monitor.

Pharmacokinetics:

Pharmacokinetics of veliparib and etoposide will be assessed to determine the drug-drug interactions. Further pharmacokinetics of carboplatin will be assessed on Day 1 of Cycle 1.

Phase 2

In the Phase 2 double-blinded portion of the study subjects with treatment-naïve ED SCLC will be randomized to one of three treatment arms in 1:1:1 ratio:

- Arm A: veliparib in combination with carboplatin/etoposide followed by veliparib monotherapy
- Arm B: veliparib in combination with carboplatin/etoposide followed by placebo monotherapy
- Arm C: placebo in combination with carboplatin/etoposide followed by placebo monotherapy

Methodology (Continued):

Dose-Escalation Criteria (Continued):

Phase 2 (Continued):

Subjects in all Phase 2 study arms will receive a minimum of 4 cycles of combination therapy unless disease progression or unacceptable toxicity warrants earlier discontinuation from the treatment. Additional 2 cycles of combination therapy (e.g., up to a total of 6 cycles) may be administered at the investigators discretion if subject status at the completion of initial 4 cycles warrants continued treatment. In the combination cycles of Arms A and B, veliparib will be administered at the RPTD defined in the Phase 1 portion of the study, Arm C will receive matching placebo. After the completion of at least 4 chemotherapy combination cycles subjects without evidence of disease progression will receive veliparib at 400 mg BID continuous dosing (Arms A), or matching placebo (Arms B and C), until disease progression or unacceptable toxicity occurs.

Subjects who will be receiving prophylactic cranial irradiation (PCI) will have maintenance veliparib interrupted for the duration of radiotherapy.

Subject randomization for Phase 2 will be stratified by baseline LDH level (> ULN versus ≤ ULN), and gender.

Pharmacodynamics (Dose Escalation and Phase 2):

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.

Tumor Assessments and Safety Follow-Up

Tumor assessments will be performed until disease progression. Tumor assessment and assessment of response will occur every 6 weeks (± 1 week) for the first 24 weeks after the first dose of study drugs, then every 9 weeks (± 1 week) thereafter. Tumor response will be determined according to the Response Evaluation Criteria in Solid Tumors (RECIST), Version 1.1. Subjects will continue on study until they meet defined discontinuation criteria. When the investigator has determined that a subject should discontinue the study, a Final Visit will be conducted. Subjects will have a 30-Day Safety Follow-Up Visit following the last dose of study drugs or placebo (dependent on cohort). If the subject begins another treatment regimen directly following protocol treatment and if a 30-Day Follow-Up Visit is not possible, all adverse events ongoing as of the end of study must be followed to a satisfactory conclusion.

Diagnosis and Main Criteria for Inclusion/Exclusion:

Inclusion:

1. Subject has histologically or cytologically confirmed ED SCLC which is newly diagnosed and chemotherapy naïve.
2. Phase 1 ONLY: histologically or cytologically confirmed advanced/metastatic solid tumors for which carboplatin/etoposide treatment is considered appropriate.
3. Subject in Phase 2 only: must have measureable disease per RECIST 1.1.
4. Subjects with ED SCLC must consent to provide available archived formalin fixed paraffin embedded (FFPE) tissue sample of SCLC lesion (primary or metastatic) for central review and biomarker analysis.
5. Subject has an Eastern Cooperative Oncology Group (ECOG) performance score of 0 to 1.
6. Subject must be ≥ 18 years of age.

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

Inclusion (Continued):

7. Subject must have adequate hematologic, renal and hepatic function as follows:
   - Bone Marrow: Absolute neutrophil count ANC ≥ 1,500/mm^3 (1.5×10^9/L); White blood cells ≥ 3,000/mm^3 (3×10^9/L); Platelets ≥ 100,000/mm^3 (100×10^9/L); Hemoglobin ≥ 9 g/dL (5.58 mmol/L)
   - Renal function: creatinine ≤ ULN or if creatinine > ULN calculated creatinine clearance via the Cockroft Gault formula of ≥ 50 mL/min
   - Hepatic function:
     - Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 × upper limits of normal (ULN). For subjects with liver metastases, AST and ALT ≤ 5 × ULN;
     - Bilirubin: ≤ 1.5 × ULN; for subjects with Gilbert's syndrome bilirubin > 1.5 × ULN is allowed if no symptoms of compromised liver function are present.
8. Subject must be able to swallow pills.
9. Female and male patients of fertile age, and/or their partners should use contraception. If male, subject and subject's female partner(s) of childbearing potential should practice at least one of the following methods of birth control. If female, subject must be either postmenopausal for at least 1 year, surgically sterile (bilateral tubal ligation, bilateral oophorectomy or hysterectomy), or the subject and the subject's male partner(s) practicing at least one of the following methods of birth control:
   - total abstinence from sexual intercourse (if it is the subject's preferred and usual lifestyle; for minimum one complete menstrual cycle prior to study drug administration and to extend 6 months after treatment);
   - vasectomized subject or partner(s);
   - hormonal contraceptives (oral, parenteral or transdermal) for at least 90 days prior to study drug administration for the subject or subject's female partner(s);
   - intrauterine device (IUD) for the subject or subject's female partner(s); or
   - double-barrier method (condoms, contraceptive sponge, diaphragm or vaginal ring with spermicidal jellies or creams) for the subject or subject's female partner(s).

   If hormonal contraceptives are used, the specific contraceptive must have been used for at least 90 days prior to study drug administration. If the subject or subject's female partner(s) is currently using a hormonal contraceptive, she should also use a barrier method during this study and for 6 months (or per local label) after study completion.

   Female subjects must have negative results for pregnancy tests performed:
   - at Screening on a serum specimen obtained within 7 days prior to initial study drug administration, and
   - prior to dosing on a urine sample obtained C1D-2 unless the serum pregnancy test was collected within 7 days of C1D-2.
10. Must voluntarily sign and date each 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):

Exclusion:

1. Phase 1 ONLY: Subject has had any prior anti-cancer therapy other than:
   - Hormonal, non-myelosuppressive, biologic, targeted, or immune therapy (must be completed ≥ 4 weeks prior to Cycle 1 Day –2).
   - One line of cytotoxic chemotherapy (must be completed ≥ 4 weeks prior to Cycle 1 Day –2).
   - Adjuvant/neoaduvant radiotherapy (must be completed ≥ 12 months prior to Cycle 1 Day –2, with field not involving > 10% of bone marrow reserve).
   - Tumor lesion irradiation with intent of symptom palliation ≥ 4 weeks prior Cycle 1 Day –2.
2. Phase 2 ONLY: Subject has had any prior chemotherapy, radiotherapy, investigational anti-cancer agents or biologic therapy for the disease under study. Single non-target lesion irradiation with intent of symptom palliation is allowed if ≥ 2 weeks prior Cycle 1 Day –2.
3. Subject has known hypersensitivity to etoposide, platinum compounds or veliparib.
4. Phase 1 ONLY: Subject has received prior myelopoietic growth factors.
5. Subject has current central nervous system (CNS) or leptomeningeal metastases or history of CNS or leptomeningeal metastases. If CNS progression is suspected, a head CT should be performed at screening.
6. Subject has a history of seizures within 12 months of Cycle 1 Day –2 or diagnosed neurological condition placing subject at the increased risk of seizures.
7. Subject has received traditional herbal anti-cancer medicine (e.g., Chinese, Asian etc.) within 14 days prior to Cycle 1 Day –2.
8. Subject has had major surgery within 6 weeks prior to Cycle 1 Day –2 (subjects must have completely recovered from any previous surgery prior to Cycle 1 Day –2).
9. Subject has clinically significant and uncontrolled major medical condition(s) including but not limited to:
   - Uncontrolled nausea/vomiting/diarrhea;
   - Active uncontrolled infection;
   - History of hepatitis B (HBV) with surface antigen (HBsAg) positivity within 3 months prior to the date of informed consent for this study (if no test has been performed within 3 months, it must be done at screening);
   - History of hepatitis C (HCV) with HCV RNA positivity within 3 months prior to the date of informed consent for this study (if no test has been performed within 3 months it must be done at screening);
   - Symptomatic congestive heart failure (New York Heart Association [NYHA] class ≥ II);
   - Unstable angina pectoris or cardiac arrhythmia;
   - Psychiatric illness/social situation that would limit compliance with study requirements;
   - Any other medical condition, which in the opinion of the Investigator, places the subject at an unacceptably high risk for toxicities.
10. Subject is pregnant or lactating.

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

Exclusion (Continued):

11. The subject has a history of another active 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, breast ductal carcinoma in situ [DCIS]).

Questions regarding the eligibility of individual subjects should be directed to the AbbVie Medical Monitor.

Investigational Products:	Veliparib
Doses:	Dose escalation cohorts: 80, 120, 160 and 200 mg BID (higher doses up to 400 mg BID may be tested) Phase 2: RPTD; Continuous monotherapy maintenance: 400 mg BID
Mode of Administration:	Oral
Investigational Products:	Placebo – BID Phase 2 ONLY
Doses:	Matching capsules for RPTD Monotherapy maintenance: matching capsules for 400 mg BID continuous
Mode of Administration:	Oral
Reference Therapy:	Carboplatin
Doses:	AUC 5 mg/mL*min
Mode of Administration:	Intravenous infusion
Reference Therapy:	Etoposide
Doses:	100 mg/m^2
Mode of Administration:	Intravenous infusion

Duration of Treatment:

Subject will remain on study drug until disease progression or unacceptable toxicity.

Criteria for Evaluation:

Efficacy:

Progression-free survival (PFS) will be derived according to disease progression (radiographic progression per RECIST version 1.1 or clinical disease progression) or death. Radiographic tumor assessments for response will be conducted by CT scanning at baseline, every 6 weeks for the first 24 weeks after beginning therapy, then every 9 weeks until disease progression.

Objective response rate (ORR) will be derived per RECIST version 1.1. Radiographic tumor assessments for response will be conducted by CT scanning at baseline, every 6 weeks for 24 weeks after beginning therapy, then every 9 weeks until disease progression.

Duration of overall response (DOR) will be derived according to disease progression (radiographic progression per RECIST version 1.1 or clinical disease progression).

Criteria for Evaluation (Continued):

Efficacy (Continued):

Overall survival will be determined by the Investigator at assessments throughout therapy. After the final visit, survival information will be collected via the Interactive Response Technology (IRT) at two month intervals (or as requested by sponsor to support data analysis).

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

Pharmacokinetic:

Blood samples for pharmacokinetics of veliparib, carboplatin and etoposide will be collected at designated time points throughout the study. Pharmacokinetics of veliparib and etoposide will be assessed to determine the drug-drug interactions. In addition, pharmacokinetics of carboplatin will be determined.

Pharmacodynamic:

Research to find biomarkers that may be predictive of veliparib activity will be conducted. Serum, plasma, blood and archived tissue samples will be collected at designated time points throughout the study.

Pharmacogenetic:

DNA samples may be analyzed for genetic factors contributing to the subject's response to veliparib, or other study treatment, in terms of pharmacokinetics, efficacy, tolerability and safety**.**

Safety:

Adverse events, laboratory profiles, physical examinations, vital signs and neurological assessments will be evaluated and recorded throughout the study.

Statistical Methods:

Efficacy:

The following end point will be analyzed using data obtained from subjects in Phase 1:

Objective Response Rate

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

The following end point will be analyzed using data obtained from subjects in Phase 2:

Progression-Free Survival

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

Overall Survival

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

Objective Response Rate

The proportion of subjects with objective response (CR or PR) as assessed by the investigator using RECIST 1.1 will be evaluated for randomized subjects.

Statistical Methods (Continued):

Efficacy (Continued):

Duration of Overall Response

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

Performance Status

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

Pharmacokinetic:

Plasma concentrations of veliparib, etoposide, and carboplatin and pharmacokinetic parameter values will be tabulated for each subject and each dose level, and summary statistics will be computed for each sampling time and each parameter.

The effects of co-administration of veliparib on etoposide pharmacokinetics will be addressed by analyzing the Cycle 1, Day 1 (veliparib with carboplatin and etoposide) and Cycle 2 Day 1 (carboplatin and etoposide alone) etoposide pharmacokinetic variables, including T_{max}, dose normalized C_{max} and dose normalized AUC.

Pharmacodynamic:

Biomarker results will be tabulated for each subject and each regimen, and summary statistics will be computed for each sampling time and each parameter. The relationship between biomarker status and clinical outcome or drug exposure may be examined.

Safety:

- The safety of veliparib in combination with carboplatin/etoposide will be assessed by evaluating the study drugs exposure, adverse events, serious adverse events, all deaths, as well as changes in laboratory determinations and vital sign parameters. Safety will be summarized per dose level using descriptive statistics for the dose escalation cohorts and per treatment arm in Phase 2.
- RPTD will be determined based on the rate of DLTs and overall tolerability of the combination of veliparib, carboplatin and etoposide with at least 9 subjects treated at the RPTD in Phase 1 and will be further evaluated in Phase 2.

Has been changed to read:

AbbVie Inc.	**Protocol Number:** M14-361
Name of Study Drug: Veliparib	**Phase of Development:** 1 – 2
Name of Active Ingredient: Veliparib	**Date of Protocol Synopsis:** 22 November 2016
Protocol Title: A Phase 1 Dose Escalation and Phase 2 Randomized Double-Blind Study of Veliparib in Combination with Carboplatin and Etoposide as a Therapy of Treatment-Naïve Extensive Stage Disease Small Cell Lung Cancer	
Objectives: **Phase 1 Dose Escalation:** Primary Objectives: ● To establish the Maximum Tolerated Dose (MTD) and to establish the Recommended Phase 2 Dose (RPTD) and schedule for veliparib in combination with carboplatin and etoposide. ● To evaluate the pharmacokinetic interaction between veliparib and etoposide. Secondary Objective: ● To evaluate the safety of maintenance veliparib monotherapy at 400 mg twice daily (BID) in subjects completing 4 cycles of carboplatin, etoposide and veliparib without evidence of disease progression. **Phase 2 Randomized Double-Blind:** Primary Objective: ● To evaluate if veliparib in combination with carboplatin and etoposide followed by veliparib maintenance monotherapy results in improved progression free survival (PFS) versus placebo in combination with carboplatin and etoposide followed by placebo monotherapy in subjects with treatment-naïve ED SCLC. Secondary Objectives: ● To evaluate if veliparib in combination with carboplatin and etoposide followed by placebo monotherapy results in improved progression free survival (PFS) versus placebo in combination with carboplatin and etoposide followed by placebo monotherapy in subjects with treatment-naïve ED SCLC. ● To evaluate if veliparib in combination with carboplatin and etoposide results in improved objective response rate (ORR) versus placebo in combination with carboplatin and etoposide at the time of completion of combination therapy. ● To evaluate if veliparib in combination with carboplatin and etoposide followed by veliparib maintenance monotherapy results in improved overall survival (OS) versus placebo in combination with carboplatin and etoposide followed by placebo monotherapy. ● To evaluate if veliparib in combination with carboplatin and etoposide followed by placebo monotherapy results in improved overall survival (OS) versus placebo in combination with carboplatin and etoposide followed by placebo monotherapy. ● To further evaluate the safety of veliparib in combination with carboplatin and etoposide followed by veliparib maintenance monotherapy.	

Objectives (Continued):

Tertiary Objectives:

- To evaluate if veliparib in combination with carboplatin and etoposide followed by veliparib maintenance monotherapy results in improved duration of overall response (DOR) versus placebo in combination with carboplatin and etoposide followed by placebo monotherapy.
- To evaluate if veliparib in combination with carboplatin and etoposide followed by placebo monotherapy results in improved duration of overall response (DOR) versus placebo in combination with carboplatin and etoposide followed by placebo monotherapy.
- To compare PFS and OS of subjects treated with veliparib in combination with carboplatin and etoposide followed by veliparib maintenance to PFS and OS of subjects treated with veliparib in combination with carboplatin and etoposide followed by placebo maintenance.
- To evaluate performance status.

Investigators:

Multicenter

Study Sites:

Approximately 65 globally

Study Population:

Phase 1: Histologically or cytologically confirmed extensive stage disease SCLC or any other advanced/metastatic solid tumor for which carboplatin/etoposide treatment is considered appropriate.

Phase 2: Histologically or cytologically confirmed treatment-naïve extensive stage disease SCLC.

Number of Subjects to be Enrolled:

Phase 1 Dose Escalation portion: Approximately: 35

Phase 2 Randomized Double-Blind portion: Approximately: 180

Methodology:

This is a Phase 1 dose escalation and Phase 2 randomized double-blind study.

Screening Procedures:

Screening procedures should be performed within 28 days of Cycle 1 Day –2. If the screening visit is performed greater than 7 days prior to Cycle 1 Day –2, the physical exam, laboratory tests, and pregnancy test (for female subjects of childbearing potential) must be repeated on Cycle 1 Day –2. Vital signs and performance status assessments will be performed on Cycle 1 Day –2 for all subjects. Baseline radiographic tumor assessments per computed tomography (CT) with IV contrast/magnetic resonance imaging (MRI) of the chest, abdomen, and pelvis will be conducted within 21 days prior to Cycle 1 Day –2. If CNS metastases are suspected, a head CT must also be performed at screening. 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.

Phase 1 Dose Escalation:

For subjects in the dose escalation portion of the study, each subject will participate in only 1 dose group and there is no provision for intra-subject dose-escalation. Study procedures will be provided in the Schedule of Assessments and Pharmacokinetic and Pharmacodynamic tables.

Methodology (Continued):

Phase 1 Dose Escalation (Continued):

The Phase 1 portion of this study will evaluate the safety, tolerability, dose limiting toxicities (DLTs), RPTD, pharmacokinetics (PK), and pharmacodynamics (PD), of veliparib/carboplatin/etoposide combination in subjects diagnosed with Extensive Stage Disease Small Cell Lung Cancer or, other advanced/metastatic solid tumor for which carboplatin/etoposide treatment is considered appropriate. Veliparib will be administered on Days –2 to 5 (7-day schedule), and, if the MTD of the 7-day schedule is not reached at ≤ 200 mg BID veliparib dose level, may be administered on Days –2 to 12 (14-day schedule) and/or Days –2 to 19 (continuous schedule) orally BID, in combination with carboplatin area under the curve 5 mg/mL*min administered on Day 1 and etoposide 100 mg/m^2 administered on Days 1 to 3 via intravenous (IV) infusion in 21-day cycles. An exception would be for the Phase 1 Cycle 2: In the 7-day schedule, veliparib in Cycle 2 will be administered on Days 2 to 5 and for the 14-day schedule, Days 2 to 12 (veliparib dose on Cycle 2 Days –2 and –1 and Cycle 2 Day 1 will be omitted to allow for the evaluation of drug-drug interaction of veliparib with etoposide).

Upon completion of 4 cycles of combination therapy, subjects without evidence of disease progression will continue on veliparib 400 mg BID until disease progression or unacceptable toxicity. Subjects who will be receiving prophylactic cranial irradiation (PCI) will have maintenance veliparib interrupted for the duration of radiotherapy.

All subjects will be monitored for DLTs during the DLT observation period (Cycle 1 Day –2 to pre-dose Cycle 2 Day 1), and treatment-related adverse events (AEs) will be evaluated throughout the course of the study for evidence of acute, delayed, or cumulative toxicities.

The dose levels of veliparib to be evaluated in the dose-escalation portion of this study were determined based on the outcome of prior clinical studies of veliparib as well as on pre-clinical toxicology, toxicokinetic, and nonclinical anti-tumor efficacy studies. The following dose levels may be evaluated in the dose-escalation portion of the study: 80, 120, 160, 200, and 240 mg BID. Reduced dose levels may be evaluated based upon review of subject safety and PK data. Intermediate dose levels may be evaluated based upon review of subject safety including, but not limited to, Grade 2 study-drug related AEs. If the MTD is not reached at veliparib 200 mg BID dose level, higher dose levels (with no more than 25% veliparib dose increments, and not exceeding single agent veliparib RPTD of 400 mg BID) may be evaluated at the discretion of the sponsor. The alternative dosing schedules can include dosing veliparib Day –2 to 12 (14-day schedule) and/or Day –2 to 19 (continuous schedule) of 21 day Cycle. The initial dose for these schedules will be 200 mg BID or the maximum administered dose (MAD), not exceeding the MTD, in the 7-day schedule. The 14-day schedule will be explored prior to continuous dosing schedule. Reduced or interim dose levels may be evaluated based on review of the safety and PK.

A "3 + 3" escalation rule will be used for the dose-escalation portion of this study, with a condition applied for the Dose Level 1, which will allow 3 additional subjects to be entered in Dose Level 1 if 2 of 6 initial subjects experience DLTs. Enrollment of the 3 additional subjects at all dose levels will depend on a review of the specific DLTs observed and discussion with the Investigators.

Dose-Escalation Criteria:

AEs, clinical laboratory results, and vital signs will be assessed throughout the study in each dose-escalation cohort.

Methodology (Continued):

Dose-Escalation Criteria (Continued):

DLTs will be assessed in each dose-escalation cohort during the DLT observation period (Cycle 1 Day –2 to pre-dose on Cycle 2 Day 1). Based on the safety and tolerability of study drugs after the first cycle of treatment has been completed in at least 3 subjects, escalation to a subsequent dose level or expansion of the current dose level will occur based upon the following criteria:

Number of Subjects with DLT in the First Cycle	Escalation Decision Rule
0 out of 3	Enter 3 subjects at the next dose level.
1 out of 3	Add 3 more subjects at current dose level. If AbbVie or the investigator considers the DLT(s) clinically significant, AbbVie will determine if it is appropriate to add more patients at this dose level. • If < 2 of 6 subjects (or < 33% of subjects) experience DLT, dose escalation will proceed to the next dose level. • If ≥ 2 of total 6 subjects (or ≥ 33% of subjects) experience DLTs, then dose escalation will be stopped.*
≥ 2 out of 3 or 6	Dose escalation will be stopped. *Additional subjects will be enrolled at the previous lower dose level as needed. The following exceptions apply to Dose Level 1: • If 2 of 6 initial subjects at Dose Level 1 experience DLTs, 3 additional subjects may be entered and the cohort will be expanded up to 9 subjects for further DLT assessment. o Enrollment of the 3 additional subjects will depend on a review of the specific DLTs observed and discussion with the Investigators. • If 2 of 9 subjects at Dose Level 1 experience DLTs, then escalation to the next dose level may proceed. • If > 2 of 9 subjects in Dose Level 1 experience drug-related DLTs, dose-escalation will stop.

* If 2 out of 6 subjects experience different DLTs, for example nausea and neutropenia, the data will be reviewed by the investigator and AbbVie to determine if 3 additional subjects should be added at that dose level. If 3 subjects will be added and none experience DLTs, this dose level will be declared the MTD.

An MTD and/or maximum administered dose (MAD), and RPTD, will be determined. The MTD is defined as the maximum dose at which < 2 of 6 or ≤ 2 of 9 subjects experience a DLT during the DLT observation period. The MAD is defined as the highest dose tested. Both MAD and MTD may be determined independently for each tested dosing schedule of veliparib. The RPTD and schedule will be determined based on the assessment of the observed toxicities, the MTD or MAD, and the overall safety profile of the study drug. The RPTD cannot exceed the lower of MTD or MAD. At the RPTD and schedule, additional subjects will be added as needed so that a total of at least 9 subjects will be treated at the RPTD during the dose escalation part of the study.

Methodology (Continued):

DLT Definition:

DLT is defined as any of the following drug-related toxicities occurring during the DLT observation period in any of the dose-escalation cohorts, with grading according to the National Cancer Institute (NCI) Common Toxicity Criteria for Adverse Events (CTCAE), Version 4.0:

1. Cycle 1 events associated with treatment delay > 14 days in initiating Cycle 2:
   a. Grade 4 thrombocytopenia (platelets < 25.0×10^9/L)
   b. Grade 4 neutropenia (absolute neutrophil count (ANC) < 0.5×10^9/L)
   c. Grade 3 febrile neutropenia with fever lasting for > 7 days
   d. Grade 4 febrile neutropenia of any duration

   NOTE: Delay of more than 14 days in initiating Cycle 2 due to factors not directly related to treatment-emergent toxicity will not be considered a DLT.
2. Grade ≥ 3 non-hematologic toxicity that represents at least 2 grade increase from baseline and is attributed to veliparib treatment:
   a. Exclusion: nausea and vomiting lasting ≤ 48 hours or inadequately treated
   b. Exclusion: electrolyte abnormalities resolving within ≤ 24 hours
   c. Exclusion: hypersensitivity reactions
   d. Exclusion: alopecia
3. Grade 2 non-hematologic toxicity that represents at least 2 grade increase from baseline, is attributed to veliparib treatment and requires a treatment delay of > 14 days in initiation of Cycle 2
4. Any toxicity that represents at least 2 grade increase from baseline, is attributed to veliparib treatment and requires at least one of:
   a. Dose modification within Cycle 1
   b. Omission of carboplatin, > 1 daily etoposide dose, or > 30% veliparib doses in Cycle 1

Subjects experiencing DLT(s) during DLT observation period (Cycle 1 Day –2 to pre-dose Cycle 2 Day 1) will require an interruption and possible discontinuation from further participation in the study. Veliparib may be reintroduced at a reduced dose, if the toxicity returns to ≤ Grade 1 or to baseline if Grade 2 at study entry. All decisions regarding continued dosing for individual subjects who experience a DLT will be medically managed by the investigator in conjunction with the AbbVie TA MD.

Pharmacokinetics:

Pharmacokinetics of veliparib and etoposide will be assessed to determine the drug-drug interactions. Further pharmacokinetics of carboplatin will be assessed on Day 1 of Cycle 1.

Phase 2 Randomized Double-Blind

The veliparib dose and schedule for the Phase 2 was determined to be 240 mg BID on a 14 day schedule based on the analysis of Phase 1 data.

Approximately 180 total subjects with treatment-naïve ED SCLC will be enrolled at the 240 mg BID veliparib/placebo dose and 14 day schedule in the Phase 2 double-blinded portion of the study. They will be randomized in a 1:1:1 ratio to one of three treatment arms:

- Arm A: veliparib in combination with carboplatin/etoposide followed by veliparib monotherapy
- Arm B: veliparib in combination with carboplatin/etoposide followed by placebo monotherapy

Methodology (Continued):

Phase 2 Randomized Double-Blind (Continued)

- Arm C: placebo in combination with carboplatin/etoposide followed by placebo monotherapy

Subjects in all Phase 2 study arms will receive a minimum of 4 cycles of combination therapy unless disease progression or unacceptable toxicity warrants earlier discontinuation from the treatment. Additional 2 cycles of combination therapy (e.g., up to a total of 6 cycles) may be administered at the investigators discretion if subject status at the completion of initial 4 cycles warrants continued combination treatment and/or if local SOC guidelines require 6 cycles of platinum-based therapy. In the combination cycles of Arms A and B, subjects will receive veliparib at 240 mg BID on a 14-day schedule, Arm C will receive matching placebo. After completion of the chemotherapy combination cycles (at least 4), subjects without evidence of disease progression will receive veliparib at 400 mg BID continuous dosing (21-day cycles) (Arms A), or matching placebo (Arms B and C) as per treatment arm assignment, until disease progression or unacceptable toxicity occurs.

Subjects who will be receiving prophylactic cranial irradiation (PCI) will have maintenance veliparib interrupted for the duration of radiotherapy.

Subject randomization for Phase 2 will be stratified by baseline LDH level (> ULN versus ≤ ULN), and gender.

Pharmacodynamics (Phase 1 Dose Escalation and Phase 2 Randomized Double-Blind):

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.

Tumor Assessments and Safety Follow-Up

Tumor assessments will be performed until radiographic disease progression. Tumor assessment and assessment of response will occur every 6 weeks (± 1 week) from C1D-2 for the first 24 weeks (Phase 1) or 30 weeks (Phase 2), then every 9 weeks (± 1 week) thereafter. Tumor response will be determined according to the Response Evaluation Criteria in Solid Tumors (RECIST), Version 1.1. Subjects will continue on study until they meet defined discontinuation criteria. When the investigator has determined that a subject should discontinue the study, a Final Visit will be conducted. Subjects will have a 30-Day Follow-Up Visit following the last dose of study drugs or placebo (Phase 2, dependent on treatment arm). If the subject begins another treatment regimen directly following protocol treatment and if a 30-Day Follow-Up Visit is not possible, all adverse events ongoing as of the end of study must be followed to a satisfactory conclusion.

Diagnosis and Main Criteria for Inclusion/Exclusion:

Inclusion:

1. Subject has histologically or cytologically confirmed ED SCLC which is newly diagnosed and chemotherapy naïve.
2. Phase 1 ONLY: histologically or cytologically confirmed advanced/metastatic solid tumors for which carboplatin/etoposide treatment is considered appropriate.
3. Subject in Phase 2 ONLY: must have measureable disease per RECIST 1.1.
4. Subjects with ED SCLC must consent to provide available archived formalin fixed paraffin embedded (FFPE) tissue sample of SCLC lesion (primary or metastatic) for central review and biomarker analysis. NOTE: If sufficient tissue is unavailable for analysis, subjects will still be allowed to enroll.

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

Inclusion (Continued):

5. Subject has an Eastern Cooperative Oncology Group (ECOG) performance score of 0 to 1.
6. Subject must be ≥ 18 years of age.
7. Subject must have adequate hematologic, renal and hepatic function as follows:
   - Bone Marrow: Absolute neutrophil count ANC ≥ 1,500/mm^3 (1.5×10^9/L); White blood cells ≥ 3,000/mm^3 (3×10^9/L); Platelets ≥ 100,000/mm^3 (100×10^9/L); Hemoglobin ≥ 9 g/dL (5.58 mmol/L)
   - Renal function: creatinine ≤ ULN or if creatinine > ULN calculated creatinine clearance via the Cockroft Gault formula of ≥ 50 mL/min
   - Hepatic function:
     - Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 × upper limits of normal (ULN). For subjects with liver metastases, AST and ALT ≤ 5 × ULN;
     - Bilirubin: ≤ 1.5 × ULN; for subjects with Gilbert's syndrome bilirubin > 1.5 × ULN is allowed if no symptoms of compromised liver function are present.
8. Subject must be able to swallow pills.
9. Female and male patients of fertile age, and/or their partners should use contraception. If male, subject and subject's female partner(s) of childbearing potential must follow the contraception recommendations as described in Section 5.2.4. If female, subject must be either postmenopausal for at least 1 year, surgically sterile (bilateral tubal ligation, bilateral oophorectomy or hysterectomy), or the subject and the subject's male partner(s) must follow the contraception recommendations as described in Section 5.2.4.

   Female subjects must have negative results for pregnancy tests performed:
   - Screening on a serum specimen obtained within 7 days prior to initial study drug administration, and
   - prior to dosing on a urine sample obtained C1D-2 unless the serum pregnancy test was collected within 7 days of C1D-2.
10. Must voluntarily sign and date each informed consent, approved by an Independent Ethics Committee (IEC)/Institutional Review Board (IRB), prior to the initiation of any screening or study specific procedures.

Exclusion:

1. Phase 1 ONLY: Subject has had any prior anti-cancer therapy other than:
   - Hormonal, non-myelosuppressive, biologic, targeted, or immune therapy (must be completed ≥ 4 weeks prior to Cycle 1 Day –2).
   - One line of cytotoxic chemotherapy (must be completed ≥ 4 weeks prior to Cycle 1 Day –2).
   - Adjuvant/neoaduvant radiotherapy (must be completed ≥ 12 months prior to Cycle 1 Day –2, with field not involving > 10% of bone marrow reserve).
   - Tumor lesion irradiation with intent of symptom palliation ≥ 4 weeks prior Cycle 1 Day –2.

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

Exclusion (Continued):

2. Phase 2 ONLY: Subject has had any prior chemotherapy, radiotherapy, investigational anti-cancer agents or biologic therapy for the disease under study. Single non-target lesion irradiation with intent of symptom palliation is allowed if ≥ 2 weeks prior Cycle 1 Day –2.
3. Subject has known hypersensitivity to etoposide, platinum compounds or veliparib.
4. Phase 1 ONLY: Subject has received prior myelopoietic growth factors.
5. Subject has current central nervous system (CNS) or leptomeningeal metastases or history of CNS or leptomeningeal metastases. If CNS metastasis is suspected, a head CT should be performed at screening.
6. Subject has a history of seizures within 12 months of Cycle 1 Day –2 or diagnosed neurological condition placing subject at the increased risk of seizures.
7. Subject has received traditional herbal anti-cancer medicine (e.g., Chinese, Asian etc.) within 14 days prior to Cycle 1 Day –2.
8. Subject has had major surgery within 6 weeks prior to Cycle 1 Day –2 (subjects must have completely recovered from any previous surgery prior to Cycle 1 Day –2).
9. Subject has clinically significant and uncontrolled major medical condition(s) including but not limited to:
   - Uncontrolled nausea/vomiting/diarrhea;
   - Active uncontrolled infection;
   - History of hepatitis B (HBV) with surface antigen (HBsAg) positivity within 3 months prior to the date of informed consent for this study (if HBsAg status is unknown it must be tested at screening);
   - History of hepatitis C (HCV) with HCV RNA positivity within 3 months prior to the date of informed consent for this study (if HCV RNA status is unknown it must be tested at screening);
   - Symptomatic congestive heart failure (New York Heart Association [NYHA] class ≥ II);
   - Unstable angina pectoris or cardiac arrhythmia;
   - Psychiatric illness/social situation that would limit compliance with study requirements;
   - Any other medical condition, which in the opinion of the Investigator, places the subject at an unacceptably high risk for toxicities.
10. Subject is pregnant or lactating.
11. The subject has a history of another active 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, breast ductal carcinoma in situ [DCIS]).

Questions regarding the eligibility of individual subjects should be directed to the AbbVie TA MD.

Investigational Products:	Veliparib
Doses:	Phase 1 Dose Escalation cohorts: 80, 120, 160, 200 and 240 mg BID (higher doses up to 400 mg BID may be tested) Phase 2 Randomized Double-Blind arms: 240 mg BID Continuous monotherapy maintenance: 400 mg BID
Mode of Administration:	Oral
Investigational Products:	Placebo – BID Phase 2 ONLY
Doses:	Combination therapy: matching capsules for 240 mg BID Continuous monotherapy maintenance: matching capsules for 400 mg BID
Mode of Administration:	Oral
Reference Therapy:	Carboplatin
Doses:	AUC 5 mg/mL*min
Mode of Administration:	Intravenous infusion
Reference Therapy:	Etoposide
Doses:	100 mg/m^2
Mode of Administration:	Intravenous infusion

Duration of Treatment:

Subject will remain on study drug until disease progression or unacceptable toxicity.

Criteria for Evaluation:

Efficacy:

Progression-free survival (PFS) will be derived according to disease progression (radiographic progression per RECIST version 1.1) or death. Radiographic tumor assessments for response will be conducted by CT scanning at baseline, every 6 weeks from C1D-2 for the first 24 weeks (Phase 1) or 30 weeks (Phase 2), then every 9 weeks until disease progression.

Objective response rate (ORR) will be derived per RECIST version 1.1. Radiographic tumor assessments for response will be conducted by CT scanning at baseline, every 6 weeks from C1D-2 for the first 24 weeks (Phase 1) or 30 weeks (Phase 2), then every 9 weeks until disease progression.

Duration of overall response (DOR) will be derived according to disease progression (radiographic progression per RECIST version 1.1).

Overall survival will be determined by the Investigator at assessments throughout therapy. After the final visit, survival information will be collected via electronic data capture (EDC) at 2 month intervals (or as requested by sponsor to support data analysis).

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

Pharmacokinetic:

Blood samples for pharmacokinetics of veliparib, carboplatin (Phase 1 Dose Escalation only) and etoposide (Phase 1 Dose Escalation only) will be collected at designated time points throughout the study. Pharmacokinetics of veliparib and etoposide will be assessed to determine the drug-drug interactions. In addition, pharmacokinetics of carboplatin will be determined.

Criteria for Evaluation (Continued):

Pharmacodynamic:

Research to find biomarkers that may be predictive of veliparib activity will be conducted. Serum, plasma, blood and archived tissue samples will be collected at designated time points throughout the study.

Pharmacogenetic:

DNA samples may be analyzed for genetic factors contributing to the subject's response to veliparib, or other study treatment, in terms of pharmacokinetics, efficacy, tolerability and safety**.**

Safety:

Adverse events, laboratory profiles, physical examinations, vital signs and neurological assessments will be evaluated and recorded throughout the study.

Statistical Methods:

Efficacy:

The following end point will be analyzed using data obtained from subjects in Phase 1 and Phase 2 separately:

Objective Response Rate

The proportion of subjects with objective response (CR or PR) as assessed by the investigator using RECIST 1.1 will be calculated for all dosed subjects.

The following end point will be analyzed using data obtained from subjects in Phase 2:

Progression-Free Survival

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

Overall Survival

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

Duration of Overall Response

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

Performance Status

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

Statistical Methods (Continued):

Pharmacokinetic:

Plasma concentrations of veliparib, etoposide, and carboplatin and pharmacokinetic parameter values will be tabulated for each subject and each dose level, and summary statistics will be computed for each sampling time and each parameter.

The effects of co-administration of veliparib on etoposide pharmacokinetics will be addressed by analyzing the Cycle 1 Day 1 (veliparib with carboplatin and etoposide) and Cycle 2 Day 1 (carboplatin and etoposide alone) etoposide pharmacokinetic variables, including T_{max}, dose normalized C_{max} and dose normalized AUC.

Pharmacodynamic:

Biomarker results will be tabulated for each subject and each regimen, and summary statistics will be computed for each sampling time and each parameter. The relationship between biomarker status and clinical outcome or drug exposure may be examined.

Safety:

- The safety of veliparib in combination with carboplatin/etoposide will be assessed by evaluating the study drugs exposure, adverse events, serious adverse events, all deaths, as well as changes in laboratory determinations and vital sign parameters. Safety will be summarized per dose level using descriptive statistics for the dose escalation cohorts and per treatment arm in Phase 2.
- RPTD was determined based on the rate of DLTs and overall tolerability of the combination of veliparib, carboplatin and etoposide with at least 9 subjects treated at the RPTD in Phase 1 and will be further evaluated in Phase 2.

Section 1.3 List of Abbreviations and Definition of Terms
Subsection Abbreviations
Add: "DICOM," "IRT," "IUS," "PoR," "TA MD" and "WOCBP"

DICOM	Digital Imaging and Communications in Medicine
IRT	Interactive Response Technology
IUS	Intrauterine hormone-releasing system
PoR	Proof of Receipt
TA MD	Therapeutic Area Medical Director
WOCBP	Women of Childbearing Potential

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

This study proposes to establish the recommended Phase 2 dose and to evaluate clinical outcomes for subjects with ED SCLC treated with veliparib added to standard therapy with carboplatin and etoposide.

Has been changed to read:

The Phase 1 Dose Escalation portion of this study proposed to establish the recommended Phase 2 dose and veliparib schedule. These were determined to be veliparib 240 mg BID on Days –2 – 12 (14-Day schedule) in combination with carboplatin AUC 5 mg/ml*hr on Day 1 and etoposide 100 mg/m^2 on Days 1 – 3 of 21-Day cycle. The Phase 2 portion of this study proposes to evaluate clinical outcomes for subjects with ED SCLC treated with veliparib added to standard therapy with carboplatin and etoposide.

Section 5.1 Overall Study Design and Plan: Description
Subsection <u>Screening Procedures</u>
Delete: subsection title and text

<u>Screening Procedures</u>

Screening procedures should be performed within 28 days prior to Cycle 1 Day –2. If the screening visit is performed greater than 7 days prior to Cycle 1 Day –2, the physical exam, laboratory tests, and pregnancy test (for female subjects of childbearing potential) must be repeated on Cycle 1 Day –2. Vital signs and performance status assessments will be performed on Cycle 1 Day –2 for all subjects. Baseline radiographic tumor assessments per computed tomography (CT)/magnetic resonance imaging (MRI) of the chest, abdomen, and head will be conducted within 21 days prior to Cycle 1 Day –2.

Section 5.1 Overall Study Design and Plan: Description
Subsection Transition from Phase 1 to Phase 2
Add: new subsection title and text

Transition from Phase 1 to Phase 2

Once the veliparib RPTD and schedule is determined, the veliparib RPTD and schedule will be communicated to all participating research sites prior to the start of enrollment into the Phase 2. Subjects from the Phase 1 Dose Escalation portion are not eligible for enrollment into the Phase 2 portion, but may continue to receive veliparib, carboplatin and etoposide at the assigned dose and schedule as long as they tolerate the study drug, show no evidence of disease progression, and do not meet any of the criteria for subject discontinuation (Section 5.4.1).

Section 5.1 Overall Study Design and Plan: Description
Subsection Randomized Double-Blind Phase 2
Subsection title and text previously read:

Randomized Double-Blind Phase 2

In the Phase 2 double-blinded portion of the study, subjects with treatment-naïve ED SCLC will be randomized in a 1:1:1 ratio to one of three treatment arms:

Arm A: RPTD of veliparib in combination with carboplatin/etoposide followed by veliparib 400 mg BID monotherapy

Arm B: RPTD of veliparib in combination with carboplatin/etoposide followed by placebo monotherapy

Arm C: placebo in combination with carboplatin/etoposide followed by placebo monotherapy

Subjects in all Phase 2 study arms will receive a minimum of 4 cycles of combination therapy unless disease progression or unacceptable toxicity warrants earlier discontinuation from the treatment. Additional 2 cycles of combination therapy (e.g., up

to a total of 6 cycles) may be administered at the investigators discretion if subject status at the completion of initial 4 cycles warrants continued treatment. In the combination cycles of Arms A and B veliparib will be administered at the RPTD defined in the Phase 1 portion of the study, Arm C will receive matching placebo. After completion of the chemotherapy combination cycles (at least 4), subjects without evidence of disease progression will receive veliparib at 400 mg BID continuous dosing (Arms A), or matching placebo (Arms B and C), until disease progression or unacceptable toxicity occurs (Figure 2). Subjects who will be receiving prophylactic cranial irradiation (PCI) will have maintenance veliparib interrupted for the duration of radiotherapy as described in Section 5.2.3.2.

Subject randomization for Phase 2 will be stratified by baseline LDH level (> ULN versus ≤ ULN), and gender.

Table 6. Treatment Schematic for Combination Cycles in Phase 2

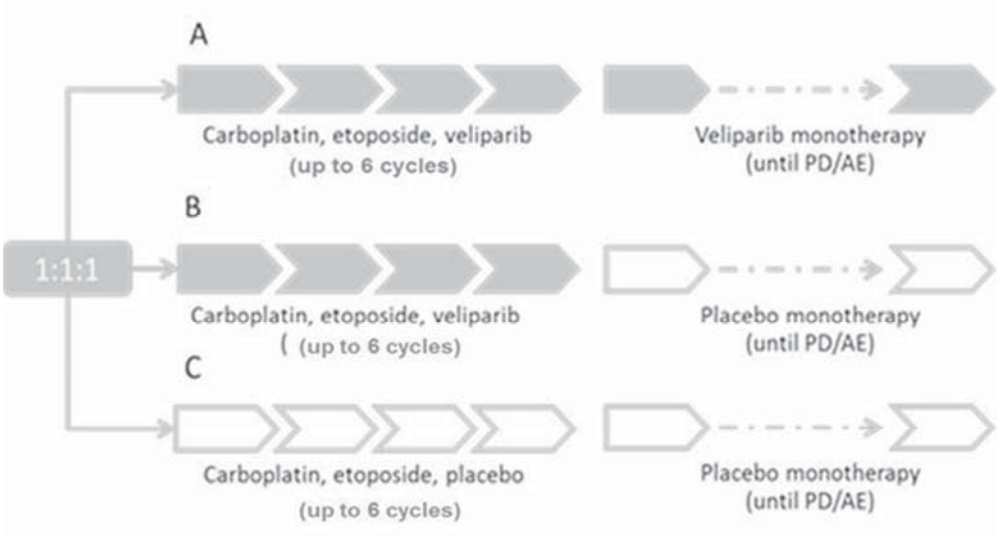
Days	**–2**	**–1**	**1**	**2**	**3**	**4**	**5**	**6 – 19**
Veliparib/Placebo	Twice a day	Twice a day	Twice a day	Twice a day	Twice a day	Twice a day	Twice a day	As RPTD
Carboplatin			Once					
Etoposide			Once	Once	Once			

Notes: Starting at Maintenance Day 1 veliparib will be dosed at 400 mg BID monotherapy continuous dosing for 21 days per cycle.

Dosing of veliparib on Days 6 – 19 will depend on the RPTD schedule, as defined in Table 1 and Table 3.

A minimum of 4 cycles of combination treatment are to be administered. If subject status at the completion of Cycle 4 warrants continued combination treatment, 2 additional combination cycles (e.g., up to a total of 6) may be administered at investigators discretion.

Figure 2. Phase 2 Treatment and Randomization Schematics



For subjects who experience toxicities due to veliparib or carboplatin/etoposide, appropriate dose modifications or dosing delays should be managed according to Section 5.7. Subsequent cycles of therapy will be administered if there is no evidence of disease progression and observed toxicities have recovered adequately as described in Section 5.7.

Has been changed to read:

Phase 2 Randomized Double-Blind

The veliparib dose and schedule for the Phase 2 was determined to be 240 mg BID on a 14 day schedule based on the analysis of Phase 1 data.

Approximately 180 total subjects with treatment-naïve ED SCLC will be enrolled at the 240 mg BID veliparib/placebo dose and 14 day schedule in the Phase 2 double-blinded portion of the study. They will be randomized in a 1:1:1 ratio to one of three treatment arms:

Arm A: veliparib 240 mg in combination with carboplatin/etoposide followed by veliparib 400 mg BID monotherapy

Arm B: veliparib 240 mg in combination with carboplatin/etoposide followed by placebo monotherapy

Arm C: placebo in combination with carboplatin/etoposide followed by placebo monotherapy

Subjects in all Phase 2 study arms will receive a minimum of 4 cycles of combination therapy unless disease progression or unacceptable toxicity warrants earlier discontinuation from the treatment. Additional 2 cycles of combination therapy (e.g., up to a total of 6 cycles) may be administered at the investigators discretion if subject status at the completion of initial 4 cycles warrants continued combination treatment and/or if local SOC guidelines require 6 cycles of platinum-based therapy. In the combination cycles of Arms A and B, subjects will receive veliparib at 240 mg BID on a 14-day schedule, Arm C will receive matching placebo. After completion of the chemotherapy combination cycles (at least 4), subjects without evidence of disease progression will receive veliparib at 400 mg BID continuous dosing (21-day cycles) (Arms A), or matching placebo (Arms B and C) as per treatment arm assignment, until disease progression or unacceptable toxicity occurs (Figure 2).

Subject randomization for Phase 2 will be stratified by baseline LDH level (> ULN versus ≤ ULN), and gender.

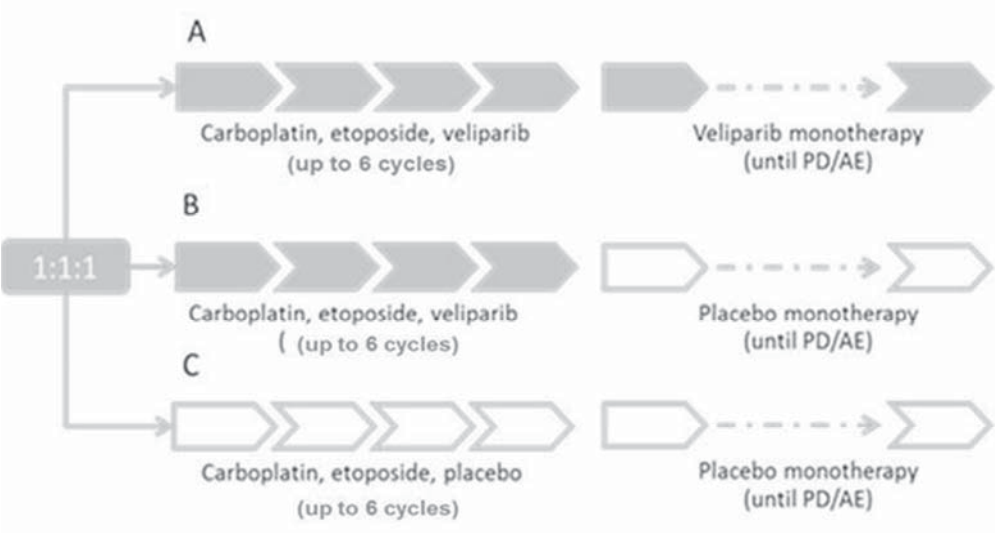
Table 6. Treatment Schematic for Combination Cycles in Phase 2

Days	**–2**	**–1**	**1**	**2**	**3**	**4 – 12**
Veliparib/Placebo	240 mg BID	240 mg BID	240 mg BID	240 mg BID	240 mg BID	240 mg BID
Carboplatin			Once			
Etoposide			Once	Once	Once	

Notes: Starting at Maintenance Day 1 veliparib will be dosed at 400 mg BID monotherapy continuous dosing for 21 days per cycle.

A minimum of 4 cycles of combination treatment are to be administered. If subject/disease status at the completion of Cycle 4 warrants continued combination treatment, up to 2 additional combination cycles (e.g., up to a total of 6) may be administered at investigators discretion.

Figure 2. Phase 2 Treatment and Randomization Schematics



For subjects who experience toxicities due to veliparib or carboplatin/etoposide, appropriate dose modifications or dosing delays should be managed according to Section 5.7. Subsequent cycles of therapy will be administered if there is no evidence of disease progression and observed toxicities have recovered adequately as described in Section 5.7.

Section 5.1 Overall Study Design and Plan: Description
Subsection Tumor Assessments and Safety Follow-Up (Phase 1 Dose Escalation and Phase 2)
Delete: subsection title and text

Tumor Assessments and Safety Follow-Up (Phase 1 Dose Escalation and Phase 2)

Tumor assessments will be performed until progression. Tumor assessment and assessment of response will occur every 6 weeks (± 1 week) for the first 24 weeks after the first dose of study drugs, then every 9 weeks thereafter (± 1 week). Tumor response

will be determined according to the Response Evaluation Criteria in Solid Tumors (RECIST), Version 1.1.

In the Phase 1 portion, subjects will receive veliparib BID in combination with carboplatin/etoposide for up to a maximum 4 cycles of treatment. In the Phase 2 portion, subjects will receive veliparib or placebo BID as applicable in combination with carboplatin/etoposide for up to 6 cycles of treatment. In Phase 1, subjects that do not progress according to a radiographic assessment (CT) at Cycle 4 may continue in the monotherapy portion veliparib or placebo as appropriate starting at Cycle 5 Day 1. In Phase 2, subjects that do not progress according to a radiographic assessment (CT) at completion of at least 4 combination chemotherapy Cycles may continue in the monotherapy portion veliparib or placebo starting at Maintenance Day 1. In the Phase 2 portion, subjects discontinuing both carboplatin and etoposide due to toxicity and without evidence of disease progression prior to the completion of 4 cycles of combination therapy may transition to monotherapy veliparib/placebo as per treatment arm assignment. All subjects will remain on study until reaching a protocol defined event of disease progression. Subjects in the Phase 2 portion of the study, who are discontinued from study treatment due to an adverse event, will remain on study/off study drugs until reaching an event of disease progression.

When an investigator has determined that a subject has met the protocol defined criteria for disease progression, as outlined in Section 5.3.3.1, a Final Visit will be conducted.

All subjects will have one Follow-Up Visit approximately 30 days after the Final Visit. 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.

In the Phase 2 portion of the study, post treatment tumor assessments (if subject discontinues before disease progression is recorded), cancer treatments and survival

information will be collected via electronic data capture (EDC) system at monthly intervals (or as requested by sponsor to support data analysis) beginning on the date the subject is registered off study and continuing for up to 2 years on all subjects until the endpoint of death, the subject has become lost to follow up, or if AbbVie terminates the study.

Section 5.2.1 Inclusion Criteria
Criterion 9 previously read:

Female and male patients of fertile age, and/or their partners should use contraception. If male, subject and subject's female partner(s) of childbearing potential should practice at least one of the following methods of birth control. If female, subject must be either postmenopausal for at least 1 year, surgically sterile (bilateral tubal ligation, bilateral oophorectomy or hysterectomy), or the subject and the subject's male partner(s) practicing at least one of the following methods of birth control:

- total abstinence from sexual intercourse (if it is the subject's preferred and usual lifestyle; for minimum one complete menstrual cycle prior to study drug administration and to extend 6 months after treatment);
- vasectomized subject or partner(s);
- hormonal contraceptives (oral, parenteral or transdermal) for at least 90 days prior to study drug administration for the subject or subject's female partner(s);
- intrauterine device (IUD) for the subject or subject's female partner(s);
- double-barrier method (condoms, contraceptive sponge, diaphragm or vaginal ring with spermicidal jellies or creams) for the subject or subject's female partner(s).

If hormonal contraceptives are used, the specific contraceptive must have been used for at least 90 days prior to study drug administration. If the subject or subject's female partner(s) is currently using a hormonal contraceptive, she should also use a barrier method during this study and for 6 months (or per local label) after study completion.

Female subjects must have negative results for pregnancy tests performed:

- at Screening on a serum specimen obtained within 7 days prior to initial study drug administration, and
- prior to dosing on a urine sample obtained C1D-2 unless the serum pregnancy test was collected within 7 days of C1D-2.

Has been changed to read:

Female and male patients of fertile age, and/or their partners should use contraception. If male, subject and subject's female partner(s) of childbearing potential must follow the contraception recommendations as described in Section 5.2.4. If female, subject must be either postmenopausal for at least 1 year, surgically sterile (bilateral tubal ligation, bilateral oophorectomy or hysterectomy), or the subject and the subject's male partner(s) must follow the contraception recommendations as described in Section 5.2.4.

Female subjects must have negative results for pregnancy tests performed:

- Screening on a serum specimen obtained within 7 days prior to initial study drug administration, and
- prior to dosing on a urine sample obtained C1D-2 unless the serum pregnancy test was collected within 7 days of C1D-2.

Section 5.2.2 Exclusion Criteria
Criterion 5, last sentence previously read:

If CNS progression is suspected, a head CT should be performed at screening.

Has been changed to read:

If CNS metastasis is suspected, a head CT should be performed at screening.

Section 5.2.2 Exclusion Criteria
Criterion 9, third and fourth bullet previously read:

- History of hepatitis B (HBV) with surface antigen (HBsAg) positivity within 3 months prior to the date of informed consent for this study (if no test has been performed within 3 months, it must be done at screening);
- History of hepatitis C (HCV) with HCV RNA positivity within 3 months prior to the date of informed consent for this study (if no test has been performed within 3 months it must be done at screening);

Has been changed to read:

- History of hepatitis B (HBV) with surface antigen (HBsAg) positivity within 3 months prior to the date of informed consent for this study (if HBsAg status is unknown it must be tested at screening);
- History of hepatitis C (HCV) with HCV RNA positivity within 3 months prior to the date of informed consent for this study (if HCV RNA status is unknown it must be tested at screening);

Section 5.2.3.1 Prior Therapy
Subsection <u>Phase 1 Dose Escalation</u>
Add: new subsection title following section title

Phase 1 Dose Escalation

Section 5.2.3.1 Prior Therapy
Subsection <u>Phase 2 Randomized Double-Blind</u>
Add: new subsection title following third paragraph

Phase 2 Randomized Double-Blind

Section 5.2.3.2 Concomitant Therapy
In-text table previously read:

Premedication:	The prophylactic antiemetics, including 5-HT3 antagonists, according to institution, National Comprehensive Cancer Network (NCCN), European Society for Medical Oncology (ESMO) or American Society of Clinical Oncology (ASCO) guidelines should be given, prior to administration of carboplatin and etoposide. Prophylaxis with anti-emetics (e.g., 5-HT3 antagonists such as ondansetron) is strongly recommended when initiating single agent veliparib maintenance therapy.
Anticancer Agents:	Other anticancer agents are not permitted during the treatment portion of the study. All subjects will receive carboplatin + etoposide with veliparib/placebo at specified timepoints during the treatment portion of the study. The locally approved carboplatin and etoposide product labels or SmPCs should be referenced to determine if there are any contraindications associated with concomitant medications (e.g., phenytoin, etc.).
Supportive Care:	Best supportive care and treatment will be given as appropriate to each subject (antiemetics, antibiotics, transfusions, nutritional support, non-radiation palliative treatment for pain, bisphosphonates or denosumab) according to institutional or clinical practice guidelines (e.g., ASCO, ESMO, or NCCN).
Growth Factors:	Biologic response modifiers administered for erythropoiesis (e.g., erythropoietin, darbepoetin alpha) and colony stimulating factors (e.g., neulasta, G-CSF, GM CSF, etc.) may be administered according to institutional or clinical practice guidelines (e.g., ASCO, ESMO, or NCCN). Growth factors prophylaxis will not be allowed in Cycle 1 (Day –2 through Day 21) of the dose escalation cohorts.
Radiation:	Prophylactic cranial irradiation (PCI) is allowed during the study in the maintenance phase of treatment at Investigators discretion. The dose of PCI should be 24 Gy in 8 fractions of 3 Gy each, or per local treatment standards. Veliparib or placebo maintenance monotherapy will be held starting 2 days prior to the initiation of radiation therapy, throughout the radiation therapy and for 4 days following radiation therapy. Palliative radiation to a non-target lesion with the intent of symptom control is allowed; non-progressing status of lesion to be irradiated must be documented prior to the procedure.
Surgery:	If the subject requires surgery during the study, then this needs to be discussed with the AbbVie Medical Monitor.
Alternate Therapy:	No traditional herbal anti-cancer medicine (e.g., Chinese, Asian, etc.) may be taken concurrently with veliparib (a 14-day washout period must be documented).

Has been changed to read:

Premedication:	The prophylactic antiemetics, including 5-HT3 antagonists, according to institution, National Comprehensive Cancer Network (NCCN), European Society for Medical Oncology (ESMO) or American Society of Clinical Oncology (ASCO) guidelines should be given, prior to administration of carboplatin and etoposide. Prophylaxis with anti-emetics (e.g., 5-HT3 antagonists such as ondansetron) is strongly recommended when initiating single agent veliparib/placebo maintenance monotherapy.
Anticancer Agents:	Other anticancer agents are not permitted during the treatment portion of the study. All subjects will receive carboplatin + etoposide with veliparib/placebo at specified timepoints during the treatment portion of the study. The locally approved carboplatin and etoposide product labels or SmPCs should be referenced to determine if there are any contraindications associated with concomitant medications (e.g., phenytoin, etc.).
Supportive Care:	Best supportive care and treatment will be given as appropriate to each subject (antiemetics, antibiotics, transfusions, nutritional support, palliative treatment for pain, bisphosphonates or denosumab) according to institutional or clinical practice guidelines (e.g., ASCO, ESMO, or NCCN).
Growth Factors:	Biologic response modifiers administered for erythropoiesis (e.g., erythropoietin, darbepoetin alpha) and colony stimulating factors (e.g., neulasta, G-CSF, GM CSF, etc.) may be administered according to institutional or clinical practice guidelines (e.g., ASCO, ESMO, or NCCN). Growth factors prophylaxis will not be allowed in Cycle 1 (Day –2 through Day 21) of the dose escalation cohorts. Growth factors prophylaxis is acceptable in Phase 2.
Radiation:	Prophylactic cranial irradiation (PCI) is allowed during the study in the Maintenance phase of treatment at Investigators discretion. The dose of PCI should be 24 Gy in 8 fractions of 3 Gy each, or per local treatment standards. Veliparib or placebo maintenance monotherapy will be held starting 2 days prior to the initiation of radiation therapy, throughout the radiation therapy and for 4 days following radiation therapy. Palliative radiation to a non-target lesion with the intent of symptom control is allowed; non-progressing status of lesion to be irradiated must be documented prior to the procedure. Radiation to non-target lesions for other reasons will not be allowed during combination treatment cycles and generally will not be allowed during maintenance; exceptional circumstances that may arise during maintenance must be discussed with AbbVie TA MD and non-progressing status of such lesions using the same modality as study tumor assessments will have to be documented prior to procedure.

Surgery:	If the subject requires surgery during the study, then this needs to be discussed with the AbbVie TA MD.
Alternate Therapy:	No traditional herbal anti-cancer medicine (e.g., Chinese, Asian, etc.) may be taken concurrently with veliparib (a 14-day washout period must be documented).

Section 5.2.4 Contraception Recommendations
Add: new section title and text

5.2.4 Contraception Recommendations

If female, subject must be either postmenopausal or permanently surgically sterile (refer to inclusion criteria for definitions of both) OR a Women of Childbearing Potential, practicing at least one of the following methods of birth control, on C1D-2 (or earlier) through at least 6 months after the last dose of study drug.

- Combined (estrogen and progestogen containing) hormonal contraception (oral, intravaginal, transdermal) associated with the inhibition of ovulation, initiated at least 1 month prior to C1D-2.
- Progestogen-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation, initiated at least 1 month prior to C1D-2.
- Bilateral tubal occlusion/ligation.
- Bilateral tubal occlusion via hysteroscopy (i.e., Essure), provided a hysterosalpingogram confirms success of the procedure.
- Vasectomized partner(s), provided the vasectomized partner verbally confirms receipt of medical assessment of the surgical success, and is the sole sexual partner of the WOCBP trial participant.
- Intrauterine device (IUD).
- Intrauterine hormone-releasing system (IUS).
- True abstinence: Refraining from heterosexual intercourse when this is in line with the preferred and usual lifestyle of the subject [periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable].

If required per local practices, male or female condom with or without spermicide OR cap, diaphragm or sponge with spermicide should be used in addition to one of the birth control methods listed above (excluding true abstinence).

If the subject or subject's female partner(s) is currently using a hormonal contraceptive, she should also use a barrier method during this study and for 6 months (or per local label) after study completion.

Male subjects who are sexually active with a WOCBP, even if the male subject has undergone a successful vasectomy, must agree from C1D-2 through at least 6 months after the last dose of study drug to use condoms and his female partner(s) must use at least one of the contraceptive measures (as defined in the protocol for female study subjects of childbearing potential).

Male subject agrees not to donate sperm from C1D-2 through at least 6 months after the last dose of study drug.

Table 7. Study Activities Phase 1 Dose Escalation
Activity "Vital Signs" previously read:

Activity	SCR[a]	C1 D-2	D1 through D3 Combination Cycles	C1 D8 and D15	C2 Through C4 D1	C2 Through C4 D8	C2 Through C4 D15	Maintenance Veliparib D1 of Each Cycle Starting in C5	Tumor Assessments Every 6 Weeks First 24 Weeks	Tumor Assessments Every 9 Weeks Thereafter	Final Visit	30-Day Follow-Up Visit
Vital Signs	X	X	X	X	X		X	X			X	X

Has been changed to read:

Activity	SCR[a]	C1 D-2	D1 through D3 Combination Cycles	C1 D8 and D15	C2 Through C4 D1	C2 Through C4 D8	C2 Through C4 D15	Maintenance Veliparib D1 of Each Cycle Starting in C5	Tumor Assessments Every 6 Weeks First 24 Weeks	Tumor Assessments Every 9 Weeks Thereafter	Final Visit	30-Day Follow-Up Visit
Vital Signs	X	X	X Cycle 1 only	X	X		X	X			X	X

Table 7. Study Activities Phase 1 Dose Escalation
Add: Activity "HBsAg, HCV RNA[n]"

Activity	SCR[a]	C1 D-2	D1 through D3 Combination Cycles	C1 D8 and D15	C2 Through C4 D1	C2 Through C4 D8	C2 Through C4 D15	Maintenance Veliparib D1 of Each Cycle Starting in C5	Tumor Assessments Every 6 Weeks First 24 Weeks	Tumor Assessments Every 9 Weeks Thereafter	Final Visit	30-Day Follow-Up Visit
HBsAg, HCV RNA[n]	X											

Table 7. Study Activities Phase 1 Dose Escalation
Table note "i." previously read:

Tumor assessments will be performed until disease progression. Tumor assessment and assessment of response will occur every 6 weeks (± 1 week) for the first 24 weeks after the first dose of study drugs, then every 9 weeks (± 1 week) thereafter. Tumor Assessments at the end of Cycle 4 should be performed 1 week prior to the conclusion of Cycle 4 with radiographic results determined and reported to ensure subjects eligibility prior to subject starting continuous monotherapy veliparib dosing at Cycle 5. A tumor assessment will 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. The scanned areas will include chest and abdomen (with image of liver and adrenal glands) at all tumor assessments. A head CT at will be performed at baseline if there is clinical suspicion of CNS metastases.

Has been changed to read:

Tumor assessments will be performed until disease progression. Tumor assessment and assessment of response will occur every 6 weeks (± 1 week) from C1D-2 for the first 24 weeks, then every 9 weeks (± 1 week) thereafter. Tumor Assessments at the end of Cycle 4 should be performed 1 week prior to the conclusion of Cycle 4 with radiographic results determined and reported to ensure subjects eligibility prior to subject starting continuous monotherapy veliparib dosing at Cycle 5. A tumor assessment will 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. The scanned areas will include chest, abdomen and pelvis at all tumor assessments. A head CT will be performed if there is clinical suspicion of CNS metastases.

Table 7. Study Activities Phase 1 Dose Escalation
Add: table note "n."

If no HBsAg/HCV RNA test has been performed within 3 months prior to the date of informed consent for this study.

Table 8. Study Activities in Phase 2
Previously read:

Activity	SCR[a]	C1 D-2	D1 through D3 Combination Cycles	C1 D8	C2 Through Last Combination Cycle D1	C2 Through Last Combination Cycle D8	C2 Through C D15	Monotherapy Veliparib/ PBO D1 of Each Cycle Starting in Maintenance per SOC	Tumor Assessments Every 6 Weeks First 24 Weeks	Tumor Assessments Every 9 Weeks Thereafter	Final Visit	30-Day Follow-Up Visit	Post Treatment Follow-Up
Informed Consent[b]	X												
Medical and History[c]	X												
Physical Exam (including weight)[d]	X	X		X[o]	X		X	X			X	X	
Performance Status (ECOG)	X	X			X		X	X			X	X	
12-Lead ECG	X										X		
Vital Signs	X	X	X	X	X		X	X			X	X	
Pregnancy Test Serum (s), Urine (u)[e]	X (s)	X (u)											
Hematology[f]	X	X		X	X	X	X	X			X	X	
Chemistry[g]	X	X			X		X	X			X	X	
Coagulation Tests	X				X C3 D1 only			X Odd cycles			X		

Activity	SCR[a]	C1 D-2	D1 through D3 Combination Cycles	C1 D8	C2 Through Last Combination Cycle D1	C2 Through Last Combination Cycle D8	C2 Through C D15	Monotherapy Veliparib/ PBO D1 of Each Cycle Starting in Maintenance per SOC	Tumor Assessments Every 6 Weeks First 24 Weeks	Tumor Assessments Every 9 Weeks Thereafter	Final Visit	30-Day Follow-Up Visit	Post Treatment Follow-Up
Urinalysis	X										X		
Clinical Disease Progression[h]					X[h]		X		X[h]		X		
Tumor Assessments[i]	X								Xi	X[i]	X		X[p]
Monitor Adverse Events/ Concomitant Medications		X	X	X	X	X	X	X			X	X	
Monitor Compliance		X		X	X			X					
Randomization		X											
Dispense Veliparib[j,l]		X			X			X[l]					
Administer Premedication[k]			X			X							
Administer Etoposide[m]			X										

Activity	SCR[a]	C1 D-2	D1 through D3 Combination Cycles	C1 D8	C2 Through Last Combination Cycle D1	C2 Through Last Combination Cycle D8	C2 Through C D15	Monotherapy Veliparib/ PBO D1 of Each Cycle Starting in Maintenance per SOC	Tumor Assessments Every 6 Weeks First 24 Weeks	Tumor Assessments Every 9 Weeks Thereafter	Final Visit	30-Day Follow-Up Visit	Post Treatment Follow-Up
Administer Carboplatin[m]			X Day 1 only										
Survival Follow-Up[n]													X

C = Cycle; D = Day, SCR = Screening; RND = Randomization; PBO = Placebo; TA = Tumor Assessments; FV = Final Visit; PT = Post-treatment; F/U = Follow-up

a. Screening visit must be performed within 28 days of Cycle 1 Day –2. If the screening visit is performed > 7 days prior to Day –2 the physical exam, laboratory tests (hematology and chemistry) and pregnancy test must be repeated on Day –2. Tumor assessments must be performed within 21 Days of Cycle 1 Day –2.

b. The informed consent must be signed and dated prior to the initiation of any screening or study specific procedure is performed.

c. A subject's medical history will be reviewed at each visit. Any changes from baseline will be recorded on the adverse event eCRF.

d. Height will be assessed at Screening only.

e. A serum pregnancy test must be performed at Screening, a urine pregnancy test on Cycle 1 Day –2 prior to dosing if > 7 days since obtaining the serum pregnancy test for women of childbearing potential. Pregnancy tests may be repeated at any time during the study at the discretion of the investigator.

f. Hematology labs do not need to be repeated if screening is within 7 days of Cycle 1 Day –2. A central laboratory will be used for the study; however, sites may use a certified local laboratory to collect a sample to dose the subject.

g. Chemistry panels do not need to be repeated if screening is within 7 days of Cycle 1 Day –2. A central laboratory will be used for the study; however, sites may use a certified local laboratory to collect a sample to manage subject therapy.

h. Clinical disease progression will include, but will not be limited to an evaluation of worsening performance status due to progressive disease, requirement for non-palliative radiation therapy, alternative chemotherapy or surgery due to progressive disease or death due to progressive disease.

i. Tumor assessments will be performed from the first dose of the study drugs until disease progression. Tumor assessment and assessment of response will occur every 6 weeks (± 1 week) for the first 24 weeks after the first dose of study drug, then 9 weeks (± 1 week) thereafter. A tumor assessment will 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.

j. Veliparib will be dosed orally at the RPTD schedule in 21-day cycles for up to 6 cycles. Veliparib will be administered after the pre medications on all days when given with chemotherapy. After completing combination therapy subjects may receive veliparib continuous dosing at 400 mg BID or placebo (each cycle will be 21 days) until disease progression or unacceptable toxicity occurs. Veliparib will be given approximately every 12 hours with a glass of water (approximately 240 mL).

k. Pre-medication will be given as per institutional guidelines.

l. Starting at Maintenance Day 1 and all subsequent monotherapy cycles, veliparib or placebo will be dispensed on Day 1.

m. Etoposide on Days 1, 2 and 3 and carboplatin on Day 1 of Combination Cycles will be administered IV by site staff after veliparib administration. Etoposide will be given prior to carboplatin, unless institutional guidelines require inverse sequence of administration.

n. Survival follow-up will be performed beginning on the date the subject is registered off study monthly and continuing for up to 2 years on all subjects until the endpoint of death, the subject has become lost to follow-up, or if AbbVie terminates the study.

o. The Cycle 1 Day 8 physical examination may be "symptom-directed."

p. Post treatment tumor assessments will be collected for up to 2 years or until progression.

Has been changed to read:

Activity	SCR[a]	C1 D-2	D1 through D3 Combination Cycles	C1 D8	C2 Through Last Combination Cycle D1	C2 Through Last Combination Cycle D8	Monotherapy Veliparib/ PBO D1 of Each Cycle Starting in Maintenance	Tumor Assessments Every 6 Weeks First 30 Weeks	Tumor Assessments Every 9 Weeks Thereafter	Post-Treatment Follow-Up	Final Visit[o]	30-Day Follow-Up Visit[p]	Survival Follow-Up
Informed Consent[b]	X												
Medical and History[c]	X												
Physical Exam (including weight)[d]	X	X		X	X		X				X	X	
Performance Status (ECOG)	X	X			X		X				X	X	
12-Lead ECG	X										X		
Vital Signs	X	X	X C1 only	X	X		X				X	X	
Pregnancy Test Serum (s), Urine (u)[e]	X (s)	X (u)											
Hematology[f]	X	X		X	X	X	X				X	X	
Chemistry[f]	X	X			X		X				X	X	
Coagulation Tests	X										X		
HBsAg, HCV RNA[g]	X												
Urinalysis	X										X		

Activity	SCR[a]	C1 D-2	D1 through D3 Combination Cycles	C1 D8	C2 Through Last Combination Cycle D1	C2 Through Last Combination Cycle D8	Monotherapy Veliparib/ PBO D1 of Each Cycle Starting in Maintenance	Tumor Assessments Every 6 Weeks First 30 Weeks	Tumor Assessments Every 9 Weeks Thereafter	Post-Treatment Follow-Up	Final Visit[o]	30-Day Follow-Up Visit[p]	Survival Follow-Up
Clinical Disease Progression[h]					X			X			X		
Tumor Assessments[i]	X							X[i]	X[i]	X[i]	X		
Monitor Adverse Events/Concomitant Medications		X	X	X	X	X	X				X	X	
Monitor Compliance		X		X	X		X						
Randomization		X											
Dispense Veliparib		X			X[j]		X[l]						
Administer Premedication[k]			X		X								
Administer Etoposide[m]			X		X								
Administer Carboplatin[m]			X Day 1 only		X								
Survival Follow-Up[n]													X

C = Cycle; D = Day, SCR = Screening; RND = Randomization; PBO = Placebo; TA = Tumor Assessments; FV = Final Visit; PT = Post-treatment; F/U = Follow-up

a. Screening visit must be performed within 28 days of Cycle 1 Day –2. If the screening visit is performed > 7 days prior to Day –2 the physical exam, laboratory tests (hematology and chemistry) and pregnancy test must be repeated on Cycle 1 Day –2. Tumor assessments must be performed within 21 Days of Cycle 1 Day –2.

b. The informed consent must be signed and dated prior to the initiation of any screening or study specific procedure being performed.

c. A subject's medical history will be reviewed at each visit. Any changes from baseline will be recorded on the adverse event eCRF.

d. Physical exam does not need to be repeated at Cycle 1 Day –2 if screening physical exam was completed within 7 days of Cycle 1 Day –2. Physical exams during combination cycles must include assessment of hearing if required by the local SmPC for carboplatin. The Cycle 1 Day 8 physical exam may be symptom directed. Height will be assessed at Screening only.

e. A serum pregnancy test must be performed at Screening, a urine pregnancy test on Cycle 1 Day –2 prior to dosing if > 7 days since obtaining the serum pregnancy test for women of childbearing potential. Pregnancy tests may be repeated at any time during the study at the discretion of the investigator.

f. Hematology and Chemistry panels do not need to be repeated at Cycle 1 Day –2 if screening labs were completed within 7 days of Cycle 1 Day –2. A central laboratory will be used for the study; however, sites may use a certified local laboratory to collect a sample to dose the subject. If local labs are drawn the sample MUST be split and also sent to central lab.

g. Only for subjects with known history of HBV or HCV without prior evidence of active disease-free status and if HBsAg/HCV RNA status within 3 months of the study entry is unknown.

h. If clinical disease progression is suspected, progression must be confirmed radiographically per RECIST 1.1. Clinical disease progression will include, but will not be limited to worsening performance status due to progressive disease, requirement for non-palliative radiation therapy, alternative chemotherapy or surgery due to progressive disease. At the Final Visit, a clinical disease progression assessment is required only for subjects who discontinue the study for reasons other than progression (clinical or radiographic).

i. Tumor assessment and assessment of response will occur every 6 weeks (± 1 week) from C1D-2 for the first 30 weeks, then every 9 weeks (± 1 week) thereafter. A tumor assessment will 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 in Post-Treatment Follow-Up should continue to receive tumor assessments at the protocol defined time points until an event of radiographic progression.

j. Veliparib will be dosed orally at 240 mg BID and 14-day schedule for up to 6 cycles. Veliparib will be administered after the pre medications on all days when given with chemotherapy. Veliparib will be given approximately every 12 hours with a glass of water (approximately 240 mL).

k. Pre-medication will be given as per institutional guidelines.

l. Starting at Maintenance Day 1 and all subsequent monotherapy cycles, veliparib or placebo will be dosed orally at 400 mg BID and continuous (21-day) dosing schedule. Subjects should remain on veliparib until disease progression or unacceptable toxicity occurs.

m. Etoposide on Days 1, 2 and 3 and carboplatin on Day 1 of Combination Cycles will be administered IV by site staff after veliparib administration. Etoposide will be given prior to carboplatin, unless institutional guidelines require inverse sequence of administration.

n. Survival follow-up will be performed at 2 month intervals after the subject discontinues the study and until the endpoint of death, the subject has become lost to follow-up, the subject specifically withdraws consent for survival follow-up or if AbbVie terminates the study.

o. 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.

p. A 30-Day Follow-Up visit must occur when the subject discontinues all study drugs due to toxicity and will transition to Post-Treatment Follow-Up. Subjects who discontinue treatment due to radiographic progression and have a Final Visit within 30 days of last dose of study drug will have one Follow-Up Visit approximately 30 days after the last dose of study drug.

Table 9. Schedule of Pharmacogenetic and Pharmacodynamic Assessments for Phase 1 Dose Escalation and Phase 2
Previously read:

Procedure	Visit Schedule	Before Drug Administration	After Drug Administration	Sampling Plan Specimen Matrix
PG Blood Sampling[a] Genetic (DNA)	Cycle 1 Day 1	Not Dose Dependent	Not Dose Dependent	Whole Blood Frozen –20°C or Colder
Plasma Markers	Screening, Cycle 2 Day 1, Cycle 3 Day 1, Cycle 4 Day 1 and Final Visit	Prior to Dose	Prior to Dosing	Blood → Plasma Frozen –70°C or Colder
Serum Markers	Screening, Cycle 2 Day 1 and Final Visit	Prior to Dose	NA	Blood → Serum Frozen –70°C or Colder
Archived Tissue Sample Collection[b]	Screening	N/A	N/A	FFPE

a. Perform once at either screening or on Cycle 1 Day 1. If not collected at this visit, it may be collected at any time throughout the study. Subjects must sign a separate informed consent prior to obtaining the PG sample.

b. Subjects must consent to provide available archival tissue for analysis. It is preferred to send FFPE blocks, however slides prepared by the local pathology laboratory are acceptable and should be prepared as described in the study specific laboratory manual.

Has been changed to read:

Procedure	Visit Schedule	Before Drug Administration	After Drug Administration	Sampling Plan Specimen Matrix
PG Blood Sampling[a] Genetic (DNA)	Cycle 1 Day –2	Not Dose Dependent	Not Dose Dependent	Whole Blood Frozen –20°C or Colder
Plasma Markers[b]	Cycle 1 Day –2, Cycle 2 Day 1, Cycle 3 Day 1, Cycle 4 Day 1 and Final Visit	Prior to Dose	Prior to Dosing	Blood → Plasma Frozen –70°C or Colder
Serum Markers[b]	Cycle 1 Day –2, Cycle 2 Day 1 and Final Visit	Prior to Dose	NA	Blood → Serum Frozen –70°C or Colder
Archived Tissue Sample Collection[c]	Cycle 1 Day –2	N/A	N/A	FFPE

a. Perform once at Cycle 1 Day –2. If not collected at this visit, it may be collected at any time throughout the study. Subjects must sign a separate informed consent prior to obtaining the PG sample.

b. Samples will not be drawn during carboplatin and/or etoposide dose delays.

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

Table 10. Schedule of Pharmacokinetic Assessments for Phase 1 Dose Escalation
Table note "a."
Add: new second and third sentence

Samples will not be drawn during carboplatin and/or etoposide dose delays. All timepoints of etoposide and carboplatin samples are referred to the start of the infusion.

Table 11. Schedule of Pharmacokinetic Assessments in Phase 2
Table note "a."
Add: new last sentence

Samples will not be drawn during carboplatin and/or etoposide dose delays.

Section 5.3.1.1 Study Procedures
Last paragraph previously read:

Screening procedures and assessments will occur within 28 days prior to Cycle 1 Day –2 except for radiographic assessments that are to be performed within 21 days of Cycle 1 Day –2. For procedures performed at Screening and repeated, the later procedure performed prior to dosing will serve as a baseline for clinical assessment. Subsequent study procedures should be performed approximately within ± 1 day on days of IV infusion of carboplatin and etoposide and ± 2 days for all safety visits and Cycle 5 of monotherapy and maintenance surrounding the scheduled study visit date. Clinical laboratory tests can be performed up to 24 hours prior to dosing.

Has been changed to read:

Screening procedures should be performed within 28 days prior to Cycle 1 Day –2. If the screening visit is performed greater than 7 days prior to Cycle 1 Day –2, the physical exam, laboratory tests, and pregnancy test (for female subjects of childbearing potential) must be repeated on Cycle 1 Day –2. Vital signs and performance status assessments will be performed on Cycle 1 Day –2 for all subjects. Baseline radiographic tumor assessments per computed tomography (CT) with IV contrast/magnetic resonance imaging (MRI) of the chest, abdomen, pelvis and head (if CNS metastases are suspected) will be conducted within 21 days prior to Cycle 1 Day –2. 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.

For procedures performed at Screening and repeated, the later procedure performed prior to dosing will serve as a baseline for clinical assessment. Subsequent study procedures should be performed approximately within ± 1 day on days of IV infusion of carboplatin and etoposide and ± 2 days for all safety visits and first Maintenance visit. Clinical laboratory tests can be performed up to 48 hours prior to dosing.

Section 5.3.1.1 Study Procedures
Subsection Physical Examination
First paragraph, first and second sentence previously read:

A physical examination, including body weight, will be performed per Table 7 and Table 8. If the Screening physical examination is performed within 7 days of Cycle 1 Day –2, it is not required to repeat the exam on Cycle 1 Day 1 unless clinically indicated.

Has been changed to read:

A physical examination, including body weight, will be performed per Table 7 and Table 8. Physical examination during combination cycles will include hearing assessment if required by carboplatin locally approved product label, local practice, or applicable SmPC. If the Screening physical examination is performed within 7 days of Cycle 1 Day –2, it is not required to repeat the exam on Cycle 1 Day –2 unless clinically indicated.

Section 5.3.1.1 Study Procedures
Subsection Hepatitis Screen
Previously read:

Subjects with history of hepatitis C (HCV) must be tested for HCV RNA at screening if no documented test result is available from within 3 months from the date of informed consent. Subjects with history of hepatitis B (HBV) must be tested for HBV surface antigen (HBsAg) at screening if no documented test result is available from within

3 months from the date of informed consent. The hepatitis test panel will be performed by a certified laboratory.

Has been changed to read:

Subjects with history of hepatitis C (HCV) must be tested for HCV RNA at screening if no documented test result is available from within 3 months from the date of informed consent, and for Phase 2 if status within 3 months of the study entry is unknown. Subjects with history of hepatitis B (HBV) must be tested for HBV surface antigen (HBsAg) at screening if no documented test result is available from within 3 months from the date of informed consent, and for Phase 2 if status within 3 months of the study entry is unknown. Testing will be performed by the sponsor-designated central laboratory.

Section 5.3.1.1 Study Procedures
Subsection Clinical Laboratory Tests
First and second paragraph previously read:

Samples for chemistry, hematology and urinalysis will be collected per Table 7 and Table 8. Specific laboratory assessments are outlined in Table 12.

A certified local laboratory may be used to perform laboratory analyses for treatment decisions. All study samples indicated in Table 12 are to be shipped to the central laboratory, and central laboratory results will be used for data analysis. The central laboratory will provide instructions regarding the collection, processing and shipping of samples.

Has been changed to read:

Samples for chemistry, hematology and urinalysis will be collected per Table 7 (Phase 1) and Table 8 (Phase 2). Specific laboratory assessments are outlined in Table 12.

All study samples will be shipped to the central laboratory, and central laboratory results will be used for data analysis. A certified local laboratory may be used to perform laboratory analyses for immediate treatment decisions; however, split or concurrent

samples must be drawn and sent to the central laboratory for analysis. The central laboratory will provide instructions regarding the collection, processing and shipping of samples.

Section 5.3.1.1 Study Procedures
Subsection Clinical Laboratory Tests
Delete: first bullet

The investigator will repeat the test to verify the out-of-range value.

Section 5.3.1.1 Study Procedures
Subsection Clinical Laboratory Tests
Add: new sixth paragraph

Study samples for central laboratory analysis may be performed within 48 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.

Table 12. Clinical Laboratory Tests
Table note "+"
Add: new third sentence

If HBsAg/HCV RNA status is unknown it must be tested at screening for Phase 2 subjects.

Section 5.3.1.1 Study Procedures
Subsection Tumor Assessments (Radiographic)
First paragraph previously read:

A CT scan will be used in the evaluation of tumor responses with RECIST version 1.1. The scanned areas will include chest and abdomen (with image of liver and adrenal glands) at all radiographic assessments, and head CT as warranted by clinical symptoms suspicion of CNS metastases.

Has been changed to read:

A CT scan with contrast will be used in the evaluation of tumor responses with RECIST version 1.1. The scanned areas will include chest, abdomen and pelvis at all radiographic assessments, and head CT as warranted by clinical suspicion of CNS metastases.

Section 5.3.1.1 Study Procedures
Subsection Tumor Assessments (Radiographic)
Add: new last paragraph

Sites may be requested to electronically transfer copies of all CT or MRI scans used for radiographic tumor assessments in the Phase 2 part of the study to AbbVie. Electronic copies of scans in DICOM format should be maintained at the sites until notification from AbbVie or end of study, whichever comes first. Instructions regarding procedures for transferring scans will be provided separately, if the request for scans becomes necessary.

Section 5.3.1.1 Study Procedures
Subsection Tumor Assessments Schedule
Previously read:

Tumor assessments will be performed until disease progression. Tumor assessment and assessment of response will occur every 6 weeks (± 1 week) for the first 24 weeks after the first dose of study drugs, then every 9 weeks (± 1 week) thereafter. Tumor response will be determined according to the Response Evaluation Criteria in Solid Tumors (RECIST), Version 1.1. 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.

For Phase 2, calendar of tumor assessments should be maintained independent of any treatment schedule delays or changes.

Has been changed to read:

Tumor assessments will be performed until radiographic disease progression. Tumor assessment and assessment of response will occur every 6 weeks (± 1 week) from C1D-2 for the first 24 weeks (Phase 1) or 30 weeks (Phase 2), then every 9 weeks (± 1 week) thereafter. Tumor response will be determined according to the Response Evaluation Criteria in Solid Tumors (RECIST), Version 1.1. 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.

For Phase 2, the protocol defined tumor assessment schedule should be maintained independent of any treatment delays or changes.

Refer to Appendix C "RECIST (Version 1.1) for Tumor Response (PFS)" for response criteria and guidelines.

Post-Treatment Follow-Up

Subjects who discontinue all study drugs prior to reaching an event of radiographic progression must enter into Post-Treatment Follow-Up. Subjects will remain on study (off study drug) and will continue to receive tumor assessments according to the protocol defined tumor assessment schedule until reaching an event of radiographic progression.

Subjects who discontinue all study drugs due to toxicity should have a 30-day Follow-up visit prior to entering into Post-Treatment Follow-Up to ensure all toxicities have resolved. Subjects will have a Final Visit and be discontinued from the study upon reaching an event of radiographic progression, if the Investigator determines they should be discontinued for any other reason or if the subject withdraws consent.

Section 5.3.1.1 Study Procedures
Subsection Survival Information (Phase 2 Only)
Subsection title and text previously read:

Survival Information (Phase 2 Only)

Subjects no longer undergoing clinical assessments will have survival information collected 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.

All subjects will be followed for survival information (i.e., the date and cause of death or last known alive date if not deceased) unless the subject requests to be withdrawn specifically from study survival follow-up; this request must be documented in the subject's medical record and signed by the Investigator.

If known, post treatment anti-cancer therapies, dates of initiation, and end dates will be collected.

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.

Has been changed to read:

Survival Follow-Up (Phase 2 Only)

All discontinued subjects will have survival information collected via electronic data capture (EDC) at two month intervals (or as requested by sponsor to support data analysis) after the subject discontinues the study and continuing until the endpoint of death, the subject has become lost to follow-up, or AbbVie terminates the study.

All subjects will be followed for survival information (i.e., the date and cause of death or last known alive date if not deceased) unless the subject requests to be withdrawn

specifically from study survival follow-up; this request must be documented in the subject's medical record and signed by the Investigator.

If known, post treatment anti-cancer therapies, dates of initiation, and end dates will be collected.

If the subject withdraws from survival 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.

Section 5.3.1.1 Study Procedures
Subsection Randomization and Subject Number Assignment
Previously read:

An Interactive Voice/Web Response System (IVRS/IWRS) will be utilized to register subjects and receive a screening number.

Subjects who complete all Screening procedures and meet the eligibility criteria will proceed to dosing. The site will access the IVR/IWR system at Screening and a unique subject number will be provided.

Subjects in Phase 2 will be randomized in a 1:1:1 ratio to carboplatin, etoposide, placebo, followed by placebo maintenance, or carboplatin, etoposide, veliparib followed by either veliparib or placebo maintenance. A subject number will be assigned after the subject signs the informed consent. The site can contact the system up to 4 calendar days prior to or on the subject's Cycle 1 Day –2 to obtain a Screening (subject) number. Subjects who complete all Screening procedures and meet the eligibility criteria will proceed to randomization. The site will contact the system prior to the subject's Cycle 1 Day –2 and a unique randomization number will be provided.

A bottle number randomization schedule and a subject randomization schedule will be generated by the Data and Statistical Science Department at AbbVie prior to the start of the study. A copy of all randomization schedules will be kept by the Data and Statistical Science Department at AbbVie and a copy will be forwarded to the IVRS/IWRS vendor.

Has been changed to read:

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

The site will access the IRT system at Screening, after the subject signs informed consent and a unique subject number will be provided. Subjects who complete all Screening procedures and meet the eligibility criteria will proceed to dosing. Subjects who sign consent and do not meet the eligibility criteria will be considered a screen failure and the reason for screen failure will be documented in the source and in the eCRF. Subjects will also be registered as a screen failure in the IRT system.

Subjects in Phase 2 who complete all Screening procedures and meet the eligibility criteria will be randomized in a 1:1:1 ratio to one of three treatment arms:

Arm A: veliparib 240 mg in combination with carboplatin/etoposide followed by veliparib 400 mg BID monotherapy

Arm B: veliparib 240 mg in combination with carboplatin/etoposide followed by placebo monotherapy

Arm C: placebo in combination with carboplatin/etoposide followed by placebo monotherapy

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

Section 5.3.1.4 Blood Samples for Pharmacogenetic Analysis
First paragraph previously read:

One 4 mL whole blood sample for DNA isolation will be collected on Cycle 1 Day 1 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 Cycle 1 Day 1, it may be collected at any time throughout the study.

Has been changed to read:

One 4 mL whole blood sample for DNA isolation will be collected on Cycle 1 Day –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 Cycle 1 Day –2, it may be collected at any time throughout the study.

Section 5.3.1.5 Collection and Handling of Pharmacodynamic Variables
Subsection Blood Collection for Plasma Markers
First sentence previously read:

Twelve (12) mL (Screening or Final Visit) or 6 mL (all other time points) of blood will be collected pre-dose by venipuncture at time points outlined in Table 9 in conjunction with PK samples, if possible.

Has been changed to read:

Twelve (12) mL (Cycle 1 Day –2 or Final Visit) or 6 mL (all other time points) of blood will be collected pre-dose by venipuncture at time points outlined in Table 9 in conjunction with PK samples, if possible.

Section 5.3.1.5 Collection and Handling of Pharmacodynamic Variables
Subsection Tissue Collection for IHC, ELISA and FISH DNA Mutational/Methylation Analysis
Heading "Archived Tissue Specimens:"
First, second and third sentence previously read:

In order for subjects' samples to be analyzed, only subjects who consent to provide available archival tissue for analysis will be included. It is recognized that samples suitable for analysis will not be available from all consenting subjects. The most recent archived biopsy is preferred and should be obtained during screening if possible.

Has been changed to read:

Subjects must consent to provide available archived tissue for analysis. It is recognized that samples suitable for analysis will not be available from all consenting subjects. The most recent archived biopsy is preferred and should be obtained at Cycle 1 Day –2, if possible.

Section 5.3.2.1 Collection of Samples for Analysis
Subsection Blood Samples for Veliparib Assay Dose Escalation
Subsection title previously read:

Blood Samples for Veliparib Assay Dose Escalation

Has been changed to read:

Blood Samples for Veliparib Assay

Section 5.3.2.1 Collection of Samples for Analysis
Subsection Blood Samples for Veliparib Assay Dose Escalation
First paragraph, first sentence previously read:

Blood samples for veliparib assay will be collected by venipuncture at the designated time points outlined in Table 10 and Table 11.

Has been changed to read:

Blood samples for veliparib assay will be collected by venipuncture at the designated time points outlined in Table 10 (Phase 1) and Table 11 (Phase 2).

Section 5.3.2.1 Collection of Samples for Analysis
Subsection Blood Samples for Veliparib Assay Dose Escalation
Last paragraph, first sentence previously read:

Approximately 7 blood samples are planned to be collected per subject in Phase 1 and 8 samples per subject in Phase 2 for pharmacokinetic analysis.

Has been changed to read:

Approximately 7 blood samples are planned to be collected per subject in Phase 1 and 6 samples per subject in Phase 2 for pharmacokinetic analysis.

Section 5.3.2.1 Collection of Samples for Analysis
Subsection Blood Samples for Etoposide Assay
Add: new last sentence

Blood samples for etoposide assay will not be collected for Phase 2 subjects.

Section 5.3.2.1 Collection of Samples for Analysis
Subsection Blood Samples for Unbound Carboplatin Assay
Add: new last sentence

Blood samples for carboplatin assay will not be collected for Phase 2 subjects.

Section 5.3.3.2 Definition of Disease Progression
Add: new last paragraph

In cases where an Investigator determines that a subject has met the criteria for clinical disease progression, every effort should be made to confirm the progression radiographically.

Section 5.4.1 Discontinuation of Individual Subjects
Second, third, fourth and fifth paragraph previously read:

In the event that a subject withdraws or is discontinued from the study, the primary reason for discontinuation and any other reason(s) for the discontinuation from the study will be recorded and a physical examination, body weight, vital signs measurement, laboratory analyses, and an assessment of adverse events will be performed as soon as possible after discontinuation from the study. If a subject discontinues for reasons other than radiographic progression and if no tumor assessment has been performed within the last 4 weeks, a tumor assessment will be performed at the Final Visit. Phase 2 subjects who discontinue treatment for reasons other than radiographic progression will continue to be

monitored by the same methods (unless medical contraindication is noted) until the earlier of disease progression or initiation of next line of treatment.

If a subject discontinues for reasons other than radiographic progression and if no tumor assessment has been performed with the last 4 weeks, a tumor assessment will be performed at the Final Visit.

If a subject is discontinued from the study with an ongoing adverse event or an unresolved laboratory result that is significantly outside of the reference range, the investigator will attempt to provide follow-up until a satisfactory clinical resolution of the laboratory result or adverse event is achieved.

In the event that a positive result is obtained on a pregnancy test for a subject or a subject reports becoming pregnant during the study, the administration of study drug to that subject must be discontinued immediately. The investigator must report a pregnancy within 1 working day of the site being aware to one of the AbbVie representatives listed in Section 6.6 or Section 7.0.

Has been changed to read:

When a subject discontinuation from the study (without reaching a protocol-defined endpoint) is planned, the Investigator is to notify the AbbVie TA MD 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 TA MD may contact the site to discuss the reason for withdrawal from the study.

If a subject is discontinued from the study with an ongoing adverse event or an unresolved laboratory result that is significantly outside of the reference range, the investigator will attempt to provide follow-up until a satisfactory clinical resolution of the laboratory result or adverse event is achieved.

In the event that a positive result is obtained on a pregnancy test for a subject or a subject reports becoming pregnant during the study, the administration of study drug to that

subject must be discontinued immediately. The investigator must report a pregnancy within 1 working day of the site being aware to one of the AbbVie representatives listed in Section 6.6 or Section 7.0.

Post-Treatment Follow-Up

Phase 2 subjects who discontinue treatment for reasons other than radiographic progression will be monitored in the Post-Treatment Follow-Up period of the study by the same imaging method (unless medical contraindication is noted) until disease progression (Table 8).

Final Visit

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 7 and Table 8. 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.

30-Day Follow-Up Visit

Subjects who discontinue treatment for reasons other than radiographic progression will have a Follow-Up Visit approximately 30 days after the last dose of study drug and will transition to Post-Treatment Follow-Up.

Subjects who discontinue treatment due to radiographic progression and have a Final Visit within 30 days of last dose of study drug will have one Follow-Up Visit approximately 30 days after the last dose of study drug.

Survival Follow-Up

All discontinued subjects will have survival information collected via electronic data capture (EDC) at 2 month intervals (or as requested by sponsor to support data analysis) after the subject discontinues the study and continuing until the endpoint of death, the subject has become lost to follow-up, or AbbVie terminates the study.

5.4.1.1 Discontinuation of Combination and Maintenance Therapies in Phase 2

Subjects will receive veliparib, carboplatin and etoposide up to a maximum of 4 – 6 combination cycles or until reaching a protocol defined event of disease progression or experiencing unmanageable toxicity. Dose reductions of carboplatin and etoposide will occur on the basis of the toxicity observed and may result in discontinuation of either agent. The subject may continue on therapy with the remaining agent in combination with veliparib. At the Investigator's discretion, carboplatin and/or etoposide administration may continue after veliparib has been discontinued. Suitable subjects will receive veliparib/placebo maintenance monotherapy as per treatment arm assignment until reaching a protocol defined event of disease progression or experiencing unmanageable toxicity.

Section 5.5.1 Treatments Administered
First paragraph and bullet list previously read:

Subjects will receive the following:

- Designated doses of veliparib BID on Days –2 through 5 or Day –2 through 12 (14-day schedule) or Day –2 to 19 (continuous schedule) + Carboplatin AUC 5 mg/mL*min administered on Day 1 and Etoposide 100 mg/m^2 administered on Days 1 through 3 of each 21-day cycle for up to 4 cycles in Phase 1 and up to 6 cycles in Phase 2.
    - Exception: Phase 1 subjects receiving non-continuous veliparib will have their Cycle 2 dosing schedule altered as follows to allow for the evaluation of veliparib effect on etoposide exposure: veliparib BID on Days 2 through 5 or Days 2 through 12 + Carboplatin AUC 5 mg/mL*min

administered on Day 1 and Etoposide 100 mg/m^2 administered on Days 1 through 3 of a 21-day cycle.

- Phase 1 subjects with SD, PR or CR at the completion of all scheduled combination therapy cycles will receive veliparib (400 mg) monotherapy, BID continuously in 21-day cycles starting on Day 1 of each cycle. Phase 2 subjects with SD, PR or CR at the completion of combination therapy cycles will receive veliparib (400 mg) or placebo monotherapy, BID continuously in 21-day cycles starting on Day 1 of each cycle.

Has been changed to read:

Phase 1 subjects will receive the following:

- Designated doses of veliparib BID on Days –2 through 5 or Day –2 through 12 (14-day schedule) or Day –2 to 19 (continuous schedule) + Carboplatin AUC 5 mg/mL*min administered on Day 1 and Etoposide 100 mg/m^2 administered on Days 1 through 3 of each 21-day cycle for up to 4 cycles.
  - Exception: Phase 1 subjects receiving non-continuous veliparib will have their Cycle 2 dosing schedule altered as follows to allow for the evaluation of veliparib effect on etoposide exposure: veliparib BID on Days 2 through 5 or Days 2 through 12 + Carboplatin AUC 5 mg/mL*min administered on Day 1 and Etoposide 100 mg/m^2 administered on Days 1 through 3 of a 21-day cycle.
- Phase 1 subjects with SD, PR or CR at the completion of all scheduled combination therapy cycles will receive veliparib (400 mg) monotherapy, BID continuously in 21-day cycles starting on Day 1 of each cycle starting at Cycle 5.

Phase 2 subjects will receive the following:

- Veliparib/Placebo 240 mg BID on Day –2 through 12 (14-day schedule) + Carboplatin AUC 5 mg/mL*min administered on Day 1 and Etoposide 100 mg/m^2 administered on Days 1 through 3 of each 21-day cycle for up to 6 cycles.

- Phase 2 subjects with SD, PR or CR at the completion of combination therapy cycles will receive veliparib (400 mg) or placebo monotherapy, BID continuously in 21-day cycles starting on Maintenance Day 1 of each cycle.

Section 5.5.1.1 Administration of Veliparib/Placebo
Third paragraph, last sentence previously read:

The subject is to contact the Investigator if additional veliparib is needed to complete BID dosing through Day 5 of the cycle.

Has been changed to read:

The subject is to contact the Investigator if additional veliparib is needed to complete BID dosing through the remainder of the cycle.

Section 5.5.1.1 Administration of Veliparib/Placebo
Last paragraph, last sentence previously read:

Subjects should return bottles of veliparib (empty, partially filled or full) to the study site prior to each cycle and at the Final Visit.

Has been changed to read:

Subjects should return bottles of veliparib (empty, partially filled or full) and the completed dosing card to the study site prior to each cycle and at the Final Visit.

Section 5.5.1.2 Administration of Carboplatin and Etoposide
First paragraph
Add: new third and fourth sentence

Carboplatin and Etoposide are to be given only after veliparib/placebo dosing on Cycle Day –2 and Day –1 are confirmed. If veliparib/placebo 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, if needed.

Section 5.5.1.2 Administration of Carboplatin and Etoposide
Subsection Calculation of Carboplatin Dose
Delete: subsection title and text

Calculation of Carboplatin Dose

The below guidance recommendation for carboplatin dose calculation is intended to reduce variability of carboplatin doses between sites.

The initial dose of carboplatin must be calculated using GFR. In the absence of renal toxicity greater than or equal to CTCAE Grade 2 (serum creatinine > 1.5 × ULN) or toxicity requiring dose modification, the dose of carboplatin does not need to be recalculated for subsequent cycles, but will be subject to dose modification for toxicity as noted in the protocol.

Carboplatin doses will be based on the subject's weight at baseline and should remain the same throughout the study. However, the doses may be recalculated based on the subject's weight at each cycle, and need to be recalculated if the subject has a weight change of greater than or equal to 10% from baseline.

In subjects with an abnormally low serum creatinine (less than 0.7 mg/dL), the creatinine clearance should be estimated using a minimum value of 0.7 mg/dL.

CALVERT FORMULA:

Carboplatin dose (mg) = target AUC × (GFR + 25)

NOTE: the GFR used in the Calvert formula cannot exceed 125 mL/min.

For the purposes of this protocol, the GFR is considered to be equivalent to the estimated creatinine clearance. The estimated creatinine clearance (mL/min) is calculated by the method of Cockcroft-Gault using the following formula:

Creatinine Clearance (mL/min) = [140-Age (years)] × Weight (kg) /
(72 × Ser Cr (mg/dL))

For female subjects: multiply the result above by 0.85.

Notes:

Body mass index (BMI) should be calculated for each subject. A BMI should be calculated using the following formula:

$$BMI = (\text{Weight in kg}) / (\text{Height in meters})^2$$

Actual weight should be used for estimation of GFR for subjects with BMI < 25.

Adjusted weight should be used for estimation of GFR for subjects with BMI ≥ 25.

Adjusted weight calculation:

$$\text{Ideal weight (kg)} = (((\text{Height (cm)}/2.54) - 60) \times 2.3) + 45.5$$

$$\text{Adjusted weight (kg)} = ((\text{Actual weight} - \text{Ideal weight}) \times 0.40) + \text{Ideal weight}$$

If a patient with BMI of ≥ 25 is currently being dosed using actual weight, adjust dose with next planned treatment.

At the time of a dose modification for toxicity:

If the creatinine at the time of a dose modification is lower than the creatinine used to calculate the previous dose, use the previous (higher) creatinine;

If the creatinine at the time of a dose modification is higher than the creatinine used to calculate the previous dose, use the current (higher) creatinine. This will ensure that the patient is actually receiving a dose reduction.

Note that carboplatin dose will be recalculated if the subject has weight change of greater than or equal to 10% from baseline.

Section 5.5.2 Identity of Investigational Products
First paragraph previously read:

Information regarding the veliparib formulation to be used in this study is presented in Table 13.

Has been changed to read:

Information regarding the veliparib/placebo formulation to be used in this study is presented in Table 13.

Table 13. Identity of Investigational Products
Last row previously read:

Study Drug	Dosage Form	Strength	Route of Administration	Manufacturer
Veliparib (ABT-888)	Capsule	20 mg or placebo*	Oral	AbbVie

Has been changed to read:

Study Drug	Dosage Form	Strength	Route of Administration	Manufacturer
Veliparib (ABT-888)	Capsule	20 mg*	Oral	AbbVie

Table 13. Identity of Investigational Products
Table note "*"
Add: new last sentence

20 mg capsule strength for Phase 1 ONLY.

Section 5.5.2.2 Packaging and Labeling
Previously read:

Veliparib (ABT-888) will be supplied by AbbVie in HDPE bottles containing either 20 mg, 40 mg, 100 mg active or their placebo capsules. Bottles will contain either 15, 24 or 50 capsules per bottle. This will allow for the 2, 5, 14, 21, or monotherapy days of administration (with one additional dose to cover loss, spillage or replacement due to vomiting within 15 minutes). Each bottle will be labelled per country requirements

including at a minimum the information required by local regulations. The label is to remain affixed to the bottle. All blank spaces on the label will be completed by site staff prior to dispensing to the subject.

AbbVie will provide study sites with instructions and training for the proper handling, storage and documentation related to all investigational supplies.

Has been changed to read:

Phase 1 Dose Escalation

Veliparib (ABT-888) will be supplied by AbbVie in HDPE bottles containing either 20 mg, 40 mg, 100 mg active capsules. Bottles will contain either 15, 24 or 50 capsules per bottle. This will allow for the 2, 5, 14, 21, or monotherapy days of administration (with one additional dose to cover loss, spillage or replacement due to vomiting within 15 minutes). Each bottle will be labelled per country requirements including at a minimum the information required by local regulations. The label is to remain affixed to the bottle. All blank spaces on the label will be completed by site staff prior to dispensing to the subject.

Phase 2 Randomized Double-Blind

Veliparib (ABT-888)/placebo will be supplied by AbbVie in HDPE bottles containing either 40 mg, 100 mg active or their placebo capsules. Bottles will contain either 15, 24 or 50 capsules per bottle. This will allow for the 14 days combination or continuous monotherapy days of administration (with additional doses to cover loss, spillage or replacement due to vomiting within 15 minutes). Each bottle will be labelled per country requirements including at a minimum the information required by local regulations. The label is to remain affixed to the bottle. All blank spaces on the label will be completed by site staff prior to dispensing to the subject.

AbbVie will provide study sites with instructions and training for the proper handling, storage and documentation related to all investigational supplies.

Section 5.5.3 Method of Assigning Subjects to Treatment Groups (Dose Escalation Portion)
Section title previously read:

Method of Assigning Subjects to Treatment Groups (Dose Escalation Portion)

Has been changed to read:

Method of Assigning Subjects to Treatment Groups (Phase 1 Dose Escalation)

Section 5.5.4 Method of Assigning Subjects to Treatment Groups (Randomized Phase 2 Portion)
Section title and text previously read:

5.5.4 Method of Assigning Subjects to Treatment Groups (Randomized Phase 2 Portion)

All subjects will be randomized using an IRT system. Before the study is initiated, directions for the IRT will be provided to each site. The site will contact the IRT within 4 calendar days prior to or on the subject's Cycle 1 Day –2 to obtain a Screening (subject) number once the subject has signed the informed consent and a study-specific procedure has been performed (i.e., central laboratory samples drawn). Once the screening number is assigned, if the subject is not enrolled in the study or is not randomized (as applicable), the reason for screen failure will be documented in the source document and in the eCRF. For others, the site will access the system and a unique randomization number will be provided.

The IRT will randomize subjects in a 1:1:1 ratio to one of the three treatment arms as follows:

- Arm A: veliparib in combination with carboplatin/etoposide followed by veliparib monotherapy
- Arm B: veliparib in combination with carboplatin/etoposide followed by placebo monotherapy
- Arm C: placebo in combination with carboplatin/etoposide followed by placebo monotherapy

Subject randomization will be stratified by: LDH (≤ ULN versus > ULN), and gender.

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.

Has been changed to read:

5.5.4 Method of Assigning Subjects to Treatment Groups (Phase 2 Randomized Double-Blind)

All subjects will be randomized using an IRT system. Before the study is initiated, the IRT user manual, which provides instruction on how to use the system via the web or phone, will be provided to each site.

Subjects who complete all Screening procedures and meet eligibility criteria may proceed to randomization. Subject randomization will be stratified by: LDH (≤ ULN versus > ULN), and gender; therefore a subject's baseline LDH value must be known prior to randomization and when accessing the IRT to perform the randomization transaction.

The site will contact the IRT to obtain a Screening (subject) number once the subject has signed the informed consent and a study-specific procedure has been performed (i.e., central laboratory samples drawn). Once the subject number is assigned, if the subject is not enrolled/randomized the reason for screen failure will be documented in the source document and in the eCRF. If the subject meets all inclusion and none of the exclusion criteria, the site will access the system to randomize the subject. The IRT will randomize subjects in a 1:1:1 ratio to one of the three treatment arms as follows:

- Arm A: veliparib in combination with carboplatin/etoposide followed by veliparib monotherapy
- Arm B: veliparib in combination with carboplatin/etoposide followed by placebo monotherapy

- Arm C: placebo in combination with carboplatin/etoposide followed by placebo monotherapy

Subject randomization will be stratified by: LDH (≤ ULN versus > ULN), and gender.

Section 5.5.5 Selection and Timing of Dose for Each Subject
Subsection Phase 2
Subsection title and text previously read:

Phase 2

Subjects will be randomized in a 1:1:1 ratio to receive carboplatin, etoposide, placebo followed by placebo maintenance or carboplatin, etoposide, veliparib followed by either veliparib or placebo maintenance for at least 4 cycles of combination treatment, unless disease progression or unacceptable toxicity warrants earlier discontinuation from the treatment. Subject whose status at the completion of the 4th cycle of combination therapy warrants, in the opinion of the investigator, continued combination treatment may receive up to two additional combination therapy cycles (e.g., up to a total of 6 cycles). After the completion of combination therapy, subjects without evidence of disease progression by most recent scheduled radiographic assessment (CT) will receive veliparib at 400 mg BID or placebo continuous schedule in 21-day cycles, until disease progression or unacceptable toxicity.

Has been changed to read:

Phase 2 Randomized Double-Blind

Subjects will complete at least 4 cycles of combination therapy, unless disease progression or unacceptable toxicity warrants earlier discontinuation from the combination treatment. Subject whose status at the completion of the 4th cycle of combination therapy warrants, in the opinion of the investigator, continued combination treatment may receive up to two additional combination therapy cycles (e.g., up to a total of 6 cycles) if required by local standard of care. After the completion of combination therapy, subjects without evidence of disease progression by most recent scheduled

radiographic assessment (CT) will receive veliparib at 400 mg BID or placebo continuous schedule in 21-day cycles, until disease progression or unacceptable toxicity.

Section 5.5.6 Blinding
First paragraph previously read:

Phase 1 is the open-label portion of the trial. Phase 2 is the randomized; double-blinded portion of the study. Placebo capsules will be identical in appearance to the veliparib capsules. All study site personnel, including the investigator, study coordinator, as well as the subjects, will remain blinded to the treatment. Subjects will be randomized via IVRS/IWRS.

Has been changed to read:

All study site personnel, including the investigator, study coordinator, as well as the subjects, will remain blinded to the treatment throughout the course of the Phase 2 portion of the study. The IRT system will provide access to blinded subject treatment information during the double-blind period, if needed.

Section 5.5.7 Treatment Compliance
Previously read:

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

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

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

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.

Has been changed to read:

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

Subjects will be instructed to return all veliparib/placebo bottles (empty, partially filled or full) and the completed dosing card to the study site personnel at each combination cycle Day 1, each Maintenance cycle Day 1, 30-Day Follow-Up Visit and/or at the Final Visit. The Investigator or his/her designated and qualified representatives will document the bottles returned and the number of capsules returned per bottle in the IRT system.

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

Subjects should be questioned regarding their adherence to the assigned treatment schedule at each study visit. The Investigator or his/her designated and qualified

representatives will also confirm that the subject took the required number of capsules per protocol.

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. The Investigator or his/her designated and qualified representatives will document compliance on the appropriate eCRF.

Section 5.5.8 Drug Accountability
Previously read:

Upon receipt of a shipment of veliparib, the representative at each site will verify that study drug supplies are received intact and in the correct amounts. This will be documented by signing and dating the Proof of Receipt or similar document respectively via direct recording in the IVRS. An accurate (running) inventory of study drug will be kept by the site, and will include the lot number, shipment number and the number of capsules dispensed, subject initials, initials of person who dispensed the drug, and the date study drug was dispensed for each subject. An overall accountability of the study drug will be performed and verified by the AbbVie monitor throughout the study and at the site close-out visit. All study drug unit doses must be inventoried, accounted for, and returned to the destruction facility or to AbbVie or destroyed per instructions from AbbVie and according to local regulations. A copy of the Drug Accountability Form, in accordance with instructions provided by the AbbVie monitor, will also be included in the shipment.

The investigator and/or named the sub-investigators agree not to supply study medication to any persons not enrolled in the study.

The site will record the dose of carboplatin and etoposide given to each subject in the source documents and on the eCRF. As the investigator will obtain both carboplatin and etoposide commercially, site inventory and accountability of carboplatin and etoposide will not be performed, and drug accountability forms will not be provided. However,

each site will be responsible for tracking the lot numbers for all carboplatin and etoposide dispensed.

Has been changed to read:

Upon receipt of a shipment of veliparib, the representative at each site will verify that study drug supplies are received intact and in the correct amounts. This will be documented by signing and dating the Proof of Receipt (PoR) or similar document respectively via direct recording in the IRT. The shipment receipt must be acknowledged in the IRT in order to become available for dispensation to subjects. All veliparib/placebo must be retained in the designated secure area under proper storage conditions. The study site will record the kit number of veliparib/placebo given to each subject in the source documents and on the eCRF.

The IRT will maintain a current and accurate inventory of study drug, accountability, reconciliation, returns, and destruction for each site. The IRT will also include the lot number, the bottle/kit numbers, and the date veliparib/placebo was dispensed for each subject.

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

The Investigator or designee will document the bottles of veliparib/placebo returned and the number of capsules on the appropriate form in the IRT. If the number of capsules taken and the number of capsules returned do not add up to the number of capsules dispensed, an explanation is required and should be documented in the IRT.

An overall accountability of the study drug will be performed and verified by the AbbVie monitor throughout the study and at the site close-out visit. All study drug unit doses must be inventoried, accounted for, and returned to the destruction facility or to AbbVie or destroyed per instructions from AbbVie and according to local regulations.

The investigator and/or named the sub-investigators agree not to supply study medication to any persons not enrolled in the study.

The site will record the dose of carboplatin and etoposide given to each subject in the source documents and on the eCRF. As the investigator will obtain both carboplatin and etoposide commercially, site inventory and accountability of carboplatin and etoposide will not be performed, and drug accountability for carboplatin and etoposide will not be performed in the IRT. However, each site will be responsible for tracking the lot numbers for all carboplatin and etoposide dispensed.

Section 5.6.4 Selection of Doses in the Study
Previously read:

The initial starting dose of 80 mg BID veliparib in the Phase 1 portion of the study was derived from the results obtained in the ECOG E2511, GOG 9923 and AbbVie M10-898 clinical studies, as well as from the non-clinical studies.

Doses for carboplatin in combination with etoposide will be given as per standard of care in first line treatment for extensive stage SCLC as per NCCN guideline 2014.[3]

The recommended dose for veliparib monotherapy is 400 mg BID. This dose is well characterized for safety and tolerability based on the experience from multiple clinical trials. The maximum dose for 100 mg veliparib capsule will not exceed 400 mg BID, the maximum dose for 40 mg veliparib capsules will not exceed 1000 mg/day, and for 20 mg capsule will not exceed 1000 mg/day.

Has been changed to read:

<u>Phase 1 Dose Escalation</u>

The initial starting dose of 80 mg BID veliparib in the Phase 1 portion of the study was derived from the results obtained in the ECOG E2511, GOG 9923 and AbbVie M10-898 clinical studies, as well as from the non-clinical studies.

Doses for carboplatin in combination with etoposide will be given as per standard of care in first line treatment for extensive stage SCLC as per NCCN guideline 2014.[3]

The dose for veliparib monotherapy is 400 mg BID. This dose is well characterized for safety and tolerability based on the experience from multiple clinical trials.

Phase 2 Randomized Double-Blind

The RPTD has been defined in the Phase 1 portion of the study as veliparib 240 mg BID administered on Days –2 – 12 (14-Day schedule), carboplatin AUC 5 mg/ml*hr administered on Day 1, etoposide 100 mg/m^2 administered on Days 1 – 3 of 21-Day cycles.

The dose for veliparib/placebo monotherapy is 400 mg BID administered continuously in 21-Day cycles.

Table 16. Guidelines for Veliparib, Carboplatin, and Etoposide Dose Reduction Levels
Table title and table previously read:

Table 16. Guidelines for Veliparib, Carboplatin, and Etoposide Dose Reduction Levels

Dose Reductions	Carboplatin	Etoposide	Veliparib
Starting Dose	AUC 5	100 mg/m^2	As assigned
Dose Reduction 1	AUC 4	75 mg/m^2	Next lower DL (assigned –1)
Dose Reduction 2	No Additional Reductions Allowed	55 mg/m^2	Next lower DL (assigned –2)

Notes: For combination therapy cycles only; for monotherapy cycles see Section 5.7.1. "Next lower DL" refers to the daily dose levels tested in the dose escalation part of the study. The dose of each drug can be reduced independently based on the observed toxicities. For veliparib dose level of 80 mg, Dose Reduction 1 is to 60 mg, Dose Reduction 2 is to 40 mg.

Has been changed to read:

Table 16. Guidelines for Veliparib, Carboplatin, and Etoposide Dose Reduction Levels During Combination Therapy

Dose Reductions	Carboplatin	Etoposide[a]	Veliparib[b]
Starting Dose	AUC 5	100 mg/m^2	Phase 1: As assigned Phase 2: 240 mg BID
Dose Reduction 1	AUC 4	75 mg/m^2	Phase 1: Next lower DL (assigned –1) Phase 2: 200 mg BID
Dose Reduction 2	No Additional Reductions Allowed	55 mg/m^2	Phase 1: Next lower DL (assigned –2) Phase 2: 160 BID

a. Refer to Section 5.7.2.1.2 for etoposide dose reduction guidelines related to bilirubin.

b. Refer to Section 5.7.1 for veliparib dose reduction guidelines for maintenance therapy. "Next lower DL" refers to the daily dose levels tested in the dose escalation part of the study. The dose of each drug can be reduced independently based on the observed toxicities. For veliparib dose level of 80 mg (Phase 1 only), Dose Reduction 1 is to 60 mg, Dose Reduction 2 is to 40 mg.

Section 5.7.1 Veliparib/Placebo Dose Reductions and Delays
Section title and text previously read:

5.7.1 Veliparib/Placebo Dose Reductions and Delays

The following are guidelines for dose reduction, delay and discontinuation of veliparib/placebo:

1. Veliparib/placebo part of combination therapy will be discontinued if both carboplatin and etoposide are discontinued prior to the completion of the planned number of combination therapy cycles.
2. For any subject who experiences Grade 3/4 toxicity which is not attributable to carboplatin/etoposide or the underlying disease, the Veliparib/placebo dose will 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 toxicity resolution re-start veliparib at a reduced dose level.

3. Two dose reductions are allowed:

   a. Combination treatment cycles: For Dose Reduction 1, the dose of Veliparib/placebo will be reduced to next lower dose level (assigned dose level -1). Veliparib/placebo may be reduced again (Dose Reduction 2, assigned dose level –2) due to toxicity (Table 16). If further dose reductions are required, this should be discussed with the AbbVie Study Designated Physician. **All veliparib/placebo dose reductions within combination treatment cycles are permanent.** Veliparib/placebo cannot be dose-reduced below 40 mg BID.

   b. Monotherapy cycles: Dose Reduction 1 to 300 mg BID, Dose Reduction 2 to 200 mg BID. Subjects requiring dose reduction of veliparib/placebo to below 200 mg BID will be discontinued from the treatment.

4. Any ≥ Grade 2 event of seizure attributed to veliparib/placebo requires discontinuation of veliparib/placebo.

5. Veliparib/placebo doses held will not affect the study calendar and will not be replaced. If veliparib/placebo-related toxicity necessitates the delay in veliparib/placebo re-initiation beyond the scheduled start of the next combination treatment cycle, the start of the cycle should be delayed until veliparib/placebo can be restarted. The AbbVie study designated physician may be contacted (Section 6.6) for subjects who require more than a 2-week delay in the re-initiation of the next cycle.

Table 17. Dose Delay or Reduction Due to Toxicity Attributable to Veliparib in the Combination Treatment Cycles

Adverse Event	Veliparib*
Any Grade 3 or 4 toxicity attributable to veliparib which is not attributable to carboplatin/etoposide or underlying disease	1. Interrupt dosing in the current cycle until Grade 1 (or Grade 2 if present at baseline) and 2. Reduce veliparib dose to next lower dose level upon dosing re-initiation

* Two dose reductions of veliparib are allowed. Veliparib dose cannot be reduced below 40 mg BID. All veliparib dose reductions in the combination treatment cycles are considered permanent. For continuous schedule of veliparib administration in cases of delayed (> 7 days) hematologic recovery or late onset (after Day 12 of the Cycle) GI toxicity skipping Days 13 – 19 doses in subsequent cycles can be considered in place of reducing the daily dose level.

Table 18. Veliparib Dose Delay or Reduction Due to Toxicity in the Monotherapy Cycles

Adverse Event	Veliparib*
Any Grade 3 or 4 toxicity attributable to veliparib	1. Interrupt dosing in the current cycle until Grade 1 (or Grade 2 if present at baseline) and 2. At resumption reduce veliparib dose to next lower monotherapy dose level

* Two dose reductions of veliparib are allowed.

Has been changed to read:

5.7.1 Veliparib/Placebo Dose Reductions and Interruptions

The following are guidelines for dose reduction, interruption and discontinuation of veliparib/placebo during combination therapy:

1. Veliparib/placebo will be discontinued if both carboplatin and etoposide are discontinued prior to the completion of the planned number of combination therapy cycles.

2. For any subject who experiences Grade 3/4 toxicity which is not attributable to carboplatin/etoposide or the underlying disease, refer to Table 17 for dosing guidelines.
3. Two dose reductions are prospectively allowed during combination therapy for subjects who experience toxicity attributable to veliparib/placebo. Refer to Table 16 for dose reduction guidelines.
    a. Veliparib dose reduction at C1D1 is allowed in case of nausea and vomiting attributable to C1D-2 and C1D-1 veliparib doses
    b. All veliparib/placebo dose reductions within combination therapy cycles are permanent.
    c. If further dose reductions (beyond prospectively allowed two) are required, sites must contact the AbbVie TA MD.
4. Any ≥ Grade 2 event of seizure attributed to veliparib/placebo requires discontinuation of veliparib/placebo.
5. Veliparib/placebo interruptions will not affect the schedule of planned study procedures and will not be replaced. If veliparib/placebo-related toxicity necessitates the delay in veliparib/placebo re-initiation beyond the scheduled start of the next combination therapy cycle, the start of the cycle should be delayed until veliparib/placebo can be restarted. The AbbVie TA MD may be contacted (Section 6.6) for subjects who require more than a 2-week delay in the re-initiation of the next cycle.

The following are guidelines for dose reduction, interruption and discontinuation of veliparib/placebo during Maintenance Therapy:

1. Dose Reduction 1: 300 mg BID.
2. Dose Reduction 2: 200 mg BID.

3. Subjects requiring dose reduction of veliparib/placebo to below 200 mg BID will be discontinued from treatment.

4. For subjects who experience any Grade 3/4 toxicity during maintenance therapy which is attributable to veliparib, refer to Table 18 for dosing guidelines.

Table 17. Dose Interruption or Reduction Due to Toxicity Attributable to Veliparib in the Combination Therapy Cycles

Adverse Event	Veliparib
Any Grade 3 or 4 toxicity attributable to veliparib which is not attributable to carboplatin/etoposide or underlying disease	1. Interrupt dosing in the current cycle until Grade 1 (or Grade 2 if present at baseline) and 2. Reduce veliparib dose to next lower dose level upon dosing re-initiation

Table 18. Veliparib Dose Interruption or Reduction Due to Toxicity Attributable to Veliparib in the Maintenance Therapy Cycles

Adverse Event	Veliparib
Any Grade 3 or 4 toxicity attributable to veliparib	1. Interrupt dosing in the current cycle until Grade 1 (or Grade 2 if present at baseline) and 2. At resumption reduce veliparib dose to next lower monotherapy dose level

Section 5.7.2 Carboplatin/Etoposide Dose Reductions and Delays
Previously read:

If a subject experiences an adverse event attributable to carboplatin or etoposide, carboplatin or etoposide may either be held or dose reduced for that cycle. At the Investigator's discretion, carboplatin and etoposide administration may continue as scheduled.

If a dose reduction or delay is required for carboplatin and/or etoposide, the Investigator should follow procedures as defined in the locally approved product label or applicable Summary of Product Characteristics (SmPC). Section 5.7.2.1 outlines suggested dose

reductions for carboplatin/etoposide if above information is not available. PD and/or PK samples will not be drawn during carboplatin and/or etoposide dose delays. If the Investigator considers an event attributable to carboplatin and/or etoposide and not veliparib, the Investigator may consider reducing the dose of both agents.

All toxicity will be graded by the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0 (CTCAE). **All carboplatin and/or etoposide dose reductions are permanent**. Re-escalation of the dose of therapy is not allowed. All toxicities should have 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.

If toxicity precludes the initiation of the dosing of carboplatin/etoposide in the cycle, and veliparib doses on Days –2 and –1 of the cycle have already been administered, veliparib should be administered again once the toxicity resolves for two days prior to carboplatin/etoposide dosing.

Has been changed to read:

If a subject experiences an adverse event attributable to carboplatin or etoposide, carboplatin or etoposide may either be interrupted or the dose reduced.

If a dose reduction or delay is required for carboplatin and/or etoposide, the Investigator should follow procedures as defined in the locally approved product label or applicable Summary of Product Characteristics (SmPC). Section 5.7.2.1 outlines suggested dose reductions for carboplatin/etoposide if above information is not available. PD and/or PK samples will not be drawn during carboplatin and/or etoposide dose delays.

Section 5.7.2.1 Guidelines for Carboplatin and Etoposide Dose Reductions and Delays
Previously read:

The below guidelines are suggested, unless described as mandatory. If a dose reduction or delay is required for carboplatin and/or etoposide, the Investigator should follow procedures according to institutional guidelines, the locally approved product label, local practice, or applicable SmPC. If the Investigator considers an event attributable to carboplatin and/or etoposide, the Investigator may consider reducing carboplatin and/or etoposide, but not veliparib/placebo. Suggested guidelines for dose reduction, delay, and discontinuation are included in Table 19 (if locally approved product label, local standard of care guideline or applicable SmPC for carboplatin/etoposide combination chemotherapy are not available).

Hematologic Toxicity

Neutropenia or Febrile Neutropenia

For febrile neutropenia with absolute neutrophil count (ANC) < 500/mm3 and a single temperature of > 38.3°C (101°F) or a sustained temperature of ≥ 38°C (100.4°F) for more than one hour, requiring intravenous antibiotics, the doses of both carboplatin and etoposide drugs should be reduced to the next lower dose level for all subsequent cycles of chemotherapy (Table 14). Implement dose reductions 1 and 2 for first and second episodes, respectively, as outlined in Table 19. Consider initiating prophylactic neutrophil growth factors (e.g., G-CSF) after the first episode. If ANC counts do not recover within 3 weeks, discontinue all protocol therapy.

For treatment delays of more than 7 days due to neutropenia, carboplatin and etoposide should be dose-reduced to next lower dose level for all subsequent cycles of chemotherapy, as outlined in Table 19.

For nadir neutropenia in the absence of fever or with fever that is successfully treated by oral antibiotics, there will be no dose adjustment.

ANC must be ≥ 1,500/mm^3 on Day 1 of each cycle (mandatory). If the counts are lower than the limit, then dosing of all drugs (carboplatin, etoposide and veliparib) should be delayed until recovery to the required ANC.

If the subject experiences fever with neutropenia, then neutrophil growth factors (e.g., G-CSF) should be given based on local standard of care guidelines, ASCO or NCCN guidelines.

Platelets

For Grade 4 nadir platelet count decrease (thrombocytopenia) (platelets < 25,000 mm3), the dose of both carboplatin and etoposide should be reduced to next lower dose level from the previous dose for all subsequent cycles of chemotherapy. Implement dose reductions 1 and 2 for the first and second episodes, respectively as outlined in Table 19. If counts do not recover within 3 weeks, discontinue all protocol therapy.

Platelet count must be > 100,000/mm^3 on Day 1 of each cycle. Doses or all drugs (carboplatin, etoposide and veliparib) should be delayed until platelet count recovers to > 100,000/mm^3.

Anemia

No dose reductions will be made for anemia. Subjects should be supported per the treating physician's discretion. The use of RBC transfusions for anemia will be allowed as clinically indicated and as per local standard of care or current NCCN guidelines. The use of growth factors for anemia is not permitted during Phase 1 Cycle 1.

If more than two dose modifications of carboplatin and etoposide are required for hematologic toxicity, e.g., in cases where an additional dose modification is needed for a toxicity which was not observed earlier, please consult the Study Designated Physician.

Non-Hematological Toxicity

Gastrointestinal Toxicity: Nausea and Vomiting

All subjects should receive antiemetics* to prevent nausea and vomiting. Specific antiemetic therapy is left to the discretion of the treating physician (steroids and 5-HT3 antagonists should be used). For vomiting Grade ≥ 3, consider hospital admission and/or use of aprepitant, if possible. Nausea/vomiting should have resolved to Grade 1 or less prior to initiation of next treatment cycle. Do not modify carboplatin and/or etoposide doses due to nausea/vomiting.

* Aprepitant, when given once daily for 14 days as a 100 mg capsule with an oral contraceptive containing 35 mcg of ethinyl estradiol and 1 mg of norethindrone, decreased the AUC of ethinyl estradiol by 43% and decreased the AUC of norethindrone by 8%. Women of childbearing potential using pregnancy contraception that includes ethinyl estradiol should not receive Aprepitant for the treatment of nausea/delayed emesis. Subjects may change to a different method of contraception if they wish to use Aprepitant.

Hepatic Toxicity

For bilirubin > 1.5 – 3.0 × ULN, not attributable to underlying disease, reduce the dose of etoposide to 50 mg/m^2. For bilirubin > 3 – 5 × ULN reduce the dose of etoposide to 30 mg/m^2. For bilirubin > 5 × ULN hold etoposide or hold all treatment if starting the next treatment cycle. When bilirubin resolves to ≤ 5 × ULN, treatment can be resumed, with etoposide dose to 30 mg/m^2. If bilirubin does not improve to ≤ 5 × ULN within 3 weeks of first occurrence, discontinue protocol therapy.

Other Grade 2/4 Non-Hematologic Toxicity

Other non-hematologic Grade 3/4 toxicity should be managed as per local SmPC guidelines and institutional standard practices.

Table 19. Suggested Guidelines for Carboplatin/Etoposide Dose Delay or Reduction

Adverse Event	Carboplatin Dose	Etoposide Dose
ANC < 1,500/mm^3 Day 1 of Cycle	Hold next cycle until ANC ≥ 1,500/mm^3.	Hold next cycle until ANC ≥ 1,500/mm^3.
Treatment delays of > 7 days due to neutropenia	Implement Dose Reduction 1 for 1st episode.	Implement Dose Reduction 1 for 1st episode and Dose Reduction 2 for 2nd episode.
Grade 3/4 febrile neutropenia with ANC < 500/mm^3, requiring IV antibiotics	Implement Dose Reduction 1 for 1st episode. Consider Prophylactic G-CSF after 1st episode.	Implement Dose Reduction 1 for 1st episode and Dose Reduction 2 for 2nd episode. Consider Prophylactic G-CSF after 1st episode.
Grade 3 nausea, vomiting or Grade 4 vomiting	Hold next cycle until resolution to Grade 1 or better. If more than 2 weeks dose delay is required consult with AbbVie medical monitor.	Hold next cycle until resolution to Grade 1 or better. If more than 2 weeks dose delay is required consult with AbbVie medical monitor.
Platelets < 100,000/mm^3 Day 1 of Cycle	Hold next cycle until platelets ≥ 100,000/mm^3.	Hold next cycle until platelets ≥ 100,000/mm^3.
Grade 4 thrombocytopenia	Implement Dose Reduction 1 for 1st episode.	Implement Dose Reduction 1 for 1st episode and Dose Reduction 2 for 2nd episode.
Bilirubin > 1.5 – 3.0 × ULN	No Change	Reduce dose to 50 mg/m^2
Bilirubin > 3 – 5 × ULN	No Change	Reduce dose to 30 mg/m^2
Bilirubin > 5 × ULN	Hold if bilirubin does not improve to ≤ 5 × ULN within 3 weeks of first occurrence, discontinue protocol therapy	Hold if bilirubin does not improve to ≤ 5 × ULN within 3 weeks of first occurrence, discontinue protocol therapy
Any other Grade 3/4 toxicity	Per local SmPC/institution guidelines	Per local SmPC/institution guidelines

Has been changed to read:

The below guidelines are suggested, unless described as mandatory. If a dose reduction or delay is required for carboplatin and/or etoposide, the Investigator should follow procedures according to institutional guidelines, the locally approved product label, local practice, or applicable SmPC. If the Investigator considers an event attributable to carboplatin and/or etoposide, the Investigator may consider reducing carboplatin and/or etoposide, but not veliparib/placebo. Suggested guidelines for dose reduction, delay, and discontinuation are included in Table 16 and Table 19 (if locally approved product label,

local standard of care guideline or applicable SmPC for carboplatin/etoposide combination chemotherapy are not available).

All carboplatin and/or etoposide dose reductions are permanent. Re-escalation of the dose of therapy is not allowed. All toxicities should have 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 toxicity precludes the initiation of the dosing of carboplatin/etoposide in the cycle, and veliparib doses on Days –2 and –1 of the cycle have already been administered, veliparib should be administered again once the toxicity resolves for two days prior to carboplatin/etoposide dosing. In such a case, a new supply of veliparib/placebo is to be dispensed, and Day –2 and Day –1 are to be repeated for that cycle.

For Phase 1 ONLY: PD and/or PK samples will not be drawn during carboplatin and/or etoposide dose delays. If the Investigator considers an event attributable to carboplatin and/or etoposide and not veliparib, the Investigator may consider reducing the dose of both agents.

5.7.2.1.1 Hematologic Toxicity

If chemotherapy must be withheld due to hematologic toxicity, CBC and platelet counts should be obtained weekly via central labs (if done locally, sample MUST be split for central lab) until the counts reach the lower limits for treatment as outlined. The treatment schedule will then proceed in the usual sequence.

Neutropenia or Febrile Neutropenia

For febrile neutropenia with absolute neutrophil count (ANC) < 500/mm^3 and a single temperature of > 38.3°C (101°F) or a sustained temperature of ≥ 38°C (100.4°F) for more than one hour, requiring intravenous antibiotics:

a. Doses of both carboplatin and etoposide drugs should be reduced to the next lower dose level for all subsequent cycles of chemotherapy. Suggested dose reduction levels are outlined in Table 14.
b. Implement dose reductions, as outlined in Table 19.
c. Initiate prophylactic neutrophil growth factors (e.g., G-CSF) after the first episode and in accordance with local SOC practices, ASCO or NCCN guidelines.
d. If ANC counts do not recover within 3 weeks, discontinue all protocol therapy.

For treatment delays of more than 7 days due to neutropenia, carboplatin and etoposide should be dose-reduced to next lower dose level for all subsequent cycles of chemotherapy, as outlined in Table 19.

For nadir neutropenia in the absence of fever or with fever that is successfully treated by oral antibiotics, there will be no dose adjustment.

ANC must be $\geq 1{,}500/mm^3$ on Day 1 of each cycle (mandatory). If the ANC is lower than $1{,}500/mm^3$, then dosing of all drugs (carboplatin, etoposide and veliparib) will be delayed until recovery to the required ANC.

Platelets

For Grade 4 nadir platelet count decrease (thrombocytopenia) (platelets $< 25{,}000\ mm^3$), the dose of both carboplatin and etoposide should be reduced to next lower dose level from the previous dose for all subsequent cycles of chemotherapy. Implement dose reductions 1 and 2 for the first and second episodes, respectively as outlined in Table 19. If counts do not recover within 3 weeks, discontinue all protocol therapy.

Platelet count must be $> 100{,}000/mm^3$ on Day 1 of each cycle (mandatory). Doses or all drugs (carboplatin, etoposide and veliparib) should be delayed until platelet count recovers to $> 100{,}000/mm^3$.

Anemia

No dose reductions will be made for anemia. Subjects should be supported per the treating physician's discretion. The use of RBC transfusions for anemia will be allowed as clinically indicated and as per local standard of care or current NCCN guidelines. The use of growth factors for anemia is not permitted during Phase 1 Cycle 1.

If more than two dose modifications of carboplatin and etoposide are required for hematologic toxicity, e.g., in cases where an additional dose modification is needed for a toxicity which was not observed earlier, please consult the AbbVie TA MD.

5.7.2.1.2 Non-Hematological Toxicity

Gastrointestinal Toxicity: Nausea and Vomiting

All subjects should receive antiemetics* to prevent nausea and vomiting. Specific antiemetic therapy is left to the discretion of the treating physician (steroids and 5-HT3 antagonists should be used). For vomiting Grade ≥ 3, consider hospital admission and/or use of aprepitant, if possible. Nausea/vomiting should have resolved to Grade 1 or less prior to initiation of next treatment cycle. Do not modify carboplatin and/or etoposide doses due to nausea/vomiting.

* Aprepitant, when given once daily for 14 days as a 100 mg capsule with an oral contraceptive containing 35 mcg of ethinyl estradiol and 1 mg of norethindrone, decreased the AUC of ethinyl estradiol by 43% and decreased the AUC of norethindrone by 8%. Women of childbearing potential using pregnancy contraception that includes ethinyl estradiol should not receive Aprepitant for the treatment of nausea/delayed emesis. Subjects may change to a different method of contraception if they wish to use Aprepitant.

Hepatic Toxicity

For bilirubin > 1.5 – 3.0 × ULN, not attributable to underlying disease, reduce the dose of etoposide to 50 mg/m^2. For bilirubin > 3 – 5 × ULN reduce the dose of etoposide to 30 mg/m^2. For bilirubin > 5 × ULN hold etoposide or hold all treatment if starting the next treatment cycle. When bilirubin resolves to ≤ 5 × ULN, treatment can be resumed, with etoposide dose to 30 mg/m^2. If bilirubin does not improve to ≤ 5 × ULN within 3 weeks of first occurrence, discontinue protocol therapy.

5.7.2.1.3 Other Grade 3/4 Non-Hematologic Toxicity

Other non-hematologic Grade 3/4 toxicity should be managed as per local SmPC guidelines and institutional standard practices.

Table 19. Suggested Guidelines for Carboplatin/Etoposide Dose Delay or Reduction

Adverse Event	Carboplatin Dose	Etoposide Dose
ANC < 1,500/mm^3 Day 1 of Cycle	Hold next cycle until ANC ≥ 1,500/mm^3.	Hold next cycle until ANC ≥ 1,500/mm^3.
Treatment delays of > 7 days due to neutropenia	Implement Dose Reduction 1 for 1st episode.	Implement Dose Reduction 1 for 1st episode and Dose Reduction 2 for 2nd episode.
Grade 3/4 febrile neutropenia with ANC < 500/mm^3, requiring IV antibiotics	Implement Dose Reduction 1 for 1st episode. Initiate Prophylactic G-CSF after 1st episode.	Implement Dose Reduction 1 for 1st episode and Dose Reduction 2 for 2nd episode. Initiate Prophylactic G-CSF after 1st episode.
Grade 3 nausea, vomiting or Grade 4 vomiting	Hold next cycle until resolution to Grade 1 or better. If more than 2 weeks dose delay is required consult with AbbVie TA MD.	Hold next cycle until resolution to Grade 1 or better. If more than 2 weeks dose delay is required consult with AbbVie TA MD.
Platelets < 100,000/mm^3 Day 1 of Cycle	Hold next cycle until platelets ≥ 100,000/mm^3.	Hold next cycle until platelets ≥ 100,000/mm^3.
Grade 4 thrombocytopenia	Implement Dose Reduction 1 for 1st episode.	Implement Dose Reduction 1 for 1st episode and Dose Reduction 2 for 2nd episode.
Bilirubin > 1.5 – 3.0 × ULN	No Change	Reduce dose to 50 mg/m^2
Bilirubin > 3 – 5 × ULN	No Change	Reduce dose to 30 mg/m^2
Bilirubin > 5 × ULN	Hold if bilirubin does not improve to ≤ 5 × ULN within 3 weeks of first occurrence, discontinue protocol therapy	Hold if bilirubin does not improve to ≤ 5 × ULN within 3 weeks of first occurrence, discontinue protocol therapy
Any other Grade 3/4 toxicity	Per local SmPC/institution guidelines	Per local SmPC/institution guidelines

Section 6.1.2 Deaths
Last paragraph previously read:

During survival follow-up, deaths attributed to progression of disease under study should be recorded only on the Study Completion/Early Discontinuation eCRF.

Has been changed to read:

During survival follow-up, deaths should be recorded on Survival eCRF.

Section 6.1.3 Lack of Efficacy or Worsening of Disease Under Study
Add: new last sentence

Refer to Appendix F for listing of events expected with progression of ED SCLC.

Section 6.1.4 Serious Adverse Events
In-text table, "Death of Subject" previously read:

An event that results in the death of a subject when not related to ED SCLC.

Has been changed to read:

An event that results in the death of a subject.

Section 6.2 Adverse Events Expected Due to SCLC or Progression of SCLC
Last paragraph previously read:

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

Has been changed to read:

These adverse events may occur alone or in various combinations and are considered expected adverse events in SCLC subjects but will not be subject to expedited reporting. These data will be captured as efficacy assessment data only.

Section 6.3 Adverse Event Severity
Last paragraph previously read:

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.

Has been changed to read:

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

Section 6.4 Relationship to Study Drug
In-text table previously read:

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.

Has been changed to read:

Reasonable Possibility	After consideration of factors including timing of the event, biologic plausibility, clinical judgment, and potential alternative causes, there is **sufficient** evidence (information to suggest a causal relationship.
No Reasonable Possibility	After consideration of factors including timing of the event, biologic plausibility, clinical judgment and potential alternative causes there is **insufficient** evidence (information to suggest a causal relationship.

Section 7.0 Protocol Deviations
"Primary Contact:" previously read:

Primary Contact:

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

Office: [redacted]
Fax:
Email:

Has been changed to read:

Primary Contact:

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

Office:
Fax:
Email: [redacted]

Section 8.1.1.1 Demographics
Previously read:

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.

Has been changed to read:

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

Smoking history can be defined as current smoker (subject who has smoked within the last 12 months and has more than 100 smoking events [for example, cigarettes] in their lifetime), never smoked (subject with a lifetime smoking history of ≤ 100 smoking events [for example, cigarettes] in lifetime) and past smoker (subject who has not smoked in past 12 months and has more than 100 smoking events [for example, cigarettes] in their lifetime).

Section 8.1.2.1 Primary Efficacy Endpoint
Last paragraph previously read:

Progression-free survival will be defined as the number of days from the date of randomization to the date of earliest disease progression (radiographic progression per RECIST version 1.1 or clinical disease progression) or death. 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. 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 available disease progression assessment (radiographic or clinical).

Has been changed to read:

Progression-free survival will be defined as the number of days from the date of randomization to the date of earliest disease progression (radiographic progression per RECIST version 1.1) or death. 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. 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 available radiographic disease progression assessment.

Section 8.1.2.3 Tertiary Efficacy Endpoints
Subsection <u>Duration of Overall Response</u>
First sentence previously read:

Duration of overall response will be defined as the number of days from the date of first response (CR or PR) to the earliest documentation of progressive disease (radiographic or clinical).

Has been changed to read:

Duration of overall response will be defined as the number of days from the date of first response (CR or PR) to the earliest documentation of radiographic progressive disease.

Section 8.2 Determination of Sample Size
Subsection Phase 2
Subsection title previously read:

Phase 2

Has been changed to read:

Phase 2 Randomized Double-Blind

Section 13.0 Completion of the Study
Last paragraph, first sentence previously read:

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

Has been changed to read:

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

Appendix B. List of Protocol Signatories
Previously read:

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

Has been changed to read:

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

Appendix C. RECIST (Version 1.1) for Tumor Response (PFS)
Subsection Methods of Measurement
First and second paragraph previously read:

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.

Has been changed to read:

Conventional CT with contrast 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 that 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 made. This decision should be guided by the tumor type under investigation and the anatomic location of the disease and the outcome of the decision should be communicated to AbbVie.

Document Approval

Study M14361 - A Phase 1 Dose Escalation and Phase 2 Randomized Double-Blind Study of Veliparib in Combination with Carboplatin and Etoposide as a Therapy of Treatment-Naïve Extensive Stage Disease Small Cell Lung Cancer - Amendment 5 - EudraCT 2014-001764-35 - 22Nov2016

Version: 1.0 **Date:** 24-Nov-2016 05:00:06 PM **Company ID:** 11242016-00F9F6813AB61A-00001-en

Signed by:	Date:	Meaning Of Signature:
[redacted]	22-Nov-2016 02:20:42 PM	Approver
	22-Nov-2016 02:22:57 PM	Approver
	22-Nov-2016 08:48:46 PM	Approver
	23-Nov-2016 03:09:40 A	Approver
	23-Nov-2016 04:27:25 AM	Approver
	23-Nov-2016 03:13:26 PM	Approver
	24-Nov-2016 05:00:05 P	Approver