1.0 Title Page

Clinical Study Protocol M06-873

A Phase 1/2a Study Evaluating the Safety, Pharmacokinetics, and Efficacy of ABT-263 in Subjects with Relapsed or Refractory Chronic Lymphocytic Leukemia

Incorporating Administrative Changes 1, 2, 3, 4, 5, and 6 and Amendments 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, and 14

AbbVie Number/ Investigational Product:	ABT-263 (navitoclax)
Date:	03 September 2020
Development Phase:	1/2a
Study Design:	This is an open-label study designed to determine the maximum tolerated dose (MTD), safety, pharmacokinetics and preliminary efficacy profile of ABT-263 in subjects with relapsed or refractory chronic lymphocytic leukemia.
Investigator:	Investigator information on file at AbbVie.
Sponsor:	AbbVie Inc. (AbbVie) and AbbVie GmbH & Co. KG
Sponsor/Emergency Contact:	[redacted] Executive Medical Director 1 North Waukegan Rd North Chicago, IL 60064 Phone: [redacted] EMAIL: [redacted]

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	03 January 2007
Amendment 1	18 September 2007
Amendment 2	31 March 2008
Amendment 3	25 November 2008
Amendment 4	17 December 2008
Administrative Change 1	03 March 2009
Administrative Change 2	30 June 2009
Amendment 5	08 October 2009
Amendment 6	21 May 2010
Amendment 7	01 December 2010
Administrative Change 3	09 December 2010
Amendment 8	11 May 2011
Amendment 9	19 October 2011
Administrative Change 4	22 October 2012
Amendment 10	18 September 2014
Administrative Change 5	16 November 2015
Amendment 11	08 August 2016
Administrative Change 6	02 March 2018
Amendment 12	26 July 2018
Amendment 13	16 January 2020

The primary purpose of this amendment is to incorporate necessary protocol modifications due to the COVID-19 (Coronavirus 2019) pandemic as follows:

- Section 3.0 – Included information on the re-evaluation of the benefit and risk to subjects participating in the study.
- Section 5.4.1 – Added that the investigator should contact the sponsor medical contact before discontinuing a subject from the study for a reason other than "planned per protocol."

- Section 5.5.1 – Added delays in study drug dosing due to the above COVID-19 testing guidance.
- Section 5.5.4 – Included instructions that in the event the subject cannot pick up study drug onsite, DTP (Direct To Patient) shipment can be made, as permitted by local regulations.
- Section 7.0 – clarified that protocol deviations may include modifications due to COVID-19.
- Section 9.1 – Added that AbbVie will modify the study protocol as necessary due to the pandemic. Investigators must also notify AbbVie if any urgent safety measures are taken.
- Section 10.1 – Added that remote monitoring may be employed as needed.
- Appendix A – Addition of COVID-19 and DTP to list of abbreviations.
- In addition, sponsor contact information updates have been made.

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

2.0 Table of Contents

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3.0 Introduction

Bcl-2 Family Proteins

The Bcl-2 family proteins are important regulators of the intrinsic apoptosis pathway. The Bcl-2 oncogene was first identified in follicular lymphoma where the t(14;18) chromosomal translocation results in significant over-expression of this protein in B-cells. In contrast to other known oncogenes, Bcl-2 does not stimulate cellular proliferation, but rather inhibits programmed cell death by protecting cells from a wide variety of pro-apoptotic stimuli, including cytokine withdrawal, irradiation, cytotoxic drugs, heat and deregulated oncogenes.[1] The Bcl-2 family of genes encodes a family of closely related proteins that possess either pro-apoptotic or anti-apoptotic activity and share up to four Bcl-2 Homology (BH) domains.[2,3,4,5] The anti-apoptotic family members Bcl-X_L, Bcl-2, Bcl-w, Bcl-B, A1 and Mcl-1 are characterized by four BH domains that are designated BH1-4. The pro-apoptotic family members can be further subdivided into multidomain proteins (Bax, Bak) and the BH3-only proteins (Bad, Bik, Bid, Bim, Hrk, Bmf, Noxa, and Puma). The interplay between these three groups of proteins serves as the gateway to the intrinsic apoptosis pathway.

The multidomain pro-apoptotic proteins Bax and Bak are direct mediators of apoptosis and are absolutely required for the initiation of the mitochondrial apoptosis pathway.[6,7,8] Anti-apoptotic Bcl-2 family proteins (e.g., Bcl-2 and Bcl-X_L) inhibit cytochrome C release by blocking Bax/Bak activation.[9] The exact mechanism of action of Bcl-2 and Bcl-X_L has not been completely elucidated, however it is known that it requires the ability to bind the pro-apoptotic Bcl-2 family members and that the ratio of pro-apoptotic to anti-apoptotic proteins is associated with cell survival.[10,11,12]

ABT-263 Activity and Pharmacokinetic Profile

ABT-263 (navitoclax) is a small molecule Bcl-2 family protein inhibitor that binds with high affinity ($K_i \leq 1$ nM) to multiple anti-apoptotic Bcl-2 family proteins including Bcl-X_L, Bcl-2, Bcl-w, and Bcl-B. ABT-263 displays potent mechanism-based

cytotoxicity ($EC_{50} \leq 1$ μM) against human tumor cell lines derived from small cell lung carcinomas and lymphoid malignancies. ABT-263 exhibits potent single agent activity against 10 of 22 leukemia and lymphoma cell lines spanning both B-cell and T-cell malignancies.

Pre-clinical experiments have been performed on primary patient derived chronic lymphocytic leukemia (CLL) samples with ABT-737, a first generation Bcl-2 family protein inhibitor. Treatment with ABT-737 induced robust, concentration-dependent apoptosis in 47 of 50 patient-derived CLL specimens regardless of the presence of feeder cells. These cells were highly sensitive with EC_{50} values of < 0.25 μM. Forty-two of the 47 lines had EC_{50} values of < 0.01 μM. ABT-263, which has similar potency as ABT-737, would be expected to have similar efficacy.

The pharmacokinetic profile of ABT-263 was evaluated in multiple animal models including: CD-1 mouse, Sprague-Dawley rat, beagle dog and cynomolgus monkey. The pharmacokinetic profile of ABT-263 is characterized by very low plasma clearance and low volumes of distribution in all species studied, with terminal half-lives in the range of 4.6 to 8.4 hours. The oral bioavailability of the compound is formulation dependent, with values of 30% to 50% obtained from prototype solid dispersion and lipid-based formulations in dog. In rat, [^{14}C] ABT-263 is slowly absorbed, with clearance of the metabolites primarily in the bile. Elimination of total radioactivity is rapid, with 90% of the dose recovered within 24-hours post-dose. Parent drug is the major component in systemic circulation.

Based on preclinical evidence, potential treatment-related side effects may include drug interactions, lymphopenia, testicular effects and thrombocytopenia. At the expected biologically effective plasma concentration in humans of 6.5 μg/mL (C_{max}), ABT-263 is likely to inhibit the metabolism of drugs that are substrates for CYP2C8 and CYP2C9 by greater than 50%. Simulation of 350 mg q.d. dosing in humans describes an AUC of 92 μg•hr/mL at steady state, with a C_{max} of ~6.5 μg/mL. Under these conditions, platelet values in patients with normal platelet values (~300 K/μL) at baseline are expected to be ~25 K/μL at steady state. At the lower end of the predicted efficacious range, an AUC of

53 μg•hr/mL (predicted 200 mg q.d. dosing in humans) is expected to be attainable while still maintaining platelet values above 50 K/μL at steady state.

ABT-263 induces apoptosis, rather than lysis of circulating platelets, which differs from typical chemotherapy induced thrombocytopenia related to myelosuppression. Limited human clinical data are available to understand the response to infusion of exogenous platelets in the presence of circulating drug levels. Platelet transfusion studies conducted in beagle dogs demonstrated that transfusion of one-day old platelets administered near the time of ABT-263 C_{max}, resulted in higher platelet levels than dogs not receiving supplemental platelets. Platelet concentrations remained higher after 24 hours with declining ABT-263 concentrations. This study suggests that infusion of platelets may have beneficial effects in treating acute thrombocytopenia following oral dosing with ABT-263.

From the pre-clinical models, there may be an opportunity in the monotherapy setting to increase efficacy without additional platelet toxicity in the setting of continuous dosing. In murine xenograft models of SCLC, 21 days of continuous dosing achieves superior tumor growth inhibition, greater increase in life span, and greater incidence of complete and overall response rates compared to the intermittent dosing schedules or 14 days of dosing and 7 days off drug. In a dog toxicology study, ABT-263 was delivered once daily for 28 days. At doses that achieve plasma concentrations within the targeted efficacious exposure range, circulating platelet counts recovered to baseline within 14 days of dosing and remained at baseline for the subsequent 14 days of dosing.

This observation of platelet recovery during continued ABT-263 dosing has also been observed in the Phase 1 clinical studies. Given that platelet nadirs typically occur in the first few days of dosing and circulating platelet counts recover during continued dosing, a lead-in period may help reduce the depth of platelet nadir.

ABT-263 Toxicology

The safety of ABT-263 has been evaluated in single- and repeat-dose (up to 6 and 9 months in duration in rats and dogs, respectively), reproductive (male and female fertility and embryo fetal development), safety pharmacology (cardiovascular, neurofunctional, and pulmonary), genetic (Ames, in vitro cytogenetics, and in vivo micronucleus), and special studies (guinea pig sensitization; lymphocyte immunophenotyping; and single-dose oral toxicity in male rats). The primary effects of ABT-263 were on the hematopoietic system (platelets and lymphocytes) and the male reproductive system (germ cell depletion), and are believed to be based on inhibition of one or more members of the Bcl-2 family of antiapoptotic proteins. Other findings included ovarian atrophy (rats only), and generally minimal and reversible liver changes (single-cell hepatocellular necrosis, increased mitotic index, and hypertrophy/hyperplasia and pigmentation of Kupffer cells) and single-cell necrosis in various tissues. ABT-263 was neither genotoxic, nor did it affect male or female fertility in rats or embryo-fetal development in rats and rabbits. ABT-263-related effects were observed on brain, testes, and circulating platelets in juvenile rats. Effects on the brain (cerebellar hypoplasia), which were not observed in adult rats, were the likely result of incomplete maturation of the blood-brain-barrier at the time dosing was initiated in the rat pups (post natal Day 7).

ABT-263 caused increases in pulmonary and peripheral vascular resistance and decreases in cardiac output in the dog following acute or multiple daily dosing. Despite the increases in vascular resistance, there were no increases in blood pressure. On Day 28 of the oral dosing study, these cardiovascular effects were associated with a mean C_{max} value of 16.6 μg/mL, whereas no statistically significant hemodynamic changes were associated with a mean C_{max} of 11.4 μg/mL.[13] Similar systemic exposures induced these effects in the acute cardiovascular study.

Chronic Lymphocytic Leukemia (CLL)

Chronic lymphocytic leukemia (CLL) is a monoclonal disorder characterized by a progressive accumulation of functionally incompetent lymphocytes. It is the most

common form of leukemia in adults in the Western World, accounting for nearly 25% of all leukemias.[15] CLL primarily affects elderly individuals however approximately one-third of patients are less than sixty years of age at diagnosis.[16] It is currently estimated that annually over 10,000 people will be diagnosed with CLL in the United States, and that almost 4,700 individuals will die of the disease.[17] The approximate 5-year survival rate for patients with CLL is 73%.[18]

CLL presents with a variable clinical course. Approximately one third of patients do not require treatment as they experience long survival and die of causes unrelated to disease. Another third have an initial indolent phase that is followed by rapid progression of the disease requiring therapy. The remaining third have aggressive disease and require treatment at the time of diagnosis. CLL patients will often have compromised bone marrow reserve due to their underlying disease. The principal complication of CLL is immunodeficiency related to myelosuppression and as a result, infection is the major cause of death in patients with CLL.[19]

Treatment decisions for patients with CLL are made based upon considerations such as age, clinical staging, expected survival, and anticipated toxicities. First line treatment options include alkylating agents, alkylator/anthracycline combination therapies and purine analogues such as fludarabine. Improvement in treatment response rates occurred with the switch from historical single-agent usage to combination therapy, such as fludarabine and cyclophosphamide, with some combinations yielding overall response rates (ORR) in excess of 90%. An alternative to combination therapy is sequential therapy. The sequential regimen of fludarabine, cyclophosphamide, and rituximab (FCR) induced ORR of 88-95% with a high incidence of complete responses (53-70%).[20-22]

In previously treated/relapsed patients, fludarabine is the most active single-agent, with ORR ranging from 50-60%, and complete remission (CR) rates from 3-13%.[23] Many patients treated previously with fludarabine can be retreated and will respond again to the same regimen.[24] However, almost all CLL patients who are treated with single agent fludarabine or in combination will ultimately become fludarabine-refractory.[25]

The treatment options for patients with fludarabine-refractory disease are limited. Campath, a fully humanized monoclonal antibody directed against CD52, is the only approved therapy for CLL patients who have been treated with alkylating agents and who have failed fludarabine therapy. Clinical trials in patients treated with Campath have demonstrated ORRs ranging from 21-33%. Progression-free survival rates ranged between 4 and 7 months.[26]

Current chemotherapeutic agents elicit their anti-tumor response by inducing apoptosis through a variety of mechanisms. However, many tumors ultimately become resistant to these agents. Bcl-2 and Bcl-X_L have been shown to confer chemotherapy resistance in both short-term survival assays in vitro and more recently, in vivo. This suggests that therapies aimed at suppressing the function of Bcl-2 and Bcl-X_L might potentially overcome this mechanism of chemotherapy resistance.[27] Preclinical studies suggest that the Bcl-2 family protein inhibitor has single agent anti-tumor activity.

Based upon the preclinical profile of ABT-263, the role of Bcl-2 family proteins in hematological malignancies, and the lack of an existing therapy that provides a survival benefit in relapsed or refractory CLL patients, clinical investigation of ABT-263 is warranted.

ABT-263 Clinical Data

Preliminary aggregate clinical data from the 3 ongoing Phase 1 studies support that ABT-263 is tolerable at doses up to 250 mg in a 21/21 day continuous dosing schedule, which achieves exposures consistent with preclinical efficacy. Anti-tumor activity has been noted in study subjects with CLL at doses ≤ 200 mg, suggesting that ABT-263 may provide a clinical benefit to subjects with CLL.

The cumulative preclinical toxicology, safety pharmacology, metabolism, pharmacokinetic, and preliminary clinical data indicate that ABT-263 has been adequately characterized and that treatment with ABT-263 represents an acceptable risk to adult subjects with cancer. Consistent with the toxicological finding of a concentration

dependent decrease in circulating platelets in animal models, thrombocytopenia appears to be a DLT for ABT-263 in humans. The ongoing clinical studies with ABT-263 will continue to evaluate its safety profile, DLT, MTD, bioavailability, pharmacokinetics, and efficacy.

This study will determine the dose limiting toxicity (DLT), the maximum-tolerated dose (MTD), and will assess the safety, pharmacokinetics, and preliminary efficacy of ABT-263 in subjects with relapsed or refractory CLL. ABT-263 will be administered orally under two different dosing schedules (14/21 day dosing schedule and 21/21 day continuous dosing schedule). The following 14/21 dose levels have been completed to date: 10 mg, 110 mg, 200 mg, and 250 mg. The following 21/21 dose levels have been completed to date: 125 mg, 200 mg, 250 mg and 300 mg.

Considering the coronavirus (COVID-19) pandemic, the benefit and risk to subjects participating in this study has been re-evaluated. Subjects receiving ABT-263 may be at an increased risk for COVID-19 infection or experience serious illness if infected. Management of these adverse events will be made on a case-by-case basis with consideration of benefit/risk. However, based on the population and disease being studied, and the anticipation that COVID-19 related risks are not expected to differ substantially between study subjects and the broader population of subjects receiving treatment for CLL, no change to the benefit/risk balance for subjects in this study is expected.

A detailed discussion of the preclinical toxicology, metabolism, and pharmacology can be found in the Investigator's Brochure.[14]

4.0 Study Objectives

The objectives of the Phase 1 portion of the study include:

- Safety assessment
- Dose limiting toxicity (DLT) determination
- Maximum tolerated dose (MTD) determination

- Recommended Phase 2 Dose (RPTD) and schedule determination
- Pharmacokinetic profile evaluation

The objectives of the Phase 2a portion of the study include:

- Safety assessment at the recommended Phase 2 dose (RPTD) and schedule
- Preliminary efficacy assessment including biomarker assessment
- Pharmacokinetic profile evaluation

The objectives of the Extension Study portion of the study include:

- Safety assessment
- Evaluation of data regarding progression free survival (PFS) and overall survival (OS)

5.0 Investigational Plan

5.1 Overall Study Design and Plan: Description

This is a Phase 1/2a study evaluating the safety, PK, and preliminary efficacy of the orally administered Bcl-2 family protein inhibitor, ABT-263, in approximately 72 subjects with relapsed or refractory chronic lymphocytic leukemia.

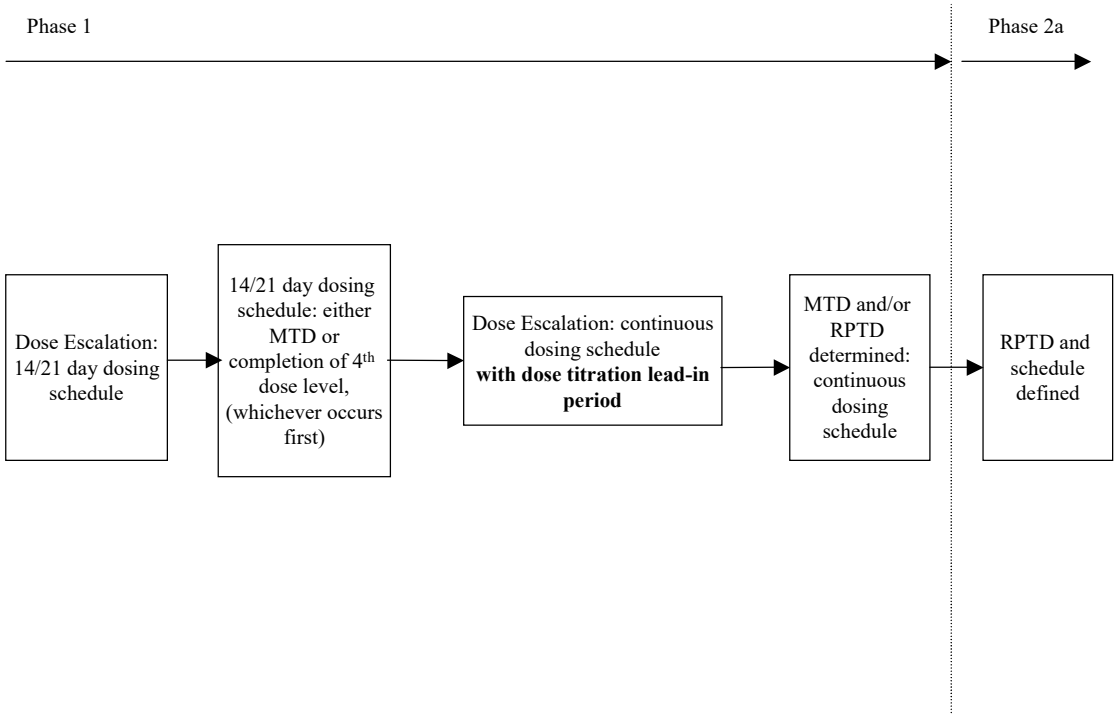
The study will consist of three distinct portions. The Phase 1 portion of the study will evaluate the pharmacokinetic profile and safety of ABT-263 administered under two different dosing schedules (14/21 day and 21/21 day) in up to 40 subjects with relapsed or refractory CLL following a dose escalation scheme in order to define the DLT and the MTD. Subjects will be enrolled at approximately eight research sites for the Phase 1 portion of the study. A continual reassessment methodology will be employed during Phase 1 to obtain a more precise estimate of the MTD and determine the recommended Phase 2 dose (RPTD).

The Phase 2a portion of the study will evaluate ABT-263 in approximately 32 subjects with CLL who have relapsed following any (but no more than 5) prior myelosuppressive/chemotherapy treatment regimen(s) at the defined RPTD and dosing schedule to obtain additional safety information and a preliminary assessment of efficacy as defined in Section 5.3.3. Subjects in the Phase 2a portion of the study will be enrolled at approximately twelve research sites.

The Extension portion of the study will continue to evaluate the safety of ABT-263 administered under two different dosing schedules (14/21 day and 21/21 day) in approximately 13 subjects with relapsed or refractory CLL. Eligible subjects will be active subjects from the Phase 1 or Phase 2a portions of the study.

Figure 1 depicts the Phase 1 and Phase 2a study design.

Figure 1. Phase 1 and Phase 2a Study Design



Continual Reassessment Method

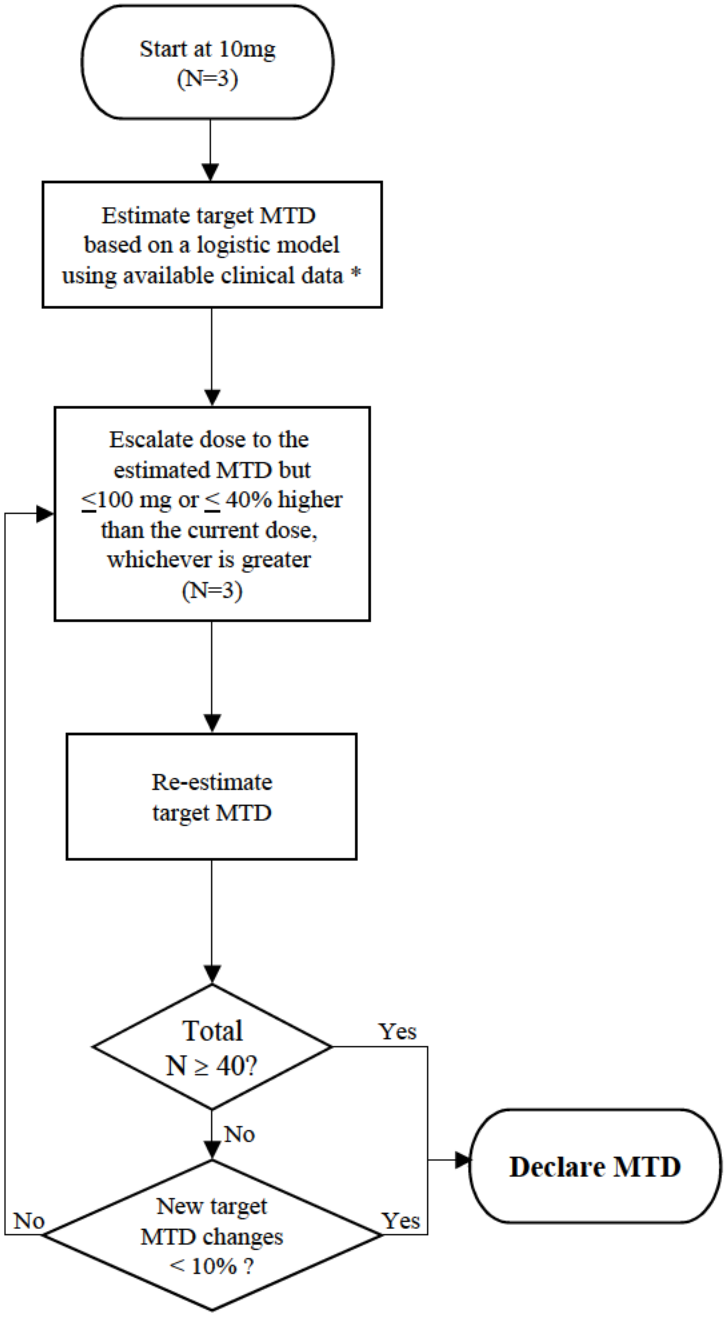
The experimental design for the Phase 1 portion of the study is an adaptation of a continual reassessment method (CRM), which is based on the concept of maximizing the number of subjects at the best current estimation of the MTD given the previous observations.[28,29] The CRM attempts to estimate the target MTD from a continuum of doses, whereas a fixed design merely selects a dose from a discrete set. If the true target dose is not among the choices set out in advance by fixed designs, they can only approximate it. A CRM based design uses a statistical model for dose and toxicity by including the accumulating data to guide selection of the next dose. Simulations and literature have shown that compared to the conventional fixed 3+3 design, the CRM typically requires fewer subjects to find the MTD, does not greatly overshoot the MTD (that is, subjects are less likely to be treated with dangerously high doses), and does not greatly underestimate the MTD. This design also minimizes the exposure of Phase 1 subjects to lower, potentially inefficacious doses.

Escalation will continue to the estimated MTD. The dose will be escalated by no more than an incremental increase of 100 mg or a 40% increase from the current dose level, whichever is greater. A minimum of 3 subjects will be enrolled in each cohort. Additional eligible subjects may be enrolled at the current dose level at the discretion of the investigator and the AbbVie Medical Monitor. If a cohort has enrolled more than 3 subjects, dose escalation decisions may be made following the completion of Cycle 1 for subjects in the intended cohort size of three. However, available data from all subjects receiving study drug will be used in dose escalation decisions. Predicted efficacious concentrations of ABT-263 are expected to occur in the dose range of 200 mg to 350 mg based on preclinical studies.

Subsequent dose levels will be selected based on an estimate from a statistical analysis. The statistical analysis will be a logistic regression model for the dose-toxicity relationship (i.e., the relationship between dose and the probability of DLT) and will incorporate data from the M06-814 study in lymphoid malignancies (with inclusion of CLL subjects) for initial modeling. The first step will be to fit the logistic regression

model and obtain the estimate of the MTD. Three subjects will be dosed at this estimated MTD. After all three subjects complete Cycle 1, a logistic regression model will be fitted using all of the data cumulatively from this study, and an updated estimate of the MTD will be obtained. Three more subjects will be dosed at the new estimated MTD, and the design will continue in this fashion, assigning subjects to the MTD as estimated from current results, until the estimated MTD changes by less than 10% or the predetermined sample size of 40 subjects is reached, whichever comes first. Complete details on the CRM design for the Phase 1 portion of the study are provided in Section 8.1.1. The following flowchart depicts the CRM design:

Figure 2. Adaptive CRM Design



* Data from M06-814 (Ph 1 study in lymphoid malignancies) will be incorporated into the prior for modeling

A minimum of 3 subjects will be enrolled in each cohort. Additional eligible subjects may be enrolled at the current dose level at the discretion of the investigator and the AbbVie Medical Monitor. If a cohort has enrolled more than 3 subjects, dose escalation decisions may be made following the completion of Cycle 1 for subjects in the intended cohort size of three. Dose adjustment decisions will be informed by subject tolerability and safety. However, adverse events occurring after the first cycle and ongoing pharmacokinetic assessment may also be considered in dose escalation decisions. If pharmacokinetic results indicate more than 25% of intersubject variability can be attributed to differences in body weight or body surface area (BSA), escalation will proceed with dosing normalized to body weight or BSA; therefore subsequent dose levels will be determined using average subject BSA or average subject weight.

If, in the opinion of the investigators and the AbbVie Medical Monitor, the observed dose limiting toxicities are likely to have resulted from a cumulative and continuous exposure to the study drug, an alternative dosing schedule for ABT-263 may be explored. The alternative schedule will be jointly determined by the sponsor and investigator, based on pharmacokinetic data and the required recovery periods for the observed DLTs. For example, an extended recovery period may be instituted or an every other day dosing schedule could be implemented.

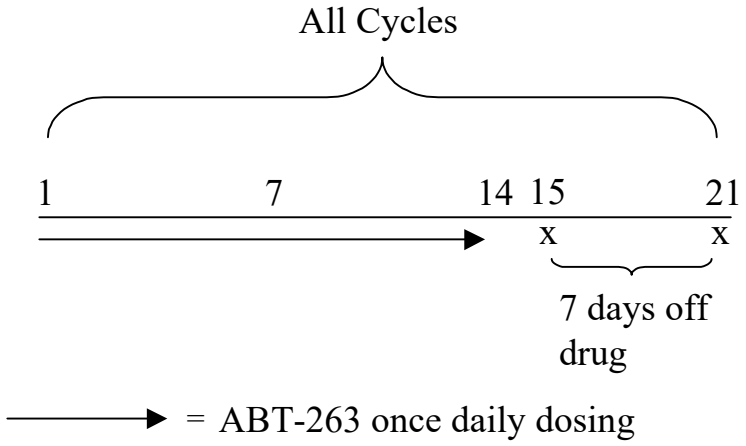
Adjustments to the dose escalation schedule may also be made based upon preliminary pharmacokinetic and safety data obtained from concurrent dose escalation studies that are being conducted with ABT-263. These decisions will be based on the judgment of the AbbVie Medical Monitor in consultation with the investigator.

Subject assessments for safety and clinical progression will continue weekly through the first 2 cycles (6 weeks). Subsequently, subject assessments for safety and clinical progression will be performed once every cycle (every 3 weeks) or more frequently, as needed.

Phase 1 -14/21 Day Dosing

ABT-263 will be administered for 14 consecutive days followed by 7 days off drug to complete a 21-day cycle. Subjects will be instructed to self-administer ABT-263 orally once daily (QD) within 30 minutes after the completion of breakfast.

Figure 3. ABT-263 Dosing Schematic – Phase 1



Additionally, a continuous dosing regimen will be evaluated and compared to the 14/21 cyclic dosing regimen.

Phase 1 – 21/21 Day Continuous Dosing

Once either the MTD is defined or dosing in the 4th dose level is completed for the 14/21 day dosing schedule, whichever occurs first, a continuous dosing schedule will be assessed. Dosing with ABT-263 under the continuous dosing schedule (21/21 day) will begin at the dose estimated to provide exposure equivalent to the highest dosing level cleared (4th dose level) or the MTD from the 14/21 day schedule. For example, if the highest dose level cleared or the MTD from the 14/21 day dosing schedule is 375 mg, the continuous starting dose (defined Cycle 1 Day 1 dose) would be (375 × 14)/21 or 250 mg. A minimum of three subjects will be enrolled in each cohort. The ABT-263 dose will be

escalated using a modified CRM as described previously for the 14/21 day regimen (Figure 2).

Prior to beginning the assigned 21/21 day continuous dosing regimen, a 7-day lead-in dose titration period will be implemented. In preclinical experiments in which stepwise increases in ABT-263 doses were administered to dogs every one or two weeks, the thrombocytopenic effect of higher doses was significantly attenuated. These data combined with the clinically observed rebound in platelet counts from nadir during continued ABT-263 dosing suggest that a lead-in period may help reduce the depth of the initial platelet nadir and provide an additional margin of safety.

Subjects will begin dosing at 100 mg on Lead-in Day 1 (LD1). This is the dose level at which a mean maximal platelet drop of approximately 60% from baseline with recovery during 14 days of dosing is expected based on observations in this study to date. The lead-in titration dose may be adjusted if the defined dose level fails to significantly mitigate ABT-263-induced thrombocytopenia following the lead-in period or the defined dose level results in significant occurrence of DLT in the lead-in period.

A subject may only proceed from the lead-in period to the defined dose level for Cycle 1 Day 1 and beyond if platelet count is $\geq 50{,}000/mm^3$ after Lead-in Day 7 and stable or increasing. If the platelet count is $< 50{,}000/mm^3$ after Lead-in Day 7, the visit day will be considered Lead-in Day 8 and the subject will continue to receive the lead-in dose until the platelet count is $\geq 50{,}000/mm^3$.

When the platelet count is $\geq 50{,}000/mm^3$, the subject will receive the lead-in dose that day**,** and the next day (defined as Cycle 1 Day 1) the subject will receive the defined dose for Cycle 1 Day 1, provided the pre-dose platelet count that day is $\geq 50{,}000/mm^3$ and platelets are stable or increasing. For example, if a subject's platelet count is $\geq 50{,}000/mm^3$ on Lead-in Day 9, the subject will take the lead-in dose on Day 9. The next day will be considered Cycle 1 Day 1 and the subject will begin receiving the defined dose for Cycle 1 Day 1. However, if the pre-dose platelet count is $< 50{,}000/mm^3$ or

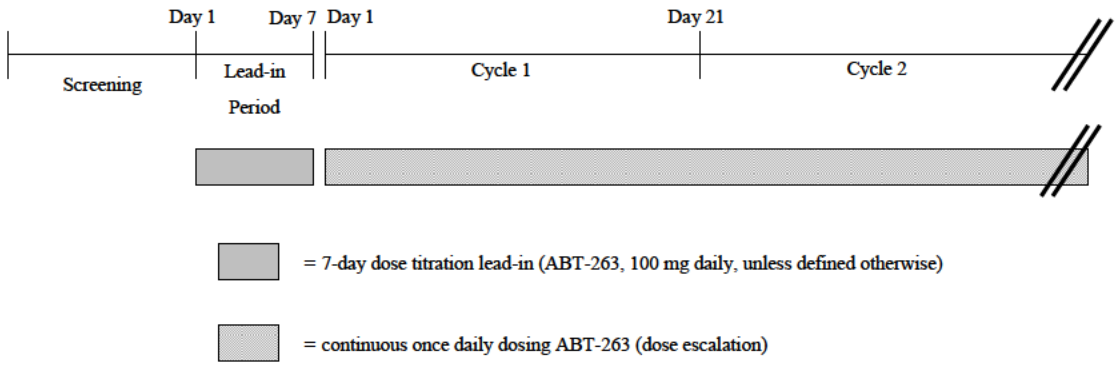
platelets are decreasing, then the day becomes Lead-in Day 10 and the subject continues dosing at the lead-in dose.

If the platelet count is < 50,000/mm^3 after 14 days at the lead in dose, the lead in dose will become the subject's dose for the duration of the study. To change from the lead in dose to a higher dose (for subjects who continue receiving the lead in dose beyond the lead in period), a discussion between the investigator and the AbbVie Medical Monitor is required.

The period for defining DLTs will be the total days dosed in the lead-in period plus 21 days dosed in Cycle 1 (28 days if subject moves to Cycle 1 Day 1 after the planned 7 day lead-in period).

For the purpose of subject assessments for safety and clinical progression under a 21/21 day dosing schedule, a cycle will be defined as 21 days. These assessments for safety and clinical progression will continue weekly through the first two cycles (6 weeks) of ABT-263. Subsequently, subject assessments for safety and clinical progression will be performed once every cycle (every 3 weeks) of ABT-263.

Figure 4. 21/21 Day Continuous Dosing Schedule for ABT-263



Intra-subject Dose Escalation in Phase 1

In order to maximize the collection of information at relevant doses and to minimize the exposure of individuals to sub-optimal doses, subjects may progressively escalate their current dose to the highest dose level tolerated through 2 cycles of ABT-263 administration. Individuals will need to complete at least two cycles at their originally assigned dose level, as well as subsequent dose levels, prior to any dose escalation.

All intra-subject dose escalation decisions will be based on the judgment of the investigator in coordination with the AbbVie Medical Monitor. Once the MTD is declared and/or the RPTD determined, subjects who remain on study and continue to tolerate the drug may escalate to the dose level determined to be the RPTD or the dose level below the RPTD. Phase 1 subjects will be allowed to switch their current dosing schedule to the recommended Phase 2a schedule once it has been declared. The RPTD will be defined by observed DLTs and/or determination of MTD.

Subject assessments for safety (physical examination, vital signs, chemistry, hematology, urinalysis, ECOG performance score and adverse event assessment) will be performed weekly during the first cycle at the new escalated dose and then may resume to once every cycle. All other procedures (platelet count, echocardiogram and ECG) will be performed according to the schedule of assessments as outlined in Table 1 and Table 2 for the subject's cumulative cycle.

Transition From Phase 1 Portion to Phase 2a Portion

Once the MTD and/or the RPTD is declared on the 21/21 day continuous dosing schedule, a safety analysis will be performed as described in Section 8.1.4. The results of the safety analysis as well as the recommended Phase 2 dose and dosing schedule will be communicated to all participating research sites prior to the start of enrollment in the Phase 2a portion of the study. Phase 1 subjects are not eligible for enrollment in the Phase 2a portion of the study, but may continue receiving ABT-263 monotherapy for up to 11 years after the last subject transitions to the Extension Study provided they continue to tolerate the drug, have no evidence of disease progression, and do not meet any of the

criteria for subject discontinuation (Section 5.4). Subjects who enter the Extension Study will continue taking ABT-263 at the same dose and schedule they were receiving in the Phase 1 portion of the study.

Subjects who enter the Extension Study must continue to meet all Inclusion and Exclusion criteria, with the exception of Laboratory Criteria. However, subjects must meet laboratory criteria as stated in Section 5.2.5.

Phase 2a

In the Phase 2a portion of the study, 250 mg of ABT-263 will be administered under a 21/21 day continuous dosing schedule. All subjects will self-administer ABT-263 within 30 minutes after the completion of breakfast unless specified otherwise.

A 7-day lead-in dose titration period will be implemented. Subjects will begin dosing at 100 mg on Lead-in Day 1 (LD1). A subject may only proceed from the lead-in period to 250 mg on Cycle 1 Day 1 and beyond if platelet count is $\geq 50{,}000/mm^3$ after Lead-in Day 7 and stable or increasing. If the platelet count is $< 50{,}000/mm^3$ after Lead-in Day 7, the visit day will be considered Lead-in Day 8 and the subject will continue to receive the lead-in dose until the platelet count is $\geq 50{,}000/mm^3$.

When the platelet count is $\geq 50{,}000/mm^3$, the subject will receive the lead-in dose that day, and the next day (defined as Cycle 1 Day 1) the subject will receive the defined dose for Cycle 1 Day 1, provided the pre-dose platelet count that day is $\geq 50{,}000/mm^3$ and platelets are stable or increasing. For example, if a subject's platelet count is $\geq 50{,}000/mm^3$ on Lead-in Day 9, the subject will take the lead-in dose on Day 9. The next day will be considered Cycle 1 Day 1 and the subject will begin receiving the defined dose for Cycle 1 Day 1. However, if the pre-dose platelet count is $< 50{,}000/mm^3$ or platelets are decreasing, then the day becomes Lead-in Day 10 and the subject continues dosing at the lead-in dose.

If the platelet count is $< 50{,}000/mm^3$ after 14 days at the lead in dose, the lead in dose will become the subject's dose for the duration of the study. To change from the lead in dose

to a higher dose (for subjects who continue receiving the lead in dose beyond the lead in period), a discussion between the investigator and the AbbVie Medical Monitor is required.

For the purpose of subject assessments for safety and clinical progression under a 21/21 day dosing schedule, a cycle will be defined as 21 days. These assessments for safety and clinical progression will continue weekly through the first two cycles (6 weeks) of ABT-263. Subsequently, subject assessments for safety and clinical progression will be performed once every cycle (every 3 weeks) of ABT-263.

If, during Phase 2a, dose-limiting toxicities are observed at a frequency higher than the definition of MTD (> 30%), the principal investigator and the AbbVie Medical Monitor will review the data and jointly determine whether dosing should continue or a new, lower recommended Phase 2 dose or alternate dosing schedule should be defined.

Subjects with stable disease in the Phase 2a portion of the study may continue receiving ABT-263 monotherapy for up to 11 years after the last subject transitions to the Extension Study, provided they continue to tolerate the drug, have no evidence of disease progression, and do not meet any of the criteria for subject discontinuation (Section 5.4). Subjects who enter the Extension Study will continue taking ABT-263 at the same dose and schedule they were receiving in the Phase 2a portion of the study.

Subjects who enter the Extension Study must continue to meet all Inclusion and Exclusion criteria, with the exception of Laboratory Criteria. However, subjects must meet laboratory criteria stated in Section 5.2.5.

5.2 Selection of Study Population

Subjects will undergo screening procedures within 14 days prior to initial study drug administration (Lead-in Day 1/Cycle 1 Day 1). Adult male and female subjects with CLL 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 Phase 1 Inclusion Criteria

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

1. The subject must be ≥ 18 years of age.
2. The subject must have relapsed or refractory CLL and require treatment in the opinion of the investigator.
3. The subject has an Eastern Cooperative Oncology Group performance score of ≤ 1.
4. Subjects receiving Selective Serotonin Reuptake Inhibitor (SSRI) anti-depressants (e.g., Prozac) must be receiving a stable dose for at least 21 days prior to the first dose of study drug.
5. The subject must have adequate bone marrow independent of growth factor support (with the exception of subjects with ANC < 1000/μL and bone marrow heavily infiltrated with underlying disease [80% or more]), renal and hepatic function, per local laboratory reference range at Screening as follows:
   - Bone marrow: Absolute Neutrophil count (ANC) ≥ 1000/μL; Platelets ≥ 75,000/mm^3 (entry platelet count must be independent of transfusion within 14 days of Screening), Hemoglobin ≥ 9.0 g/dL;
   - Renal function: Serum creatinine ≤ 2.0 mg/dL or calculated creatinine clearance ≥ 50 mL/min;
   - Hepatic function and enzymes: AST and ALT ≤ 3.0 × the upper normal limit (ULN) of institution's normal range; Bilirubin ≤ 1.5 × ULN. Subjects with Gilbert's Syndrome may have a Bilirubin > 1.5 × ULN;
   - Coagulation: aPTT, PT, not to exceed 1.2 × ULN.
6. Female subjects must be surgically sterile, postmenopausal (for at least 1 year), or have negative results for a pregnancy test performed as follows:
   - At Screening on a serum sample obtained within 14 days prior to initial study drug administration, and

- Prior to dosing on a urine sample obtained on Cycle 1 Day 1 or Lead-in Day 1 (lead-in period) if it has been > 7 days since obtaining the serum pregnancy test results.

7. All female subjects not surgically sterile or postmenopausal (for at least 1 year) and non-vasectomized male subjects must practice at least one of the following methods of birth control:
   - total abstinence from sexual intercourse (minimum one complete menstrual cycle);
   - a vasectomized partner;
   - hormonal contraceptives (oral, parenteral or transdermal) for at least 3 months prior to study drug administration;
   - double-barrier method (including condoms, contraceptive sponge, diaphragm or vaginal ring with spermicidal jellies or cream).
8. The subject must voluntarily sign and date an informed consent, approved by an Independent Ethics Committee (IEC)/Institutional Review Board (IRB), prior to the initiation of any screening or study-specific procedures.

5.2.2 Phase 1 Exclusion Criteria

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

1. The subject has a history or is clinically suspicious for cancer-related Central Nervous System (CNS) disease.
2. The subject has undergone an allogeneic or autologous stem cell transplant.
3. The subject has a recent history (within 1 year prior to first dose of study drug) of an underlying, predisposing condition of bleeding or currently exhibits signs of bleeding.
4. The subject has active peptic ulcer disease or other potentially hemorrhagic esophagitis/gastritis.

5. The subject has active immune thrombocytopenic purpura or a history of being refractory to platelet transfusions (within 1 year prior to the first dose of study drug).
6. The subject has received aspirin within 7 days prior to the first dose of study drug.
7. The subject is currently receiving or requires anticoagulation therapy or any drugs or herbal supplements that affect platelet function, with the exception of low-dose anticoagulation medications that are used to maintain the patency of a central intravenous catheter.
8. Subject has received steroid therapy for anti-neoplastic intent within 7 days prior to the first dose of study drug with the exception of inhaled steroids for asthma, topical steroids, or replacement/stress corticosteroids.
9. The subject has received any anti-cancer therapy including chemotherapy, immunotherapy, radiotherapy, hormonal (with the exception of hormones for thyroid conditions or estrogen replacement therapy [ERT]), or any investigational therapy within 14 days prior to the first dose of study drug, or has not recovered to less than grade 2 clinically significant adverse effect(s)/toxicity(ies) of the previous therapy.
10. The subject has received a biologic within 30 days prior to the first dose of study drug.
11. The subject has consumed grapefruit or grapefruit products within 3 days prior to the first dose of study drug.
12. The subject has a significant history of cardiovascular disease (e.g., myocardial infarction [MI], thrombotic, or thromboembolic event in the last 6 months), renal, neurologic, psychiatric, endocrinologic, metabolic, immunologic, or hepatic disease that in the opinion of the investigator would adversely affect his/her participating in this study.
13. A female subject is pregnant or breast-feeding.

14. The subject has tested positive for HIV (due to potential drug-drug interactions between anti-retroviral medications and ABT-263, as well as anticipated ABT-263 mechanism based lymphopenia that may potentially increase the risk of opportunistic infections and potential drug-drug interactions with certain anti-infective agents).
15. The subject has a history of other active malignancies within the past 3 years prior to study entry, with the exception of:
    - adequately treated *in situ* carcinoma of the cervix uteri;
    - basal or squamous cell carcinoma of the skin;
    - previous malignancy confined and surgically resected with curative intent.
16. The subject exhibits evidence of other clinically significant uncontrolled condition(s) including, but not limited to:
    - Uncontrolled systemic infection (viral, bacterial, or fungal)
    - diagnosis of fever and neutropenia within 1 week prior to study drug administration.

5.2.3 Phase 2a Inclusion Criteria

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

1. The subject must be ≥ 18 years of age.
2. The subject must have CLL and require treatment in the opinion of the investigator.
3. The subject has relapsed disease and has received no more than 5 prior myelosuppressive/chemotherapy regimens.
4. Subject has an Eastern Cooperative Oncology Group performance score of ≤ 1.
5. Subjects receiving Selective Serotonin Reuptake Inhibitor (SSRI) anti-depressants (e.g., Prozac) must be receiving a stable dose for at least 21 days prior to the first dose of study drug.

6. The subject must have adequate bone marrow independent of growth factor support (with the exception of subjects with ANC < 1000/μL and bone marrow heavily infiltrated with underlying disease [80% or more]), renal and hepatic function, per local laboratory reference range at Screening as follows:

   - Bone marrow: Absolute Neutrophil count (ANC) ≥ 1000/μL; Platelets ≥ 75,000/mm^3 (entry platelet count must be independent of transfusion within 14 days of Screening); Hemoglobin ≥ 9.0 g/dL;
   - Renal function: Serum creatinine ≤ 2.0 mg/dL or calculated creatinine clearance ≥ 50 mL/min;
   - Hepatic function and enzymes: AST and ALT ≤ 3.0 × the upper normal limit (ULN) of institution's normal range; Bilirubin ≤ 1.5 × ULN. Subjects with Gilbert's Syndrome may have a Bilirubin > 1.5 × ULN;
   - Coagulation: aPTT, PT must not exceed 1.2 × ULN.

7. Female subjects must be surgically sterile, postmenopausal (for at least 1 year), or have negative results for a pregnancy test performed as follows:

   - At Screening on a serum sample obtained within 14 days prior to initial study drug administration, and
   - Prior to dosing on a urine sample obtained on Lead-in Day 1 if it has been > 7 days since obtaining the serum pregnancy test results.

8. All female subjects not surgically sterile or postmenopausal (for at least 1 year) and non-vasectomized male subjects must practice at least one of the following methods of birth control:

   - total abstinence from sexual intercourse (minimum one complete menstrual cycle);
   - a vasectomized partner;
   - hormonal contraceptives (oral, parenteral or transdermal) for at least 3 months prior to study drug administration;
   - double-barrier method (including condoms, contraceptive sponge, diaphragm or vaginal ring with spermicidal jellies or cream).

9. The subject must voluntarily sign and date an informed consent, approved by an Independent Ethics Committee (IEC)/Institutional Review Board (IRB), prior to the initiation of any screening or study-specific procedures.

5.2.4 Phase 2a Exclusion Criteria

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

1. The subject has a history or is clinically suspicious for cancer-related Central Nervous System (CNS) disease.
2. The subject has a recent history (within 1 year prior to first dose of study drug) of an underlying, predisposing condition of bleeding or currently exhibits signs of bleeding.
3. The subject has undergone an allogeneic or autologous stem cell transplant.
4. The subject has active peptic ulcer disease or other potentially hemorrhagic esophagitis/gastritis.
5. The subject has active immune thrombocytopenic purpura or a history of being refractory to platelet transfusions (within 1 year prior to the first dose of study drug).
6. The subject is currently receiving or requires anticoagulation therapy or any drugs or herbal supplements that affect platelet function, with the exception of low-dose anticoagulation medications that are used to maintain the patency of a central intravenous catheter.
7. The subject has received steroid therapy for anti-neoplastic intent within 7 days prior to the first dose of study drug with the exception of inhaled steroids for asthma, topical steroids or replacement/stress corticosteroids.
8. The subject has received aspirin within 7 days prior to the first dose of study drug.

9. The subject has received any anti-cancer therapy including chemotherapy, immunotherapy, radiotherapy, hormonal (with the exception of hormones for thyroid conditions or estrogen replacement therapy [ERT]), or any investigational therapy within 14 days prior to the first dose of study drug, or has not recovered to less than grade 2 clinically significant adverse effect(s)/toxicity(ies) of the previous therapy.
10. The subject has received a biologic within 30 days prior to the first dose of study drug.
11. The subject has consumed grapefruit or grapefruit products within 3 days prior to the first dose of study drug.
12. The subject has a significant history of cardiovascular disease (e.g., myocardial infarction [MI], thrombotic, or thromboembolic event in the last 6 months), renal, neurologic, psychiatric, endocrinologic, metabolic, immunologic, or hepatic disease that in the opinion of the investigator would adversely affect his/her participating in this study.
13. A female subject is pregnant or breast-feeding.
14. The subject has tested positive for HIV (due to potential drug-drug interactions between anti-retroviral medications and ABT-263, as well as anticipated ABT-263 mechanism based lymphopenia that may potentially increase the risk of opportunistic infections and potential drug-drug interactions with certain anti-infective agents).
15. The subject has a history of other active malignancies within the past 3 years prior to study entry, with the exception of:
    - adequately treated *in situ* carcinoma of the cervix uteri;
    - basal or squamous cell carcinoma of the skin;
    - previous malignancy confined and surgically resected with curative intent.

16. The subject exhibits evidence of other clinically significant uncontrolled condition(s) including, but not limited to:
    - uncontrolled systemic infection (viral, bacterial, or fungal);
    - diagnosis of fever and neutropenia within one week prior to study drug administration.
17. The subject has received known CYP3A inhibitors (e.g., ketoconazole) within 7 days prior to first dose of study drug.

5.2.5 Extension Study Inclusion Criteria

Subjects who enter the Extension Study must continue to meet all Inclusion and Exclusion criteria (excluding laboratory parameters) from Phase 1 or in Phase 2a as listed above. Subjects entering the Extension Study must also have stable lab values per applicable laboratory reference ranges.

- Subjects must meet the following hematology and coagulation lab criteria:
    - Platelet counts must be $\geq 25{,}000/mm^3$ (untransfused). Platelet counts $\leq 50{,}000/mm^3$ must be stable and monitored at an increased frequency at the discretion of the investigator.
    - Absolute Neutrophil count (ANC) $\geq 500/\mu L$. ANC $\geq 500/\mu L$ and $< 1{,}000/\mu L$ should be monitored at an increased frequency at the discretion of the investigator.
    - Hemoglobin of ≥ 8.0 g/dL.
    - aPTT, PT is not to exceed $1.2 \times$ ULN.
- Subjects must meet the following chemistry criteria:
    - Subjects' chemistry values must not exceed Grade 2. Grade 2 chemistry labs should be monitored at an increased frequency at the discretion of the investigator.
    - Serum creatinine $\leq 3.0 \times$ the upper normal limit (ULN) of institution's normal range.

- AST and ALT ≤ 5.0 × the upper normal limit (ULN) of institution's normal range.
- Bilirubin ≤ 3.0 × ULN. Subjects with Gilbert's Syndrome may be allowed to have a Bilirubin > 3.0 × ULN based on a joint decision between the investigator and AbbVie medical monitor.

5.2.6 Prior and Concomitant Therapy

If a subject reports taking any over-the-counter or prescription medication, vitamins, and/or herbal supplements or if administration of any medication becomes necessary from the time of screening and throughout the study, the name of the medication, dosage information including dose and frequency, date(s) of administration including start and end dates, and reason for use must be recorded on the appropriate case report form (CRF). AbbVie will provide subject diaries to serve as a tool for the subjects to record concomitant medications and adverse events.

Steroid therapy, for anti-neoplastic intent, will not be allowed within 7 days prior to the first dose of study drug and during ABT-263 administration with the exception of inhaled steroids for asthma, topical steroids, or replacement/stress corticosteroids.

Aspirin will not be allowed within 7 days prior to the first dose of study drug or during ABT-263 administration. However, subjects who have previously received aspirin therapy for thrombosis prevention, may resume a low dose (i.e., maximum 100 mg QD) of aspirin if platelet counts are stable (≥ 50,000/mm^3) through 2 Cycles of ABT-263 administration. All decisions regarding treatment with aspirin therapy will be determined by the investigator in conjunction with the AbbVie Medical Monitor.

CYP3A inhibitors such as ketoconazole and clarithromycin are not allowed 7 days prior to the first dose of study drug or during ABT-263 administration.

Anti-cancer therapy including chemotherapy, immunotherapy, radiotherapy, hormonal (with the exception of hormones for thyroid conditions or estrogen replacement therapy [ERT]), and other investigational agents will not be allowed within 14 days prior to the

first dose of study drug, or has not recovered to less than grade 2 clinically significant adverse effect(s)/toxicity(ies) of the previous therapy. These agents will not be allowed during ABT-263 administration.

Biologics will not be allowed within 30 days prior to the first dose of study drug and during ABT-263 administration.

Colony stimulating factors (G-CSF, GM-CSF) or human erythropoietin will be considered during administration of ABT-263 if deemed necessary by the investigator and if mutually agreed upon by AbbVie Medical Monitor.

Best supportive care and treatment will be allowed for each subject (antiemetics, antibiotics, transfusions, nutritional support, pain control, etc.) with the exception of the following:

- Plavix, ibuprofen, Aggrastat and other anticoagulants, drugs or herbal supplements that affect platelet function (due to expected dose limiting toxicity of thrombocytopenia). Administration of heparin to keep subject's infusion lines patent is allowed. Low-dose anticoagulation medications that are used to maintain the patency of a central intravenous catheter are allowed.
- disulfiram (due to percentage of ethanol content in the drug formulation).

Concomitant medications of the following categories could potentially lead to adverse reaction(s). It is important to assess whether potential study subjects are taking any of the cautionary medications. If a potential study subject is taking any of the medications in the categories described below, the investigator will assess and document the use of medications known or suspected to fall in the following medication categories. A sample list of medications that fall into the cautionary categories mentioned below can be found in Appendix E. It is not possible to produce a 100% exhaustive list of medications that fall into the categories, so if in question, please refer to the appropriate product label. If the investigator determines that such a medication is medically necessary, the investigator will notify the AbbVie Medical Monitor and discuss the investigator's use of these

medications and the investigator's plans to medically monitor the potential study subject under consideration.

- CYP2C8 substrates such as glitazones and select statins (due to expected inhibition of the metabolism of CYP2C8 substrates).
- CYP2C9 substrates such as phenytoin and tolbutamide (due to expected inhibition of the metabolism of CYP2C9 substrates).
- CYP3A inducers such as rifampin and carbamazepine (due to possible induction of the metabolism of ABT-263).

If clinically indicated, anti-herpes and anti-PCP (Pneumocystis carinii pneumonia) prophylaxis should be considered. Although there is a potential for drug-drug interactions, there is likely to be limited potential clinical effects, therefore Bactrim (trimethoprim-sulfamethoxazole) can be considered for PCP prophylaxis with close clinical monitoring.

A list of common medications in the excluded classifications described above is provided in Appendix E. This is a partial list; all medications in these classifications are excluded.

Contact the AbbVie Medical Monitor identified in Section 6.5, if there are any questions regarding concomitant or prior therapies.

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

5.3.1 Efficacy and Safety Measurements Assessed and Flow Chart

Study procedures will be performed as summarized in Table 1 through Table 6 below for the Phase 1 and Phase 2a portions of the study.

Study procedures for subjects in the Extension Study can be found in Appendix G.

Table 1. Schedule of Assessments – 14/21 Day Dosing (Phase 1)

Procedure	Screening[a]	Cycle 1 Day 1 (C1D1)	Cycle 1 Day 2 (C1D2)	Cycle 1 Day 3 (C1D3)	Cycle 1 Day 14 (C1D14)	Weekly Through Cycle 2	Day 1 of Each Cycle After Cycle 2[b]	End of Every 3rd Cycle	Final Visit[r]	30 Day Safety Follow-Up[r]
Informed Consent	X									
Physical Exam (including weight)	X[c]	X				X[d]	X		X	X
Medical History	X	X								
Oncologic History	X									
Vital Signs	X	X				X	X		X	X
12-lead ECG[e]	X	X			X		X[e]		X	
2D Echocardiogram with Doppler[f]	X	X			X		X[f]		X	
Platelet Count[g]	X	X	X	X	X	X	X		X	X
Lymphocyte Enumeration[h]	X				X			X	X	
Pregnancy Test[i]	X	X								
Chemistry[j]	X	X	X	X		X	X		X	X
Hematology[j]	X	X	X	X		X	X		X	X
Urinalysis[j]	X	X				X	X		X	X
Performance Status (ECOG)	X	X				X	X		X	X
Tumor Assessments[k]	X[l]							X[m,n]	X	
Bone Marrow Aspirate and Biopsy[n]	X[o]									
Adverse Event/Concomitant Medications Assessment	X[p]	X			X	X	X		X	X[q]

Table 1. Schedule of Assessments – 14/21 Day Dosing (Phase 1) (Continued)

Procedure	Screening[a]	Cycle 1 Day 1 (C1D1)	Cycle 1 Day 2 (C1D2)	Cycle 1 Day 3 (C1D3)	Cycle 1 Day 14 (C1D14)	Weekly Through Cycle 2	Day 1 of Each Cycle After Cycle 2[b]	End of Every 3rd Cycle	Final Visit[r]	30 Day Safety Follow-Up[r]
Dispense Meds/Subject Dosing Log		X				X	X			
Collect Unused Study Drug						X	X		X	

a. Screening procedures must be performed within 14 days prior to study drug administration, except tumor assessment scans (if clinically indicated) and bone marrow aspirate/biopsy, which must be performed within 21 days prior to study drug administration.

b. Study procedures (except platelets) may be performed within 72 hours prior to Day 1 for each cycle. Platelets counts must be performed within 24 hours prior to dosing on Day 1 of each cycle.

c. Height will be assessed at Screening only.

d. A symptom directed physical exam may be performed weekly through Cycle 2.

e. ECG will be performed at Screening, Day 1 and Day 14 of Cycle 1, Day 1 of each subsequent cycle and at the Final Visit for all subjects in the first 2 cohorts. ECG will be performed at Screening, Day 1 and Day 14 of Cycle 1, Day 1 and Day 14 of Cycle 3 and at the Final Visit for subjects in subsequent cohorts. Every effort should be made to obtain all ECGs approximately 4-8 hours post-dose (however, 6-8 hours post-dose is preferred), and if possible at approximately the same time of day. If pharmacokinetic data indicates the C_{max} of parent drug or a major metabolite occurs at a time different than this specified range, the timing of the ECG may be modified. Repeat ECGs will be performed whenever clinically necessary.

f. 2D Echocardiogram with Doppler will be performed at Screening, Day 1 and Day 14 of Cycle 1, Day 1 of each subsequent cycle and at the Final Visit for all subjects in the first 2 cohorts. Echocardiogram with Doppler will be performed at Screening, Day 1 and Day 14 of Cycle 1, Day 1 and Day 14 of Cycle 3 and at the Final Visit for subjects in subsequent cohorts. Every effort should be made to obtain all echocardiograms approximately 4-8 hours post-dose (however, 6-8 hours post-dose is preferred), and if possible at approximately the same time of day. If pharmacokinetic data indicates the C_{max} of parent drug or a major metabolite occurs at a time different than this specified range, the timing of the echocardiogram may be modified. Repeat echocardiograms will be performed whenever clinically necessary.

g. Platelet counts will be performed Cycle 1: Pre-dose on Days 1, 2, 3, 4, 5, 6, 8, 14 (in addition, at all PK time points per Table 4), Day 16 and as needed; Subsequent Cycles: Days 1, 3, 5, 8, 16 and as needed. If the investigator and the AbbVie Medical Monitor jointly agree that platelet counts through Cycle 4 have been stable, then the frequency of platelet counts in Cycle 5 and beyond may be decreased to Day 1 of each cycle and as needed. If platelet count performed on any given day is less than 50,000/mm^3, additional platelet counts should be performed every day or at the discretion of the investigator.

Table 1. Schedule of Assessments – 14/21 Day Dosing (Phase 1) (Continued)

h. Lymphocyte enumeration will be performed at Screening, Day 14 of Cycle 1, end of Cycle 4, the end of every 3rd cycle thereafter and at the Final Visit.

i. For women of child bearing potential, a serum sample is to be tested at Screening and a urine sample (if it has been > 7 days since obtaining the serum pregnancy test results) is to be tested prior to dosing on Day 1 of the first cycle.

j. The specific laboratory tests required for chemistry, hematology and urinalysis are listed in Table 7. Triglycerides will only be collected at Screening and at the Final Visit. Amylase and lipase will be collected at Screening, Cycle 1 Day 14, and Final Visit. For any subjects who are at high risk for tumor lysis syndrome (TLS) during Cycle 2 and beyond, additional samples for hematology and chemistry may be collected as per the management guidelines in Section 6.7.4.

k. Assessment for tumor response will be performed at the end of Cycle 2, end of Cycle 4, end of every 4 cycles through Cycle 20 (i.e., C8, C12, C16, C20), end of every 8 cycles thereafter (i.e., C28, C36, C44. . .) and at the Final Visit. Analysis of peripheral blood for tumor response will be performed on Day 1 (pre-dose) of the following cycle for every tumor assessment.

l. A CT scan will be performed at Screening (within 21 days prior to study drug administration).

m. Assessments for tumor response will be repeated at least 2 months after NCI-WG criteria for a complete remission (CR or CRi) or partial remission (PR) are first met.

n. If clinical and laboratory criteria for a CR or PR are met, a bone marrow aspirate/biopsy and CT scan should be performed at least 2 months after the criteria are first met in order to confirm a CR or PR.

o. Bone marrow aspirate/biopsy will be done at Screening (within 21 days prior to study drug administration) unless a bone marrow aspirate and biopsy was obtained within 12 weeks of starting study drug without intervening treatment and is representative of the subject's existing disease.

p. Serious adverse event assessment will be performed at Screening after informed consent has been obtained.

q. Adverse events will be followed until satisfactory clinical resolution of the adverse event is achieved.

r. For subjects who continue in the Extension Study, the Final Visit and 30 Day Safety Follow-Up Visit procedures will be performed upon completion of the Extension Study. Refer to Appendix G for the Schedule of Assessments for subjects enrolled in the Extension Study.

Note: A schedule of assessments for subjects enrolled in Phase 1 – 21/21 Day Dosing can be found in Table 2. A schedule of assessments for subjects enrolled in Phase 2a can be found in Table 3. Pharmacokinetic (PK) collection time points for Phase 1 are located in Table 4 and Table 5. PK collection time points for Phase 2a are located in Table 6. Biomarker collection time points for Phase 1 are in Table 8. Biomarker collection time points for Phase 2a are located in Table 9.

Table 2. Schedule of Assessments – 21/21 Day Dosing with Lead-in Period (Phase 1)

Procedure	Screening[a]	Lead-in Day 1 (LD1)	Lead-in Day 2 (LD2)	Lead-in Day 3 (LD3)	Cycle 1 Day 1 (C1D1)	Cycle 1 Day 2 (C1D2)	Cycle 1 Day 3 (C1D3)	Cycle 1 Day 14 (C1D14)	Weekly Through Cycle 2	Day 1 of Each Cycle After Cycle 2[b]	End of Every 3rd Cycle	Final Visit[r]	30 Day Safety Follow-Up[r]
Informed Consent	X												
Physical Exam (including weight)	X[c]	X			X				X[d]	X		X	X
Medical History	X	X											
Oncologic History	X												
Vital Signs	X	X			X				X	X		X	X
12-lead ECG[e]	X	X			X			X				X	
2D Echocardiogram with Doppler[f]	X	X			X			X				X	
Platelet Count[g]	X	X	X	X	X	X	X	X	X	X		X	X
Lymphocyte Enumeration[h]	X							X			X	X	
Pregnancy Test[i]	X	X											
Chemistry[j]	X	X	X	X	X	X	X		X	X		X	X
Hematology[j]	X	X	X	X	X	X	X		X	X		X	X
Urinalysis[j]	X	X			X				X	X		X	X

Table 2. Schedule of Assessments – 21/21 Day Dosing with Lead-in Period (Phase 1) (Continued)

Procedure	Screening[a]	Lead-in Day 1 (LD1)	Lead-in Day 2 (LD2)	Lead-in Day 3 (LD3)	Cycle 1 Day 1 (C1D1)	Cycle 1 Day 2 (C1D2)	Cycle 1 Day 3 (C1D3)	Cycle 1 Day 14 (C1D14)	Weekly Through Cycle 2	Day 1 of Each Cycle After Cycle 2[b]	End of Every 3rd Cycle	Final Visit[r]	30 Day Safety Follow-Up[r]
Performance Status (ECOG)	X	X			X				X	X		X	X
Tumor Assessments[k]	X[l]										X[m,n]	X	
Bone Marrow Aspirate and Biopsy[n]	X[o]												
Adverse Event/Concomitant Medications Assessment	X[p]	X			X			X	X	X		X	X[q]
Dispense Meds/Subject Dosing Log		X			X				X	X			
Collect Unused Study Drug									X	X		X	

a. Screening procedures must be performed within 14 days prior to study drug administration, except baseline tumor assessment (if clinically indicated) and bone marrow aspirate/biopsy, which must be performed within 21 days prior to study drug administration.

b. Study procedures (except platelets) may be performed within 72 hours prior to Day 1 for each cycle. Platelets counts must be performed within 24 hours prior to dosing on Day 1 of each cycle.

c. Height will be assessed at Screening only.

d. A symptom directed physical exam may be performed weekly through Cycle 2.

e. ECG will be performed at Screening, Lead-in Day 1, Day 1 and Day 14 of Cycle 1, Day 1 and Day 14 of Cycle 3 and at the Final Visit. Every effort should be made to obtain all ECGs approximately 4-8 hours post-dose (however, 6-8 hours post-dose is preferred), and if possible at approximately the same time of day. If pharmacokinetic data indicates the C_{max} of parent drug or a major metabolite occurs at a time different than this specified range, the timing of the ECG may be modified. Repeat ECGs will be performed whenever clinically necessary.

f. 2D Echocardiogram with Doppler will be performed at Screening, Lead-in Day 1, Day 1 and Day 14 of Cycle 1, Day 1 and Day 14 of Cycle 3 and at the Final Visit. Every effort should be made to obtain all echocardiograms approximately 4-8 hours post-dose (however, 6-8 hours post-dose is preferred), and if possible at approximately the same time of day. If pharmacokinetic data indicates the C_{max} of parent drug or a major metabolite occurs at a time different than this specified range, the timing of the echocardiogram may be modified. Repeat echocardiograms will be performed whenever clinically necessary.

Table 2. Schedule of Assessments – 21/21 Day Dosing with Lead-in Period (Phase 1) (Continued)

g. Platelet counts will be performed at Screening, Lead-in Days 1, 2, 3, 5 and 7 and then daily if the lead-in period extends beyond Day 7. Cycle 1: Pre-dose on Days 1, 2, 3, 5, 8, 14 (in addition, at all PK time points per Table 4), Day 16, and as needed. Subsequent Cycles: Weekly and as needed. If the investigator and the AbbVie Medical Monitor jointly agree that platelet counts through Cycle 4 have been stable, then the frequency of platelet counts in Cycle 5 and beyond may be decreased to Day 1 of each cycle and as needed. If platelet count on any given day is less than 50,000/mm^3, additional platelet counts should be performed every day or at the discretion of the investigator.

h. Lymphocyte enumeration will be performed at Screening, Day 14 of Cycle 1, end of Cycle 4, the end of every 3rd cycle thereafter and at the Final Visit.

i. For women of child bearing potential, a serum sample is to be tested at Screening and a urine sample is to be tested (if it has been > 7 days since obtaining the serum pregnancy test results) prior to dosing on Lead-in Day 1 (lead-in period).

j. The specific laboratory tests required for chemistry, hematology and urinalysis are listed in Table 7. Triglycerides will only be collected at Screening and at the Final Visit. Amylase and lipase will be collected at Screening, Cycle 1 Day 14, and Final Visit. For any subjects who are at high risk for tumor lysis syndrome (TLS) during Cycle 2 and beyond, additional samples for hematology and chemistry may be collected as per the management guidelines in Section 6.7.4.

k. Assessment for tumor response will be performed at the end of Cycle 2, end of Cycle 4, end of every 4 cycles through Cycle 20 (i.e., C8, C12, C16, C20), end of every 8 cycles thereafter (i.e., C28, C36, C44. . .) and at the Final Visit. Analysis of peripheral blood for tumor response will be performed on Day 1 (pre-dose) of the following cycle for every tumor assessment.

l. A CT scan will be performed at Screening (within 21 days prior to study drug administration).

m. Assessments for tumor response will be repeated at least 2 months after NCI-WG criteria for a complete remission (CR or CRi) or partial remission (PR) are first met.

n. If clinical and laboratory criteria for a CR or PR are met, a bone marrow aspirate/biopsy and CT scan should be performed at least 2 months after the criteria are first met in order to confirm a CR or PR.

o. Bone marrow aspirate/biopsy will be done at Screening (within 21 days prior to study drug administration) unless a bone marrow aspirate and biopsy was obtained within 12 weeks of starting study drug without intervening treatment and is representative of the subject's existing disease.

p. Serious adverse event assessment will be performed at Screening after informed consent has been obtained.

q. Adverse events will be followed until satisfactory clinical resolution of the adverse event is achieved.

r. For subjects who continue in the Extension Study, the Final Visit and 30 Day Safety Follow-Up Visit procedures will be performed upon completion of the Extension Study. Refer to Appendix G for the Schedule of Assessments for subjects enrolled in the Extension Study.

Note: A schedule of assessments for subjects enrolled in Phase 1 – 14/21 Day Dosing can be found in Table 1. A schedule of assessments for subjects enrolled in Phase 2a can be found in Table 3. Pharmacokinetic (PK) collection time points for Phase 1 are located in Table 4 and Table 5. PK collection time points for Phase 2a are located in Table 6. Biomarker collection time points for Phase 1 are in Table 8. Biomarker collection time points for Phase 2a are in Table 9.

Table 3. Schedule of Assessments (Phase 2a) –21/21 Day Continuous Dosing Schedule with Lead-in Period

Procedure	Screening[a]	LD1	LD2	LD3	C1 D1	C1 D2	C1 D3	C1 D15	Weekly Through C2	D1 of Each Cycle After C2[b]	End of Every 3rd Cycle	C5 D1	C9 D1	Final Visit[s]	30 Day Safety Follow-Up[s]	Post-Treatment
Informed Consent	X															
Physical Exam (including weight)	X[c]	X			X				X[d]	X				X	X	
Medical History	X	X														
Oncologic History	X															
Vital Signs	X	X			X				X	X				X	X	
12-lead ECG[e]	X							X				X	X	X		
2D Echocardiogram with Doppler[f]	X							X				X	X	X		
Platelet Count[g]	X	X	X	X	X	X	X	X	X	X		X	X	X	X	
Lymphocyte Enumeration[h]	X							X			X			X		
Pregnancy Test[i]	X	X														
Chemistry[j]	X	X	X	X	X	X	X		X	X				X	X	
Hematology[j]	X	X	X	X	X	X	X		X	X				X	X	
Urinalysis[j]	X	X			X				X	X				X	X	
Performance Status (ECOG)	X	X			X				X	X				X	X	
Tumor Assessments[k]	X[l]										X[m,n]			X		
Bone Marrow Aspirate/Biopsy[n]	X[o]															
Clinical Disease Progression Assessment					X					X				X		
Adverse Event/Concomitant Medications Assessment	X[p]	X			X			X	X	X				X	X[q]	

Table 3. Schedule of Assessments (Phase 2a) – 21/21 Day Continuous Dosing Schedule with Lead-in Period (Continued)

Procedure	Screening[a]	LD1	LD2	LD3	C1 D1	C1 D2	C1 D3	C1 D15	Weekly Through C2	D1 of Each Cycle After C2[b]	End of Every 3rd Cycle	C5 D1	C9 D1	Final Visit[s]	30 Day Safety Follow-Up[s]	Post-Treatment
Dispense Meds/Subject Dosing Log		X			X				X	X						
Collect Unused Study Drug									X	X				X		
Survival Assessment(s)[r]																X

C = Cycle; D = Day; L = Lead-in

a. Screening procedures must be performed within 14 days prior to study drug administration, except baseline tumor assessment scans (if clinically indicated) and bone marrow aspirate/biopsy, which must be performed within 21 days prior to study drug administration.

b. Study procedures (except platelets) may be performed within 72 hours prior to Day 1 for each cycle. Platelet counts must be performed within 24 hours prior to dosing on Day 1 of each cycle.

c. Height will be assessed at Screening only.

d. A symptom directed physical exam may be performed weekly through Cycle 2.

e. Every effort should be made to obtain all ECGs approximately 4 to 8 hours post-dose (however, 6 to 8 hours post-dose is preferred), and if possible at approximately the same time of day. Repeat ECGs will be performed whenever clinically necessary. If necessary, ECGs may be performed within 3 days of the visit, except Screening, which must be performed within 14 days prior to study drug administration.

f. Every effort should be made to obtain all echocardiograms approximately 4 to 8 hours post dose (however, 6 to 8 hours post dose is preferred), and if possible at approximately the same time of day. Repeat echocardiograms will be performed whenever clinically necessary. If necessary, ECHOs may be performed within 3 days of the visit, except Screening, which must be performed within 14 days prior to study drug administration.

g. Platelet counts will be performed at Screening, Lead-in Days 1, 2, 3, 5 and 7 and then daily if the lead-in period extends beyond Day 7. Cycle 1: Pre-dose on Days 1, 2, 3, 5, 8, 15 and as needed. Subsequent Cycles: Weekly and as needed. If platelet count on any given day is less than 50,000/mm^3, additional platelet counts should be performed every day or at the discretion of the investigator. If the investigator and the AbbVie Medical Monitor jointly agree that platelet counts through Cycle 4 have been stable, then the frequency of platelet counts in Cycle 5 and beyond may be decreased to Day 1 of each Cycle and as needed.

Table 3. Schedule of Assessments (Phase 2a) – 21/21 Day Continuous Dosing Schedule with Lead-in Period (Continued)

h. Lymphocyte enumeration will be performed at Screening, Day 15 of Cycle 1, end of Cycle 4, the end of every 3rd cycle thereafter and at the Final Visit.

i. For women of childbearing potential, a serum sample is to be tested at Screening and a urine sample is to be tested (if it has been > 7 days since obtaining the serum pregnancy test results) prior to dosing on Lead-in Day 1 (lead-in period).

j. The specific laboratory tests required for chemistry, hematology and urinalysis are listed in Table 7. Triglycerides will only be collected at Screening and at the Final Visit. Amylase and lipase will be collected at Screening, Cycle 1 Day 15, and Final Visit. For any subjects who are at high risk for tumor lysis syndrome (TLS) during Cycle 2 and beyond, additional samples for hematology and chemistry may be collected as per the management guidelines in Section 6.7.4.

k Assessment for tumor response will be performed at the end of Cycle 2, end of Cycle 4, end of every 4 cycles through Cycle 20 (i.e., C8, C12, C16, C20), end of every 8 cycles thereafter (i.e., C28, C36, C44. . .) and at the Final Visit. Analysis of peripheral blood for tumor response will be performed on Day 1 (pre-dose) of the following cycle for every tumor assessment.

l. A CT scan will be performed at Screening (within 21 days prior to study drug administration).

m. Assessments for tumor response will be repeated 2 months after NCI-WG (1996) criteria for a complete remission (CR) are first met and/or at least 2 months after IWCLL updated NCI-WG (2008) criteria for a complete remission (CR or CRi) or partial remission (PR) are first met.

n. If clinical and laboratory criteria for a CR or PR are met), a bone marrow aspirate/biopsy and CT scan should be performed at least 2 months after the criteria are first met in order to confirm a CR or PR. A bone marrow aspirate/biopsy will be performed at the end of Cycle 8 (for all subjects regardless of response) if the subject is continuing to receive ABT-263.

o. Bone marrow aspirate/biopsy will be done at Screening (within 21 days prior to study drug administration) unless a bone marrow aspirate and biopsy was obtained within 12 weeks of starting study drug without intervening treatment and is representative of the subject's existing disease.

p. Serious adverse event assessment will be performed at Screening after informed consent has been obtained.

q. Adverse events will be followed until satisfactory clinical resolution of the adverse event is achieved.

r. Survival assessments will be collected every 3 months for 2 years following discontinuation from the study (including the extension portion of the study). In Protocol Amendment #12 this information will no longer be collected.

s. For subjects who continue in the Extension Study, the Final Visit and 30 Day Safety Follow-Up Visit procedures will be performed upon completion of the Extension Study. Refer to Appendix G for the Schedule of Assessments for subjects enrolled in the Extension Study.

Note: A schedule of assessments for subjects enrolled in Phase 1 can be found in Table 1 and Table 2. Pharmacokinetic (PK) collection time points for Phase 1 are located in Table 4 and Table 5. PK collection time points for Phase 2a are located in Table 6. Biomarker collection time points for Phase 1 are in Table 8. Biomarker collection time points for Phase 2a are located in Table 9.

Table 4. Schedule of Blood Collection for ABT-263 Assay (Pharmacokinetic Sampling) – Phase 1, Cycle 1

Phase	Cycle 1 Day 1	Cycle 1 Day 2	Cycle 1 Day 14
Phase 1 – 14/21 day schedule	0 (pre-dose) 2, 4, 6, 8 hours post-dose	24 hours post-dose Day 1 (pre-dose Day 2)	0 (pre-dose) 2, 4, 6, 8 hours post-dose
Phase 1 – 21/21 day schedule – with lead-in	0 (pre-dose) 2, 4, 6, 8 hours post-dose	24 hours post-dose Day 1 (pre-dose Day 2)	0 (pre-dose) 2, 4, 6, 8 hours post-dose

All 0 hour (pre-dose) PK samples will be collected around the same time for platelet sample collection.

Note: In addition, serial pharmacokinetic samples will be obtained from subjects who develop Grade 4 thrombocytopenia (< 25,000/mm^3). The first pharmacokinetic sample should be collected as soon as possible after determination of the Grade 4 thrombocytopenia and then 24 and 48 hours thereafter.

Table 5. Schedule of Blood Collection for ABT-263 Assay (Pharmacokinetic Sampling) – Phase 1, Cycle 2 and Beyond

Phase	Cycle 2 Day 3	Cycle 2 Day 8	Cycle 2 Day 14	Cycle 3 Day 1	Cycle 3 Day 14	Day 14 of Cycles 6, 9, 12 and 15
Phase 1 – 14/21 day schedule	0 hour (pre-dose)	0 hour (pre-dose)	0 hour (pre-dose)	4 to 8 hours post-dose (immediately after ECG)	0 hour (pre-dose) and 4 to 8 hours post-dose (immediately after ECG)	0 (pre-dose)
Phase	**Cycle 2 Day 3**	**Cycle 2 Day 8**	**Cycle 2 Day 14**	**Cycle 3 Day 1**	**Cycle 3 Day 14**	**Day 1 of Cycles 6, 9, 12 and 15**
Phase 1 – 21/21 day schedule – with lead-in	0 hour (pre-dose)	0 hour (pre-dose)	0 hour (pre-dose)	4 to 8 hours post-dose (immediately after ECG)	0 hour (pre-dose) and 4 to 8 hours post-dose (immediately after ECG)	0 (pre-dose)

All 0 hour (pre-dose) PK samples will be collected around the same time for platelet sample collection.

Note: In addition, serial pharmacokinetic samples will be obtained from subjects (including subjects in the Extension Study) who develop Grade 4 thrombocytopenia (< 25,000/mm^3). The first pharmacokinetic sample should be collected as soon as possible after determination of the Grade 4 thrombocytopenia and then 24 and 48 hours thereafter. Starting with Protocol Amendment 13, PK samples will NOT be collected.

Table 6. Schedule of Blood Collection for ABT-263 Assay (Pharmacokinetic Sampling) – Phase 2a, 21/21 Day Continuous Dosing Schedule

Procedure	Cycle 1 Day 15	Cycle 3 Day 1	Day 1 of Cycles 5 and 9
Phase 2a	0 (pre-dose) and 4 to 8 hours post-dose (immediately after ECG)	0 (pre-dose)	0 (pre-dose) and 4 to 8 hours post-dose (immediately after ECG)

All 0 hour (pre-dose) PK samples will be collected around the same time for platelet sample collection.

Note: In addition, serial pharmacokinetic samples will be obtained from subjects (including subjects in the Extension Study) who develop Grade 4 thrombocytopenia ($< 25{,}000/mm^3$). The first pharmacokinetic sample should be collected as soon as possible after determination of the Grade 4 thrombocytopenia and then 24 and 48 hours thereafter. Starting with Protocol Amendment 13, PK samples will NOT be collected.

5.3.1.1 Study Procedures

For subjects who continue in the Extension Study, the Final Visit, and 30 Day Safety Follow-Up Visit procedures will be performed only once upon completion of the Extension Study.

Study visits may be impacted due to the COVID-19 pandemic. This may include changes such as phone or virtual visits, visits at alternative locations, or changes in the visit frequency and timing of study procedures, among others. Additional details are provided in the subsequent section. Every effort should be made to ensure the safety of subjects and site staff, while maintaining the integrity of the study. If visits cannot be conducted onsite due to travel restrictions or other pandemic-related reasons, follow the updates below how to proceed.

COVID-19 Pandemic-Related Acceptable Protocol Modifications

During the COVID-19 pandemic, if it is not possible for all study procedures to be performed as specified due to travel restrictions or other reasons, the following modifications are allowed:

- If permitted by local regulations, the IRB/IEC and the subject, the subject visits may be conducted in the subject's home residence.
- Some study visits and/or activities may be performed by phone/virtually. These are indicated by a hashtag (#) in the activity table (Appendix G)
  - During a virtual visit, activities that do not need to be performed are indicated by a (#) in the activity table (Appendix G).
- Study visits and/or activities may be performed by a local clinic/hospital/laboratory. All procedures performed at local facilities must be performed by appropriately qualified personnel.
- Study Visits and/or activities should be performed as scheduled whenever possible. If it is not possible to do so due to the pandemic, perform the activity at the earliest feasible opportunity. Laboratory draws must be obtained within 24 hours from the scheduled visit.

Informed Consent

Signed informed consent will be obtained from the subject or the subject's legally acceptable representative before any study-specific procedures are undertaken or before any prohibited medications are withheld from the subject in order to participate in this study. Informed consent is also required for the pharmacodynamic (PD) and pharmacogenetic (PG) sampling portions of the study. A separate informed consent will be required for subjects entering the Extension Study. Details about how informed consent will be obtained and documented are provided in Section 9.3.

Due to the COVID-19 pandemic, it is possible that additional protocol modifications not outlined in this protocol may become necessary. If this situation arises, in addition to the study informed consent, additional verbal consent may be obtained prior to these adaptations or substantial changes in study conduct in accordance with local regulations.

Medical History

The following will be collected during the Screening Visit:

- Complete medical history, including documentation of any clinically significant medical condition
- History of tobacco and alcohol use
- Detailed oncology history including:
- Histology
- Date of cancer diagnosis
- Stage
- Any surgical procedures
- Treatments administered (including dates and type of modality)

At each visit, the subject's medical history will be reviewed and any changes from baseline will be recorded on the adverse event CRF. On Cycle 1 Day 1 (14/21 day dosing schedule), any changes observed from the Screening assessments prior to dosing will be recorded in the subject's medical history. During the lead-in period, any changes from the

Screening assessment prior to dosing will be recorded in the subject's history on Lead-in Day 1 (21/21 day dosing schedule). All medication (prescription or over-the-counter, including vitamins and/or herbal supplements) will be recorded beginning with the Screening Visit and continuing until 30 days following the last dose of ABT-263.

Physical Examination

A physical examination (including weight) will be performed at Screening, Day 1 of Cycle 1, Day 1 of each subsequent cycle (or within 72 hours prior), at the Final Visit and at the Safety Follow-up Visit. During the lead-in period (21/21 day dosing schedule), a physical examination (including weight) will also be performed at Lead-in Day 1. A symptom-directed physical examination may be performed weekly through the first 2 cycles and when necessary. Height will be measured only at Screening. The physical examination performed at Screening will serve as the baseline physical examination for clinical assessment. For the Extension Study, a physical examination will be performed at Day 1, every 4 cycles (e.g., Cycle 4 Day 1, Cycle 8 Day 1, etc.), Final Visit and at the Safety Follow-up Visit. Any significant physical examination findings after dosing will be recorded as adverse events.

Vital Signs

Body temperature (oral or tympanic), blood pressure and pulse will be measured at Screening, Day 1 of Cycle 1, weekly through the first 2 cycles, Day 1 of each subsequent cycle (or within 72 hours prior), at the Final Visit and at the Safety Follow-up Visit. During the lead-in period (21/21 day dosing schedule), body temperature (oral), blood pressure and pulse will also be measured at Lead-in Day 1. The vital signs measurements at Screening will serve as the baseline measurements for clinical assessment. For the Extension Study, body temperature, blood pressure and pulse will be measured at Day 1, every 4 cycles (e.g., Cycle 4 Day 1, Cycle 8 Day 1, etc.), Final Visit and at the Safety Follow-up Visit.

In Phase 1, blood pressure and pulse rate will be measured approximately 30 to 60 minutes after study drug administration.

Blood pressure and pulse rate will be measured after the subject has been sitting for at least 5 minutes on days study drug is administered in the clinic.

COVID-19 Pandemic-Related Acceptable Protocol Modifications

Due to the COVID-19 pandemic, subject visits may be conducted via phone or video conference. In these situations, weight, and vital signs measurements may be performed by the subject or caregiver as needed.

Platelet Count

The platelet count measurement obtained on Cycle 1 Day 1 (pre-dose) will serve as the baseline for clinical assessment for the 14/21 day dosing schedule. The platelet count measurement obtained on Lead-in Day 1 (pre-dose) will serve as the baseline for clinical assessment for the 21/21 day dosing schedule with lead-in period.

If platelet count on any given day is less than 50,000/mm^3, additional platelet counts should be performed every day or at the discretion of the investigator.

If a platelet transfusion is deemed necessary, a post-transfusion platelet count should be obtained within 10 to 60 minutes.

Platelet counts < 25,000/mm^3 should be confirmed the same day by manual reading and a separate peripheral draw. Additional platelet counts will be obtained from a subject if ABT-263 is either held or interrupted per the management guidelines in Section 6.7.1 and Section 6.7.2.

All platelet count measurements obtained during Cycle 1 through Cycle 4 in the Phase 1 portion of the study will be either entered immediately on the eCRF or faxed to the Oncology Safety Management Team within 24 hours of report availability via the contact information provided in Section 6.5.

COVID-19 Pandemic-Related Acceptable Protocol Modifications

If travel restrictions or other changes in local regulations in light of the COVID-19 pandemic prevent the subject from having blood drawn for laboratory testing at the study site, if possible, arrange for subjects to have laboratory work done at a local lab, hospital, or other facility. Local lab results should be obtained along with reference ranges and kept within the subjects' source documentation. Local lab results should be reviewed by the investigator as soon as possible. If laboratory samples cannot be obtained, study drug administration may be continued provided the investigator has reviewed all prior laboratory results and confirms and discusses with the subject that there is no safety concern for the subject to continue use of the study drug in the absence of current labs. The subject should be scheduled for laboratory draws as soon as feasible within 14 days from the scheduled visit.

The platelet count schedule of assessment may be modified as information is obtained regarding the expected decrease in platelets in response to study drug administration. This will be based upon discussion between the investigator and the AbbVie Medical Monitor.

Platelet count assessments will be performed stat and assessed by the investigator prior to study drug administration as follows:

Phase 1 – 14/21 Day Dosing Schedule:

Screening

Cycle 1:

- Days 1, 2, 3, 4, 5, 6, 8, 14 and 16
- Platelet counts performed in Cycle 1 can be obtained within 24 hours prior to the visit, except on Days 1 and 14 when platelet counts are required at all of the pharmacokinetic sampling time points as indicated in Table 4 and Table 5.
- As needed

Subsequent Cycles:

- Days 1, 3, 5, 8 and 16
- As needed
- If the investigator and the AbbVie Medical Monitor jointly agree that platelet counts through Cycle 4 have been stable, then the frequency of platelet counts in Cycle 5 and beyond may be decreased to Day 1 of each cycle and as needed.

Final Visit and Safety Follow-up Visit

For the Extension Study, platelet count assessments will be performed at Day 1, every 4 cycles (e.g., Cycle 4 Day 1, Cycle 8 Day 1, etc.), Final Visit and at the Safety Follow-up Visit.

Phase 1 – 21/21 Day Dosing Schedule:

Screening

During the lead-in period, the following platelet counts will be obtained:

- Lead-in Days 1, 2, 3, 5 and 7
- Daily if lead-in period extends beyond Day 7 (i.e., Lead-in Days 8-14)

Cycle 1:

- Days 1, 2, 3, 5, 8, 14 and 16
- Platelet counts performed in Cycle 1 can be obtained within 24 hours prior to the visit, except on Days 1 and 14 when platelet counts are required at all of the pharmacokinetic sampling time points as indicated in Table 4.
- As needed

Subsequent Cycles:

- Weekly

- As needed
- If the investigator and the AbbVie Medical Monitor jointly agree that platelet counts through Cycle 4 have been stable, then the frequency of platelet counts in Cycle 5 and beyond may be decreased to Day 1 of each cycle and as needed.

Final Visit and Safety Follow-up Visit

For the Extension Study, platelet count assessments will be performed at Day 1, every 4 cycles (e.g., Cycle 4 Day 1, Cycle 8 Day 1, etc.), Final Visit and at the Safety Follow-up Visit.

Phase 2a:

Screening

During the lead-in period, the following platelet counts will also be obtained:

- Lead-in Days 1, 2, 3, 5 and 7
- Daily if lead-in period extends beyond Day 7 (i.e., Lead-in Days 8-14)

Cycle 1:

- Days 1, 2, 3, 5, 8 and 15
- As needed

Subsequent Cycles:

- Weekly
- As needed
- If the investigator and the AbbVie Medical Monitor jointly agree that platelet counts through Cycle 4 have been stable, then the frequency of platelet counts in Cycle 5 and beyond may be decreased to Day 1 of each cycle and as needed.

Final Visit and Safety Follow-up Visit

For the Extension Study, platelet count assessments will be performed at Day 1, every 4 cycles (e.g., Cycle 4 Day 1, Cycle 8 Day 1, etc.), Final Visit and at the Safety Follow-up Visit.

Lymphocyte Enumeration

Lymphocyte enumeration to identify B and T cell lymphocyte subpopulations will be performed at Screening, Day 14 of Cycle 1 (14/21 day dosing schedule), Day 15 of Cycle 1 (21/21 day dosing schedule), end of Cycle 4, at the end of every 3rd cycle thereafter, and at the Final Visit for each subject. The lymphocyte enumeration results from Screening will serve as the baseline for clinical assessment. For the Extension Study, lymphocyte enumeration will be performed if deemed necessary by the investigator and at the Final Visit.

All lymphocyte enumeration results obtained in the Phase 1 portion of the study will be either entered immediately on the eCRF or faxed to the Oncology Safety Management Team within 24 hours of report availability via the contact information provided in Section 6.5.

ECOG Performance Status

The ECOG performance status[39] will be assessed at Screening, Day 1 of Cycle 1, weekly through the first 2 cycles, Day 1 of each subsequent cycle (or within 72 hours prior), at the Final Visit and at the Safety Follow-up Visit. For the Extension Study, the ECOG performance status will be assessed at the Final Visit and Safety Follow-up Visit.

Grade	Description
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, 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.

During the lead-in period, ECOG performance status will also be assessed on Lead-in Day 1 (21/21 day dosing schedule).

The ECOG performance status assessed at Screening will serve as the baseline for clinical assessment.

12-Lead Electrocardiogram (ECG) (Phase 1)

A 12-lead resting ECG will be performed for all subjects in the first 2 cohorts of the study at Screening, Day 1 and Day 14 of Cycle 1, Day 1 of each subsequent cycle and at the Final Visit. For subsequent cohorts, an ECG will be performed at Screening, Day 1 and Day 14 of Cycle 1, Day 1 and Day 14 of Cycle 3 and at the Final Visit. For the Extension Study, a 12-lead resting ECG will be performed at the Final Visit.

If necessary, the Cycle 1 Day 14 and Cycle 3 Day 14 ECGs may be performed within 3 days prior to Day 14. During the lead-in period, an ECG will also be performed on Lead-in Day 1. The test results will be assessed for each subject on an ongoing basis by the AbbVie Medical Monitor and an independent cardiology expert, and monitoring may be adjusted depending on the observation of any clinically significant findings.

Every effort should be made to obtain all ECGs approximately 4-8 hours post-dose (however, 6-8 hours post-dose is preferred), and if possible at approximately the same time of day. If pharmacokinetic data indicates the C_{max} of parent drug or a major metabolite occurs at a time different than this specified range, the timing of the ECG may be modified. A qualified physician will sign and date the ECGs, determine if any findings outside normal physiological variation are clinically significant (in consultation with a

cardiologist, if necessary) and document this on the appropriate CRF. The original ECG tracing with physician assessment will be retained in the subject's records at the study site and a copy will be faxed to the Oncology Safety Management Team within 24 hours of report availability via the contact information provided in Section 6.5. The ECG measurement obtained at Screening will be used to document baseline status of the subject so that safety comparisons can be made, if necessary. Repeat ECGs will be performed whenever clinically necessary.

12-Lead Electrocardiogram (ECG) (Phase 2a)

A 12-lead resting ECG will be performed for all subjects in Phase 2a at the following visits:

- Screening
- Cycle 1 Day 15
- Cycle 5 Day 1
- Cycle 9 Day 1
- Final Visit

For the Extension Study, a 12-lead resting ECG will be performed at the Final Visit.

If necessary, ECGs may be performed within 3 days of the visit, except Screening, which must be performed within 14 days prior to study drug administration.

The test results will be assessed for each subject on an ongoing basis by the AbbVie Medical Monitor and an independent cardiology expert, and monitoring may be adjusted depending on the observation of any clinically significant findings.

Every effort should be made to obtain all ECGs approximately 4-8 hours post-dose (however, 6-8 hours post-dose is preferred), and if possible at approximately the same time of day. If pharmacokinetic data indicates the C_{max} of parent drug or a major metabolite occurs at a time different than this specified range, the timing of the ECG may be modified. A qualified physician will sign and date the ECGs, determine if any findings

outside normal physiological variation are clinically significant (in consultation with a cardiologist, if necessary) and document this on the appropriate CRF. The original ECG tracing with physician assessment will be retained in the subject's records at the study site and a copy will be faxed to the Oncology Safety Management Team within 5 days of report availability via the contact information provided in Section 6.5. The QT, QTc and heart rate will be recorded for all ECGs on the eCRF. The ECG measurement obtained at Screening will be used to document baseline status of the subject so that safety comparisons can be made, if necessary. Repeat ECGs will be performed whenever clinically necessary.

2D Echocardiogram with Doppler (Phase 1)

A 2D echocardiogram with Doppler will be performed for all subjects in the first 2 cohorts at Screening, Day 1 and Day 14 of Cycle 1, Day 1 of each subsequent cycle and at the Final Visit. For subsequent cohorts, an echocardiogram with Doppler will be performed at Screening, Day 1 and Day 14 of Cycle 1, Day 1 and Day 14 of Cycle 3 and at the Final Visit. If necessary, the Cycle 1 Day 14 and Cycle 3 Day 14 echocardiograms may be performed within 3 days prior to Day 14. During the lead-in period, an echocardiogram will also be performed on Lead-in Day 1. For the Extension Study, a 2D echocardiogram with Doppler will be performed at the Final Visit.

The test results for each subject will be assessed on an ongoing basis by the AbbVie Medical Monitor and an independent cardiology expert, and monitoring may be adjusted depending on the observation of any clinically significant findings.

Every effort should be made to obtain all echocardiograms approximately 4-8 hours post-dose (however, 6-8 hours post-dose is preferred), and if possible at approximately the same time of day. If pharmacokinetic data indicates the C_{max} of parent drug or a major metabolite occurs at a time different than this specified range, the timing of the echocardiogram may be modified. A qualified physician will sign and date the echocardiogram reports, determine if any findings outside normal physiological variation are clinically significant and document this on the appropriate CRF. The original

echocardiogram report with physician assessment will be retained in the subject's records at the study site and a copy will be faxed to the Oncology Safety Management Team within 24 hours of report availability via the contact information provided in Section 6.5. In addition, AbbVie (or designee) will require access to the recording of the echocardiogram as necessary. The echocardiogram results obtained at Screening will be used to document baseline status of the subject so that safety comparisons can be made, if necessary. Repeat echocardiograms will be performed whenever clinically necessary.

2D Echocardiogram with Doppler (Phase 2a)

A 2D echocardiogram with Doppler will be performed for all subjects in Phase 2a at the following visits:

- Screening
- Cycle 1 Day 15
- Cycle 5 Day 1
- Cycle 9 Day 1
- Final Visit

For the Extension Study, a 2D echocardiogram with Doppler will be performed at the Final Visit.

If necessary, ECHOs may be performed within 3 days of the visit except Screening, which must be performed within 14 days prior to study drug administration.

The test results for each subject will be assessed on an ongoing basis by the AbbVie Medical Monitor and an independent cardiology expert, and monitoring may be adjusted depending on the observation of any clinically significant findings.

Every effort should be made to obtain all echocardiograms approximately 4-8 hours post-dose (however, 6-8 hours post-dose is preferred), and if possible at approximately the same time of day. If pharmacokinetic data indicates the C_{max} of parent drug or a major metabolite occurs at a time different than this specified range, the timing of the

echocardiogram may be modified. A qualified physician will sign and date the echocardiogram reports, determine if any findings outside normal physiological variation are clinically significant and document this on the appropriate CRF. The original echocardiogram report with physician assessment will be retained in the subject's records at the study site and a copy will be faxed to the Oncology Safety Management Team within 5 days of report availability via the contact information provided in Section 6.5. In addition, AbbVie (or designee) will require access to the recording of the echocardiogram as necessary. The echocardiogram results obtained at Screening will be used to document baseline status of the subject so that safety comparisons can be made, if necessary. Repeat echocardiograms will be performed whenever clinically necessary. The sponsor (AbbVie) may choose to introduce performance of serial echocardiograms to be evaluated by an independent cardiologist.

Bone Marrow Aspirate and Biopsy

A bone marrow aspirate and biopsy will be done at Screening (within 21 days prior to the first dose of study drug) unless a bone marrow aspirate and biopsy was obtained within 12 weeks of starting study drug without intervening treatment and is representative of the subject's existing disease. The bone marrow aspirate and biopsy should be performed after all other eligibility criteria have been met, unless otherwise obtained through standard of care. Bone marrow aspirates and biopsies performed as standard of care throughout the study should also be captured on a case report form.

In the Phase 2a portion of the study, a bone marrow aspirate/biopsy will be performed at the end of Cycle 8 (for all subjects regardless of response) if the subject is continuing to receive ABT-263.

If a subject meets all the clinical and laboratory criteria for a complete remission (CR), a bone marrow aspirate and biopsy should be performed at least 2 months after the criteria are first met in order to confirm a CR. In the Phase 2a portion of the study, a bone marrow aspirate and biopsy should be performed at least 2 months after the IWCLL

updated NCI-WG (2008) criteria are first met and 2 months after NCI-WG (1996) criteria are first met in order to confirm a CR.

Computed Tomography (CT) Scans and Magnetic Resonance Imaging (MRI)

A CT scan of involved anatomic regions (or MRI, if medically indicated) will be done at Screening (within 21 days prior to the first dose of study drug). CT scans and MRIs performed as standard of care throughout the study should also be captured on a case report form.

Phase 1

If a subject meets all the clinical and laboratory criteria for a complete remission (CR) or a partial remission (PR), a CT scan should be performed at least 2 months after the criteria are first met in order to confirm a CR or PR.

Phase 2a

If a subject meets all the clinical and laboratory criteria for a complete remission (CR) or a partial remission (PR), a CT scan should be performed at least 2 months after the criteria are first met in order to confirm a CR or PR.

Tumor Assessments

Analysis of peripheral blood, physical examination, bone marrow aspirate and biopsy, CT scan of involved anatomic regions and MRI (if medically indicated), will be utilized for disease assessment as described above.

Phase 1

Subjects will be evaluated against the IWCLL updated NCI-WG (January 2008) criteria[31] (physical examination/CT/MRI) at the end of Cycle 2, the end of Cycle 4, end of every 4 cycles through Cycle 20 (i.e., C8, C12, C16, C20), end of every 8 cycles thereafter (i.e., C28, C36, C44. . .) and at the Final Visit. For the Extension Study, subjects will be evaluated against the IWCLL updated NCI-WG (January 2008) criteria (physical

examination/CT/MRI) at the Final Visit. Analysis of peripheral blood will be evaluated against the NCI-WG criteria for tumor response assessment on Day 1 (pre-dose) of the following cycle for every tumor assessment. For example, when a subject completes Cycle 2, the laboratory values from Day 1 of Cycle 3 (pre-dose) will be used to assess tumor response.

The tumor assessment performed at Screening will serve as the baseline for clinical assessment. Assessments for tumor response will be repeated at least 2 months after NCI-WG criteria for complete remission (CR or CRi) are first met. Assessments for tumor response will be repeated at least 2 months after criteria for a partial remission (PR) are first met. Response criteria will be assessed while subjects continue treatment with ABT-263. Response criteria definitions are outlined in Section 5.3.3.1.

Phase 2a

Subjects will be evaluated against the NCI-WG (1996) criteria[30] and the IWCLL updated NCI-WG (January 2008) criteria[31] (physical examination/CT/MRI) at the end of Cycle 2, the end of Cycle 4, end of every 4 cycles through Cycle 20 (i.e., C8, C12, C16, C20), end of every 8 cycles thereafter (i.e., C28, C36, C44. . .) and at the Final Visit. For the Extension Study, subjects will be evaluated against the NCI-WG (1996) criteria and the IWCLL updated NCI-WG (January 2008) criteria (physical examination/CT/MRI) at the Final Visit. Analysis of peripheral blood will be evaluated against the NCI-WG criteria for tumor response assessment on Day 1 (pre-dose) of the following cycle for every tumor assessment. For example, when a subject completes Cycle 2, the laboratory values from Day 1 of Cycle 3 (pre-dose) will be used to assess tumor response.

The tumor assessment performed at Screening will serve as the baseline for clinical assessment. Assessments for tumor response will be repeated 2 months after NCI-WG (1996) criteria for complete remission (CR) are first met and/or at least 2 months after the IWCLL updated NCI-WG (2008) criteria for complete remission (CR or CRi) are first met. Assessments for tumor response will be repeated at least 2 months after criteria for a partial remission (PR) are first met. Response criteria will be assessed while

subjects continue treatment with ABT-263. Response criteria definitions are outlined in Section 5.3.3.1.

Disease Progression Assessment (Extension Study)

Subjects should be evaluated for disease progression at a minimum of every 4 cycles and as deemed appropriate by the investigator per standard of care for tumor assessments. At each visit, the investigator should assess whether or not there is evidence of disease progression and record the date of progression on the paper Case Report Form if applicable. If a CT scan, MRI, or bone marrow aspirate or biopsy is performed per standard of care, the data should be recorded on the appropriate paper Case Report Form. Subjects exhibiting disease progression should be discontinued from the study per Section 5.4.1.

Pregnancy Test

For female subjects of childbearing potential, the local reference laboratory will perform a serum pregnancy test at Screening and a urine pregnancy test before dosing on Cycle 1 Day 1 (14/21 day dosing schedule) or Lead-in Day 1 (21/21 day dosing schedule), if it has been > 7 days since obtaining the serum pregnancy test results. The test results must be reviewed and determined to be negative prior to dosing.

Subjects considered not of childbearing potential must be documented as being surgically sterile or post-menopausal (for at least 1 year).

Survival (Phase 2a)

Survival information (i.e., the date and cause of death, post-treatment cancer therapies, etc.) will be collected at 3 month intervals after the last study visit for a period of 2 years after the subject has discontinued from the study. In Protocol Amendment #12 this information will be no longer collected.

Clinical Laboratory Tests

Phase 1

In the Phase 1 portion of the study, local laboratories will be utilized to process and provide results for the clinical laboratory tests. Subjects who move into the Extension Study from Phase 1 will continue to use local laboratories for the clinical laboratory tests. The principal investigator or sub-investigator will review, initial and date all laboratory results. The laboratory test results will be collected on the electronic Case Report Forms. The laboratory test results from the Extension Study will be collected on paper Case Report Forms.

Hematology, chemistry and urinalysis samples will be collected at Screening, Cycle 1 Day 1, Cycle 1 Days 2 and 3 (chemistry and hematology only), weekly through the first 2 cycles, Day 1 of each subsequent cycle (or within 72 hours prior), at the Final Visit and at the Safety Follow-up Visit.

For the Extension Study, hematology and chemistry will be collected at Day 1, every 4 cycles (e.g., Cycle 4 Day 1, Cycle 8 Day 1, etc.), Final Visit and at the Safety Follow-up Visit.

During the lead-in period, hematology, chemistry and urinalysis samples will also be collected on Lead-in Day 1 and Lead-in Days 2 and 3 (chemistry and hematology only).

For any subjects who are at high risk for tumor lysis syndrome (TLS) during Cycle 2 and beyond, additional samples for hematology and chemistry may be collected as per the management guidelines in Section 6.7.4. ANC $\geq$ 500/µL and < 1,000/µL should be monitored at an increased frequency at the discretion of the investigator. Grade 2 chemistry labs should be monitored at an increased frequency at the discretion of the investigator.

The laboratory test results from Screening (except platelet count) will serve as the baseline for clinical assessment.

All laboratory measurements obtained through Day 1 of Cycle 2 in the Phase 1 portion of the study will be either entered on the eCRF or faxed to the Oncology Safety Management Team within 24 hours of report availability via the contact information provided in Section 6.5.

Phase 2a

Hematology, chemistry and urinalysis samples will be collected at Screening, Cycle 1 Day 1, Cycle 1 Days 2 and 3 (chemistry and hematology only), weekly through the first 2 cycles, Day 1 of each subsequent cycle (or within 72 hours prior), at Final Visit and at the Safety Follow-up Visit.

For the Extension Study, hematology and chemistry will be collected at Day 1, every 4 cycles (e.g., Cycle 4 Day 1, Cycle 8 Day 1, etc.), Final Visit and at the Safety Follow-up Visit.

During the lead-in period (21/21 day dosing schedule), hematology, chemistry and urinalysis samples will also be collected on Lead-in Day 1 and Lead-in Days 2 and 3 (chemistry and hematology only).

For any subjects who are at high risk for tumor lysis syndrome (TLS) during Cycle 2 and beyond, additional samples for hematology and chemistry may be collected as per the management guidelines in Section 6.7.4. ANC $\geq$ 500/µL and < 1,000/µL should be monitored at an increased frequency at the discretion of the investigator. Grade 2 chemistry labs should be monitored at an increased frequency at the discretion of the investigator.

Local laboratories will be utilized in Phase 2a to process and provide results for the hematology samples. The principal investigator or sub-investigator will review, initial and date all laboratory results. The hematology test results will be collected on the electronic Case Report Forms. All other (i.e., lymphocyte enumeration, chemistry and urinalysis) clinical laboratory samples obtained in Phase 2a will be assessed using a certified central laboratory (Quest Diagnostics). The central laboratory for this study will

provide instructions regarding the collection, processing and shipping of these samples. All laboratory samples, except hematology samples, should be shipped to the central laboratory.

Starting with Protocol Amendment 13, subjects in the Extension Study from Phase 2a will use local laboratories for all clinical laboratory samples.

The local laboratory test results from the Extension Study will be collected on paper Case Report Forms.

A certified local reference laboratory may perform chemistry tests for immediate subject management in Phase 2a; however split or concurrent samples must be drawn and sent to the central laboratory for analysis.

Local laboratories will be utilized to process and provide results for all platelet counts. Platelet count results must be available and reviewed prior to dosing. The laboratory test results from Screening (except platelet count) will serve as the baseline for clinical assessment.

Table 7. Clinical Laboratory Tests

Hematology	Clinical Chemistry[a,b]	Urinalysis
Hematocrit Hemoglobin Red blood cell (RBC) count White blood cell (WBC) count Neutrophils Bands Lymphocytes Monocytes Basophils Eosinophils Platelet count (estimate not acceptable) Prothrombin time (PT) Activated partial thromboplastin time (aPTT) Mean platelet volume (MPV) Mean corpuscular hemoglobin (MCH) Mean corpuscular volume (MCV) Mean corpuscular hemoglobin concentration (MCHC) Reticulocyte count	Blood urea nitrogen (BUN) Creatinine Total bilirubin Serum glutamic-pyruvic transaminase (SGPT/ALT) Serum glutamic-oxaloacetic transaminase (SGOT/AST) Alkaline phosphatase Sodium Potassium Calcium Inorganic phosphorus Uric acid Cholesterol Total protein Glucose Triglycerides Albumin Lactate dehydrogenase (LDH) Magnesium Chloride Bicarbonate Amylase (only at Screening, C1D14 or C1D15 and Final Visit) Lipase (only at Screening, C1D14 or C1D15 and Final Visit)	Specific gravity Ketones pH Protein Blood Glucose Microscopic examination (as indicated)

a. Chemistry tests should be obtained under fasting conditions if possible.

b. Triglycerides will only be performed at Screening and Final Visit.

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

- The investigator may repeat the test to verify the out-of-range value.
- 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.

Assignment of Subject Numbers

Phase 1

The results of all screening and pre-dose Study Day 1 (or Lead-in Day 1 for lead-in period) evaluations must be within clinically acceptable limits (per inclusion criteria in Section 5.2.1), upon review by the investigator with the concurrence of the AbbVie Medical Monitor or designee, before a subject can be administered study drug. Screening results will be faxed to the Clinical Team Leader as indicated in Section 7.0. Subjects will not be enrolled in the study if laboratory or other screening results are not within clinically acceptable limits. Subjects who meet the inclusion criteria and do not meet any of the exclusion criteria will be assigned a unique subject number by AbbVie, as described in Section 5.5.3.

Phase 2a

The results of all screening and pre-dose Lead-in Day 1 evaluations must be within clinically acceptable limits (per inclusion criteria in Section 5.2.1), upon review by the investigator before a subject can be administered study drug. Subjects will not be enrolled in the study if laboratory or other screening results are not within clinically acceptable limits. Subjects who meet the inclusion criteria and do not meet any of the exclusion criteria will be assigned a unique subject number by AbbVie, as described in Section 5.5.3.

Extension Study

Subjects who meet the inclusion criteria and do not meet any of the exclusion criteria (refer to Section 5.2) and who continue in the Extension Study will retain the subject number that was assigned in the Phase 1 or Phase 2a portion of the study.

5.3.1.2 Meals and Dietary Requirements

Subjects will self-administer ABT-263 orally once daily (QD) within 30 minutes following the completion of breakfast, unless otherwise specified. Subjects may not

consume grapefruit or grapefruit products within the 3-day period prior to initial study drug administration and until the last treatment cycle is completed due to possible CYP3A mediated metabolic interaction.

5.3.1.3 Blood Samples for Pharmacogenetic Analyses

DNA

All Sites

Phase 1 and 2a: Optional

One 4 mL blood sample for DNA isolation will be collected at Screening (preferred) or prior to treatment on Lead-in Day 1 (21/21 day dosing schedule) or Cycle 1 Day 1 (14/21 day dosing schedule) from each subject who consents to provide samples for pharmacogenetic analysis. The collection, processing, and shipping of the specimens should be performed as described in the M06-873 laboratory manual.

Samples will be shipped to AbbVie for DNA extraction and long-term storage. AbbVie or a designated laboratory will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.

If pharmacogenetic testing is performed, results from individual subjects will be kept coded and confidential. Samples will be coded so that subject identities will not be available to the scientists conducting the genotyping analysis. The samples will be retained while research on ABT-263 or Bcl-2 inhibitors continues. Upon completion of the research, the samples will be destroyed.

5.3.1.4 Specimens for Pharmacodynamic Analyses

Blood Collection for Proteomics

All Sites

Phase 1: Optional

Approximately 4 mL of blood will be collected by venipuncture into one 4 mL EDTA (purple top) tube at Screening (preferred) or prior to treatment on Day 1, Cycle 1 Day 14, Cycle 2 Day 14, and an additional sample will be prepared at Final Visit, including the Final Visit of the Extension Study, from all subjects who consent to participate. The collection, processing, and shipping of the specimens should be performed as described in the M06-873 laboratory manual. The complete process of centrifugation, transfer to cryovial, and freezing should be accomplished in less than 1 hour from blood draw.

Phase 2a: Required

Approximately 6 mL of blood will be collected by venipuncture into one 6 mL EDTA (purple top) tube at Screening (preferred) or prior to treatment on Day 1, Cycle 1 Day 15, Cycle 2 Day 15 and an additional sample will be prepared at Final Visit. Including the Final Visit of the Extension Study. In Protocol Amendment #12 this sample will no longer be required to be collected from subjects in the extension study. The collection, processing, and shipping of the specimens should be performed as described in the M06-873 laboratory manual. The complete process of centrifugation, transfer to cryovial, and freezing should be accomplished in less than 1 hour from blood draw.

Blood Collection and Storage for Bcl-2 Family Analysis

All Sites

Phase 1 and 2a: Required

Approximately 2 mL of blood will be collected by venipuncture into pediatric EDTA tubes at Screening (preferred) or prior to treatment on Lead-in Day 1 (21/21 day dosing schedule) or Cycle 1 Day 1 (14/21 day dosing schedule), Cycle 1 Day 14 (14/21 day

dosing schedule), or Cycle 1 Day 15 (21/21 day dosing schedule), end of Cycle 4, and Final Visit. Including the Final Visit of the Extension Study. In Protocol Amendment #12 this sample will no longer be required to be collected from subjects in the extension study.

The collection, processing, and shipping of the specimens should be performed as described in the M06-873 laboratory manual. It is preferable for the process of inversion, fixing, mixing and freezing occur within 30 minutes of the blood draw.

ACD Tube of Blood for ZAP70/CD38-Ship Day of Draw

US Sites Only

Phase 1: Optional

Phase 2a: Required

Approximately 6 mL of blood will be collected by venipuncture into appropriately labeled 6 mL ACD tube (yellow top) at Screening (preferred) or prior to treatment on Lead-in Day 1 (21/21 day dosing schedule) or Cycle 1 Day 1 (14/21 day dosing schedule), end of Cycle 4 and an additional sample will be prepared at Final Visit. The specimen must be shipped Monday-Thursday and on the same day of collection. The collection, processing, and shipping of the specimens should be performed as described in the M06-873 laboratory manual.

Heparin Tube of Blood for CGH/FISH-Ship Day of Draw

Australian Sites and US Sites

Phase 1 and 2a: Required

Approximately 6 mL of blood will be collected by venipuncture into appropriately labeled 6 mL heparin tube (green top) at Screening (preferred) or prior to treatment on Lead-in Day 1 (21/21 day dosing schedule) or Cycle 1 Day 1 (14/21 day dosing schedule), end of Cycle 4 and at Final Visit including the Final Visit of the Extension Study. In Protocol Amendment #12 this sample will no longer be required to be collected from subjects in

the extension study. The collection, processing, and shipping of the specimens should be performed as described in the M06-873 laboratory manual.

Bone Marrow Aspirate/Biopsy Collection

All Sites

Phase 2a Only: Required

Bone Marrow Aspirate

Bone marrow aspirates should be drawn at baseline into a green top heparin tube in conjunction with the diagnostic biopsy for all subjects in Phase 2a at Screening and at the end of Cycle 8 if the subject is continuing to receive ABT-263. If a bone marrow aspirate was obtained within 12 weeks of starting study drug without intervening treatment and is representative of the subject's existing disease, a Screening sample does not need to be obtained. A portion of the aspirate may be processed according to the institutional standard procedures (for tumor assessment) and a portion must be processed according to the M06-873 lab manual for pharmacodynamic analysis of tumor cells. If a procedure other than what is described in the M06-873 lab manual is used, a description of the procedure should be provided to AbbVie.

Bone Marrow Core Biopsy

If bone marrow aspirate is not collected, a bone marrow core biopsy may be obtained at Screening and the end of Cycle 8 for Phase 2a. The core may be processed according to the institutional standard procedures or per the M06-873 lab manual. If a procedure other than what is described in the M06-873 lab manual is used, a description of the procedure should be provided to AbbVie.

Bcl-2/Bim Ratio-Ship Day of Draw

Australian Sites and US Sites

Phase 1 and 2a: Optional

Approximately 4 mL of blood will be collected by venipuncture into an appropriately labeled 4 mL heparin tube (green top) at Screening (preferred) or prior to treatment on Lead-in Day 1 (21/21 day dosing schedule) or Cycle 1 Day 1 (14/21 day dosing schedule), end of Cycle 4 and Final Visit. The specimen must be shipped Monday-Thursday and on the same day of collection. The collection, processing, and shipping of the specimens should be performed as described in the M06-873 laboratory manual.

Assays for in vivo Apoptosis of CLL Cells-Ship Day of Draw

Australian Sites Only

Phase 1 and 2a: Optional

Approximately 6 mL of blood (and/or 1 mL of bone marrow aspirate, if patient is undergoing a bone marrow biopsy) will be collected by venipuncture (or aspirate) into an appropriately labeled 6 mL heparin tube (green top) at Screening (preferred) or prior to treatment on Lead-in Day 1 (21/21 day dosing schedule) or Cycle 1 Day 1 (14/21 day dosing schedule), Cycle 1 Day 7 or Cycle 1 Day 8, Cycle 1 Day 14 or Cycle 1 Day 15, Cycle 2 Day 1, Cycle 2 Day 7 or Cycle 2 Day 8, and Cycle 2 Day 14 or Cycle 2 Day 15. The collection, processing, and shipping of the specimens should be performed as described in the M06-873 laboratory manual.

Assays for in vitro Sensitivity of CLL Cells-Ship Day of Draw

Australian Sites Only

Phase 1 and 2a: Optional

Approximately 10 mL of blood (and/or 1 mL of bone marrow aspirate, if patient is undergoing a bone marrow biopsy) will be collected by venipuncture (or aspirate) into an

appropriately labeled 10 mL EDTA tube (pink top) at Screening (preferred) or prior to treatment on Lead-in Day 1 (21/21 day dosing schedule) or Cycle 1 Day 1 (14/21 day dosing schedule), Cycle 1 Day 14 or Cycle 1 Day 15 and Cycle 3 Day 1 (prior to treatment). The collection, processing, and shipping of the specimens should be performed as described in the M06-873 laboratory manual.

Table 8. Schedule of Biomarker Sample Collection (Phase 1)

	Screening[a]	C1D7	C1D14	C2D1	C2D7	C2D14	C3D1	End of C4	Final Visit[f]
Pharmacogenetics[b]	4 mL								
Proteomics-plasma[b]	4 mL		4 mL			4 mL			4 mL
CD38/ZAP 70[b,c]	6 mL							6 mL	
Bcl-2 Family analysis	2 mL		2 mL					2 mL	2 mL
CGH/FISH[d]	6 mL							6 mL	
Bcl-2/Bim Ratio[b,d]	4 mL							4 mL	
Markers of apoptosis[a,b,e]	6 mL	6 mL	6 mL	6 mL	6 mL	6 mL			
In vitro sensitivity[a,b,e]	10 mL		10 mL				10 mL		

C = Cycle; D = Day

a. Screening samples not collected at the time of screening should be collected pre-dose on Lead-in Day 1 (21/21 day dosing) or Cycle 1 Day 1 (14/21 day dosing), however, every effort should be made to collect at screening to decrease the blood volumes obtained on Lead-in Day 1/Cycle 1 Day 1.

b. Blood collection is optional in the Phase 1 portion of the study.

c. Study will only be performed in the US.

d. Studies will only be performed in US and Australia.

e. Studies will only be performed in Australia.

f. For subjects who continue in the Extension Study, the Final Visit procedures will be performed upon completion of the Extension Study. Refer to Appendix G for the Schedule of Assessments for subjects enrolled in the Extension Study.

Table 9. Schedule of Biomarker Sample Collection (Phase 2a)

	Screening[a]	C1D7	C1D15	C2D1	C2D7	C2D15	C3D1	End of C4	End of C8	Final Visit[h]
Pharmacogenetics[b]	4 mL									
Proteomics-plasma	6 mL		6 mL			6 mL				6 mL
CD38/ZAP 70[c]	6 mL							6 mL		
Bcl-2 Family analysis	2 mL		2 mL					2 mL		2 mL
CGH/FISH[d]	6 mL							6 mL		6 mL
Bcl-2/Bim Ratio[b,d]	4 mL							4 mL		
Markers of apoptosis[a,b,e]	6 mL	6 mL	6 mL	6 mL	6 mL	6 mL				
In vitro sensitivity[a,b,e]	10 mL		10 mL				10 mL			
Tumor cells bone marrow aspirate	2 mL[f]								2 mL[g]	

C = Cycle; D = Day

a. Screening samples not collected at the time of screening should be collected pre-dose on Lead-in Day 1, however, every effort should be made to collect at Screening to decrease the blood volumes obtained on Lead-in Day 1.

b. Blood collection is optional in the Phase 2a portion of the study.

c. Study will only be performed in the US.

d. Studies will only be performed in US and Australia.

e. Studies will only be performed in Australia.

f. If a bone marrow aspirate was obtained within 12 weeks of starting study drug without intervening treatment and is representative of the subject's existing disease, a Screening sample does not need to be obtained.

g. A bone marrow aspirate/biopsy will be performed at the end of Cycle 8, if the subject is continuing to receive ABT-263.

h. Prior to Amendment 12, subjects who continue in the Extension Study, the Final Visit procedures were performed upon completion of the Extension Study, collection of these specimens are no longer required. Refer to Appendix G for the Schedule of Assessments for subjects enrolled in the Extension Study.

5.3.1.5 Disposition of Samples for Pharmacogenetic/Pharmacodynamic Analyses

The blood samples for pharmacogenetic and pharmacodynamic analyses will be shipped from the study site to AbbVie or designate according to instructions from AbbVie. The samples should be labeled with the drug number name, type of sample (e.g., blood), the protocol number, the subject number, the study cycle and day and/or collection date. An

inventory of the samples included will accompany the package. Arrangements will be made with AbbVie for the shipment of stored samples to:

Attn: AbbVie Sample Receiving
[redacted]
c/o: Delivery Services
1150 S. Northpoint Blvd.
Waukegan, IL 60085
Phone: (847) 937-0889
Fax: (847) 938-9898
Email: sample.receiving@abbvie.com

5.3.2 Drug Concentration Measurements

5.3.2.1 Collection of Samples for Analysis

Blood Samples for ABT-263 Assay

Phase 1 – 14/21 Day Dosing Schedule

Blood samples for ABT-263 assay will be collected by venipuncture into 3 mL evacuated potassium EDTA-containing collection tubes during Cycle 1 at the following times: Day 1, pre-dose (0 hour) and at 2, 4, 6, 8 and 24 (C1D2 pre-dose) hours after dosing; Day 14, pre-dose (0 hour) and at 2, 4, 6 and 8 hours after dosing. Sufficient blood will be collected to provide approximately 1 mL plasma from each sample. A total of 11 blood samples (approximately 33 mL) will be collected per subject for pharmacokinetic analysis during Cycle 1. Blood samples will be collected in subsequent cycles as follows: pre-dose on Cycle 2, Days 3, 8 and 14; Cycle 3, Day 1 (4-8 hours post-dose immediately after ECG) and Day 14 (pre-dose and 4-8 hours post-dose immediately after ECG). Additional blood samples will be collected pre-dose (0 hour) on Day 14 of Cycles 6, 9, 12 and 15. See Table 4 and Table 5 for a schedule of the blood collection for ABT-263 assay.

Phase 1 - 21/21 Day Dosing Schedule

Blood samples for ABT-263 assay will be collected by venipuncture into 3 mL evacuated potassium EDTA-containing collection tubes during Cycle 1 at the following times: Day 1, pre-dose (0 hour) and at 2, 4, 6, 8 and 24 (C1D2 pre-dose) hours after dosing; Day 14, pre-dose (0 hour) and at 2, 4, 6 and 8 hours after dosing. Sufficient blood will be collected to provide approximately 1 mL plasma from each sample. A total of 11 blood samples (approximately 33 mL) will be collected per subject for pharmacokinetic analysis during Cycle 1. Blood samples will be collected in subsequent cycles as follows: pre-dose on Cycle 2, Days 3, 8 and 14; Cycle 3, Day 1 (4-8 hours post-dose immediately after ECG) and Day 14 (pre-dose and 4-8 hours post-dose immediately after ECG). Additional blood samples will be collected pre-dose (0 hour) on Day 1 of Cycles 6, 9, 12 and 15.

See Table 4 and Table 5 for a schedule of the blood collection for ABT-263 assay.

Phase 2a

Blood samples for ABT-263 assay will be collected by venipuncture into 3 mL evacuated potassium EDTA-containing collection tubes during Cycle 1 at the following times: Day 15 (pre-dose [0 hour] and 4-8 hours post-dose immediately after ECG). Sufficient blood will be collected to provide approximately 1 mL plasma from each sample. A total of 2 blood samples (approximately 6 mL) will be collected per subject for pharmacokinetic analysis during Cycle 1. Additional blood samples will be collected pre-dose (0 hour) on Cycle 3 Day 1 and pre-dose (0 hour) and 4-8 hours post-dose (immediately after ECG) on Day 1 of Cycles 5 and 9.

See Table 6 for a schedule of the blood collection for ABT-263 assay.

Phase 1, Phase 2a and Extension Study

In addition, serial pharmacokinetic samples will be obtained from subjects who develop Grade 4 thrombocytopenia (< 25,000/mm^3). The first pharmacokinetic sample should be collected as soon as possible after determination of the first Grade 4 thrombocytopenia

event and then 24 and 48 hours thereafter. Starting with Protocol Amendment 13, PK samples will NOT be collected.

Blood and plasma samples must be protected from direct sunlight during collection, processing and storage. Immediately after collection, the blood samples will be inverted several times to ensure good mixing of the blood and anticoagulant, and will be placed in an ice bath.

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 dosing will be the same for all subjects. The date and time (to the nearest minute) of each blood sample collection will be recorded on the eCRF. In addition, the date and time (to the nearest minute) of dose and whether or not doses were taken within 30 minutes of completing breakfast for the pre-dose (0 hour) PK sampling day and for the 2 days prior to each PK sampling day will be recorded on the eCRF. Sites should ensure that the data are captured via source document (e.g., subject calendar, clinic notes).

5.3.2.2 Handling/Processing of Samples

Blood Samples for ABT-263 Assay

The processing of all pharmacokinetic specimens should be performed as described in the M06-873 laboratory manual.

5.3.2.3 Disposition of Samples for ABT-263 Assay

Samples should be labeled using the labels provided by AbbVie with the drug number name, type of sample (plasma), the protocol number, the subject number, the study cycle and day and the planned time of sampling relative to dosing. The frozen plasma samples for ABT-263 assay will be packed in dry ice sufficient to last during transport and shipped from the study site to AbbVie according to instructions from AbbVie. An inventory of the samples included will accompany the package. Arrangements will be made with AbbVie for the shipment of samples to:

Attn: AbbVie Sample Receiving
[redacted]
c/o Delivery Services
1150 S. Northpoint Blvd.
Waukegan, IL 60085
Phone: (847) 937-0889
Fax: (847) 938-9898
Email: sample.receiving@abbvie.com

5.3.2.4 Measurement Methods

Analysis of Plasma Samples

Plasma concentrations of ABT-263 will be determined under the supervision of the Drug Analysis Department at AbbVie.

5.3.3 Efficacy Variables

For the Phase 2a portion of the study, all efficacy analyses are exploratory in nature. The exploratory efficacy endpoints include tumor response (determined using NCI-WG Criteria), progression free survival (PFS), time to tumor progression (TTP), overall survival (OS), duration of overall response and ECOG performance status. Analyses of these endpoints are described in Section 8.1.3.

5.3.3.1 NCI-WG Criteria for Tumor Response

Only subjects with active disease requiring treatment (in the opinion of the investigator) will be enrolled in the study. Response over the course of therapy will be evaluated using the 1996 National Cancer Institute Working Group Guidelines for Chronic Lymphocytic Leukemia (NCI-WG) criteria[30] and the International Workshop for Chronic Lymphocytic Leukemia (IWCLL) updated 2008 National Cancer Institute Working Group Guidelines (NCI-WG) for Chronic Lymphocytic Leukemia criteria.[31] Response criteria will be assessed while subjects continue treatment with ABT-263.

5.3.3.1.1 NCI-WG Criteria - 1996

Methods of Measurement

Disease response and progression will be assessed by analysis of peripheral blood, clinical examination, radiographic techniques when clinically indicated (e.g., splenomegaly, lymphadenopathy), and bone marrow aspirate and biopsy (if needed to confirm active disease at baseline and to confirm a CR).

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than four weeks 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). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is required.

The diameter, in two planes, of the largest palpable nodes in each of the following sites should be measured: cervical, axillary, supraclavicular, inguinal, and femoral.

CT is the preferred method to measure lesions selected for response assessment. MRI may be used if medically indicated (e.g., severe contrast allergy). Conventional CT and MRI should be performed with cuts of 7 mm or less in slice thickness contiguously.

For accurate objective response evaluation, ultrasound (US) should not be used to measure tumor lesions. However, US is a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions and thyroid nodules. US might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.

Cytology and histology can be used to differentiate between partial remission (PR) and complete remission (CR) in rare cases (e.g., after treatment to differentiate between residual benign lesions and residual malignant lesions in tumor types such as germ cell tumors).

Assessment of response will be performed by the investigator and documented on the appropriate CRF.

Complete Remission (CR) requires all of the following for a period of at least 2 months:

1. Absence of lymphadenopathy by physical examination and appropriate radiographic techniques.
2. No hepatomegaly or splenomegaly by physical examination and appropriate radiographic techniques.
3. Absence of constitutional symptoms.
4. Normal CBC as exhibited by:
   - Polymorphonuclear leukocytes ≥ 1,500/μL.
   - Platelets > l00,000/μL.
   - Hemoglobin > 11.0 g/dL (untransfused).
5. Bone marrow aspirate and biopsy should be performed 2 months after clinical and laboratory results demonstrate that all of the requirements above have been met to demonstrate that a CR has been achieved. The marrow sample must be at least normocellular for age, with less than 30% of nucleated cells being lymphocytes. Lymphoid nodules should be absent. If the bone marrow is hypocellular, a repeat determination should be made in 4 weeks. Samples should be re-reviewed in conjunction with the prior pathology.

Partial Remission (PR) requires all of the following for a period of at least 2 months:

1. ≥ 50% decrease in peripheral blood lymphocyte count from the pretreatment baseline value.
2. ≥ 50% reduction in lymphadenopathy.
3. ≥ 50% reduction in the size of the liver and/or spleen (if abnormal prior to therapy).

In addition **one or more** of the following criteria must be met:

- Polymorphonuclear leukocytes ≥ 1,500/μL or 50% improvement over baseline.
- Platelets > l00,000/μL or 50% improvement over baseline.
- Hemoglobin > 11.0 g/dL or 50% improvement over baseline without transfusions.

Progressive Disease (PD) requires at least one of the following:

1. ≥ 50% increase in the sum of the products of at least two lymph nodes on two consecutive determinations 2 weeks apart (at least one node must be ≥ 2 cm); appearance of new palpable lymph nodes.
2. ≥ 50% increase in the size of the liver and/or spleen as determined by measurement below the respective costal margin; appearance of palpable hepatomegaly or splenomegaly, which was not previously present.
3. ≥ 50% increase in the absolute number of circulating lymphocytes with at least 5,000/μL.
4. Transformation to a more aggressive histology (e.g., Richter's syndrome or PLL with > 55% prolymphocytes).

Subjects who have not achieved a CR or a PR, or who have not exhibited PD will be considered to have Stable Disease (SD).

Subjects who meet the criteria above for a CR but exhibit persistent bone marrow lymphoid infiltration will be referred to as nodular PRs (nPR). In addition, subjects who meet the criteria above for a CR but exhibit persistent thrombocytopenia or anemia unrelated to disease activity and attributable to a persistent drug toxicity will be considered PR's.

A summary of the criteria described above is included in Table 10.

Table 10. NCI-WG Criteria for Tumor Response (1996)

Criteria	Complete Remission (CR)	Nodular Partial Remission (nPR)#	Partial Remission (PR)	Progressive Disease (PD)
Symptoms	Absent	Absent	Absent or present	Not specified
Lymphadenopathy	Absent	Absent	≥ 50% reduction	≥ 50% increase* or new nodes
Hepatomegaly and/or Splenomegaly	Absent	Absent	≥ 50% reduction	≥ 50% increase or new hepatomegaly and/or splenomegaly
Neutrophils/ Polymorphonuclear Leukocytes ($\times 10^9$/L)	≥ 1.5	≥ 1.5	≥ 1.5 or ≥ 50% improvement from baseline	Not specified
Lymphocytes ($\times 10^9$/L)	< 4	< 4	≥ 50% reduction from baseline	≥ 50% increase with at least 5×10^9/L
Platelets ($\times 10^9$/L)	> 100	> 100	> 100 or ≥ 50% improvement from baseline	Not specified
Hemoglobin (g/dL) untransfused	> 11	> 11	> 11 or ≥ 50% improvement from baseline	Not specified
Bone Marrow Aspirate/Biopsy	Normocelluar < 30% lymphocytes; No intestinal or nodular infiltrates	Normocelluar < 30% lymphocytes; Nodular infiltrates	May be normal (i.e., < 30% lymphocytes without interstitial or nodular infiltrates) or persistent disease	Not specified
Other	*NA*	*NA*	*NA*	Transformation to RS or PLL

NA = not applicable; RS = Richter syndrome; PLL = Prolymphocytic Leukemia (with > 55% prolymphocytes); # = nPR is no longer applicable due to the utilization of immunohistochemistry; * = sum of products of at least 2 lymph nodes

5.3.3.1.2 IWCLL Updated NCI-WG Criteria – 2008

Methods of Measurement

Disease response and progression will be assessed by analysis of peripheral blood, clinical examination, radiographic techniques to assess splenomegaly, lymphadenopathy and/or bone marrow aspirate and biopsy to confirm active disease at baseline and if needed to confirm a CR.

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks 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). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is required.

The diameter, in two planes, of the largest palpable nodes in each of the following sites should be measured: cervical, axillary, supraclavicular, inguinal, and femoral.

CT is the preferred method to measure lesions selected for response assessment. MRI may be used if medically indicated (e.g., severe contrast allergy). Conventional CT and MRI should be performed with cuts of 7 mm or less in slice thickness contiguously.

For accurate objective response evaluation, ultrasound (US) should not be used to measure tumor lesions. However, US is a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions and thyroid nodules. US might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.

Assessment of response will be performed by the investigator and documented on the appropriate CRF.

Complete Remission (CR) requires all of the following for a period of at least 2 months:

1. Absence of clonal lymphocytes in the peripheral blood.
2. Absence of significant lymphadenopathy by physical examination and appropriate radiographic techniques. A CT scan of the abdomen, pelvis and thorax should be performed if previously abnormal. Lymph nodes should not be larger than 1.5 cm in diameter.
3. No hepatomegaly or splenomegaly by physical examination. A CT scan of the abdomen should be performed at response assessment if found to be abnormal prior to the start of study drug or if physical exam is inconclusive at the time of evaluation.
4. Absence of constitutional symptoms.
5. Normal CBC as exhibited by:
    - Polymorphonuclear leukocytes ≥ 1,500/μL without G-CSF support.
    - Platelets > 100,000/μL.
    - Hemoglobin > 11.0 g/dL (untransfused or without erythropoietin support).

Bone marrow aspirate and biopsy should be performed at least 2 months after clinical and laboratory results demonstrate that all of the requirements above have been met to demonstrate that a CR has been achieved. The marrow should be analyzed by flow cytometry and/or immunochemistry to demonstrate that the marrow is free of clonal B-CLL cells. Note: cases with residual CLL cells by conventional flow cytometry or immunohistochemistry are defined as a PR.

Subjects who fulfill all the criteria for a CR, but who have persistent anemia, thrombocytopenia or neutropenia apparently unrelated to CLL, but related to drug toxicity should be considered as a different category of remission, CR with incomplete bone

marrow recovery (CRi). The marrow evaluation should be performed with scrutiny and not show any clonal infiltrate. Subjects should be monitored prospectively to determine whether or not their outcome differs from that of patients with detectable residual disease or with non-cytopenic PR.

Partial Remission (PR) requires at least two of the following for a period of at least 2 months:

1. ≥ 50% decrease in peripheral blood lymphocyte count from the pretreatment baseline value.
2. ≥ 50% reduction in lymphadenopathy (assessed by CT scan):
   - In the sum of products of up to 6 lymph nodes, or
   - In one lymph node diameter if only a single lymph node was present at baseline.
3. No increase in any lymph node, and no new enlarged lymph node. In small lymph nodes (< 2 cm), an increase of < 25% is not considered to be significant.
4. ≥ 50% reduction in the size of the liver and/or spleen (if abnormal prior to therapy) as defined by CT scan.

In addition **one or more** of the following criteria must be met:

- Polymorphonuclear leukocytes ≥ 1,500/μL or 50% improvement over baseline without G-CSF support.
- Platelets > 100,000/μL or 50% improvement over baseline.
- Hemoglobin > 11.0 g/dL or 50% improvement over baseline without transfusions or erythropoietin support.

Progressive Disease (PD) requires at least one of the following:

1. Appearance of any new lesions such as enlarged lymph nodes (> 1.5 cm), splenomegaly, hepatomegaly or other organ infiltrates.

2. ≥ 50% increase in the sum of the products of diameters of multiple nodes
3. ≥ 50% in the greatest determined diameter of any previous site. A lymph node of 1-1.5 cm must increase by ≥ 50% to a size greater than 1.5 cm in the longest axis. A lymph node of more than 1.5 cm must increase to more than 2.0 cm in the longest axis.
4. ≥ 50% increase in the size of the liver and/or spleen or the de novo appearance of hepatomegaly or splenomegaly.
5. ≥ 50% increase in the absolute number of blood lymphocytes with at least 5,000 B-lymphocytes per μL.
6. Transformation to a more aggressive histology (e.g., Richter's syndrome or PLL with > 55% prolymphocytes).
7. Occurrence of cytopenia (neutropenia, anemia or thrombocytopenia) attributable to CLL.
    - The progression of any cytopenia (unrelated to autoimmune cytopenia), as documented by a decrease of Hb levels by more than 2 g/dL or to less than 10 g/dL, or by a decrease of platelet counts by more than 50% or to less than 100,000/μL, defines disease progression, if the marrow biopsy demonstrates an infiltrate of clonal CLL cells.

Subjects who have not achieved a CR or a PR, or who have not exhibited PD will be considered to have Stable Disease (SD).

A summary of the criteria described above is included in Table 11.

Table 11. IWCLL Updated NCI-WG Criteria for Tumor Response (2008)

Criteria	Complete Remission (CR)	Partial Remission (PR)	Progressive Disease (PD)	Stable Disease (SD)
Lymphadenopathy	None above 1.5 cm	≥ 50% reduction	≥ 50% increase	Change of –49% to +49%
Hepatomegaly and/or Splenomegaly	Absent	≥ 50% reduction	≥ 50% increase or new hepatomegaly and/or splenomegaly	Change of –49% to +49%
Constitutional Symptoms	Absent	Present	Present	Present
Polymorphonuclear Leukocytes	≥ 1500/µL	≥ 1500/µL or > 50% improvement over baseline without G-CSF support	Not specified	Not specified
Circulating clonal B-lymphocytes	None	≥ 50% reduction from baseline	≥ 50% increase over baseline	Change of –49% to +49%
Platelets	> 100,000/µL	> 100,000/µL or ≥ 50% improvement from baseline	Decrease of ≥ 50% from baseline secondary to CLL	Change of –49% to +49%
Hemoglobin	> 11 g/dL (untransfused and without erythropoietin)	> 11 g/dL or ≥ 50% improvement from baseline	Decrease of > 2 g/dL from baseline secondary to CLL	Increase < 11 g/dl or < 50% over baseline or decrease < 2 g/dL
Bone Marrow Aspirate/Biopsy	Normocellular, < 30% lymphocytes, no B-lymphoid nodules, Hypocellular marrow defines CRi	≥ 30% lymphocytes, or B-lymphoid nodules, or not done	Increase of lymphocytes to more than 30% from normal	No change in marrow infiltrate

5.3.3.1.3 Definition of Clinical Disease Progression (Phase 2a)

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

- Constitutional symptoms attributable to CLL progression (e.g., unintentional weight loss, significant fatigue [e.g., ECOG performance score ≥ 2], persistent fevers without signs of infection or night sweats)
- Requirement for palliative radiation, chemotherapy, surgery, immunotherapy or biologics
- Death from disease progression

5.3.4 Safety Variables

The following safety evaluations will be performed during the study: adverse event monitoring, vital signs, physical examination, platelet counts, lymphocyte enumeration, ECG, echocardiogram, and laboratory assessments.

5.3.5 Pharmacokinetic Variables

Values for the pharmacokinetic parameters of ABT-263, including the maximum observed plasma concentration (C_{max}), the time to C_{max} (peak time, T_{max}), the terminal phase elimination rate constant (β), terminal elimination half-life ($t_{1/2}$), the area under the plasma concentration-time curve (AUC) from time 0 to 24 hours (AUC_{0-24}) for the dose on C1D1 in Phase 1 will be determined using noncompartmental methods. For C1D14 in Phase 1, values will be determined for C_{max}, T_{max} and AUC from time 0 to 8 hours (AUC_{0-8}).

5.3.6 Pharmacogenetic Variables

DNA samples may be analyzed for genetic factors contributing to the subject's response to ABT-263 in terms of pharmacokinetics, efficacy and safety. The samples may also be used for the development of a diagnostic test for such a drug response. Such genetic factors may include, for example, drug metabolizing enzymes, drug transport proteins, and Bcl-2 family members. Genetic studies in general may include determination of the relationship of genetic haplotypes and drug metabolism, transport, therapeutic response and adverse events. If clear differences of pharmacokinetics, safety or efficacy are noted during the clinical development of ABT-263 and believed to have a genetic basis, these

samples may be analyzed as part of a multicenter, multi-study project to identify genetic factors involved in the response to study drugs. The samples may also be used for the development of a diagnostic test for drug response.

5.3.7 Pharmacodynamic Variables

Several putative biomarkers of efficacy and response will be evaluated in this protocol with the goal of defining the relationship between drug concentration and disease status.

Examination of the proteomic profiles of patients in the ABT-263 clinical trials may reveal patterns of protein/peptide concentrations that may be further evaluated in future clinical studies to determine any prognostic value and any correlation with clinical response. Plasma samples will be analyzed for predictive or drug-responsive proteomic markers. In addition circulating tumor-derived DNA or RNA may be extracted from plasma and assessed for expression or methylation and mutational status of genes relevant to either the disease status or ABT-263 mechanism of action.

In the event that any plasma or serum samples are unused, remaining samples will be banked for use in diagnostic test development efforts. Measurement of relevant RNAs and proteins including the Bcl-2 family members in CLL cells in the blood, pre-treatment, during therapy and at time of relapse, may be examined for putative stratification markers for correlation with efficacy. Additional studies may include determination of the Bcl-2/Bim ratio at the mitochondrial level, a highly predictive marker of sensitivity to the Bcl-2 family inhibitors. For sites in Australia, additional studies may include assays to measure in vivo apoptosis and in vitro studies of patient CLL cell sensitivity to ABT-263.

Fluorescent *In-situ* Hybridization (FISH) may be conducted on CLL whole blood samples from patients participating in this study to assess amplifications and translocations in the Bcl-2 gene and other genes which may prove to be informative including standard CLL cytogenetic markers. Whole genome analysis by CGH array may also be performed on CLL samples to identify genomic markers of CLL. The potential relationship between amplification of these genes and the clinical outcome in these patients will be examined as

a stratification tool. Biospecimens collected during the course of this study may be banked and used in the future to investigate new scientific questions related to this study.

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 will discontinue a subject from the study at any time if the investigator considers it necessary for any reason including:

- The investigator believes it is in the best interest of the subject.
- The subject's response to therapy is unsatisfactory, as evidenced by progression of disease.
- The subject experiences toxicities that require more than a 3-week dose interruption.
- The subject requires more than two dose reductions, in the absence of objective response to ABT-263.
- The subject requires radiotherapy, cancer-related surgery, or alternate anti-neoplastic agents during the study period.
- The subject becomes pregnant or begins breastfeeding.
- The occurrence of an adverse event that precludes further investigational drug administration.
- Noncompliance with the protocol.
- The subject requires anti-coagulant or anti-platelet therapy during the study period.

In addition, subjects in the Extension Study may also be discontinued for following reasons:

- The Extension Study has been ongoing for 11 years since the transition of the last subject into the Extension Study.
- ABT-263 becomes commercially available.

- AbbVie no longer pursues ABT-263 in this indication.

The investigator will inform AbbVie prior to discontinuing a subject from the study by contacting the Clinical Team Leader as identified in Section 7.0.

During the COVID-19 pandemic, it has been necessary to employ mitigation strategies to enable the investigator to ensure subject safety and continuity of care.

The investigator should contact the sponsor medical contact before discontinuing a subject from the study for a reason other than "planned per protocol," to ensure all acceptable mitigation steps have been explored.

All subjects will be included for analysis of safety data. Subjects in the Phase 1 portion of the study who withdraw from the study will not be replaced unless they are not evaluable. Evaluable subjects are defined as those subjects who:

- Experience a DLT
- Complete at least 80% of dosing in the first cycle (of either 14/21 or 21/21 day dosing schedule)

In the event that a subject withdraws or is discontinued from the study, reason(s) for the discontinuation from the study will be recorded. A physical examination, ECG, echocardiogram, vital signs measurement, laboratory analyses, performance status assessment, collection of unused study drug, an assessment of adverse events and tumor assessment (if needed) will be performed as soon as possible after discontinuation from the study.

A Safety Follow-up Visit should be performed for all subjects approximately 30 days following discontinuation of ABT-263 and then as clinically appropriate for safety assessment. The subject will be followed until a satisfactory clinical resolution of the adverse event(s) is achieved. If the subject refuses a follow-up visit or the visit is not performed, the reason should be noted in the subject's source documentation.

In the event of a positive pregnancy test for a subject during the study, the administration of study drug to that subject must be discontinued immediately. The investigator will report the positive pregnancy test result by telephone within 1 working day to the contact listed in Section 6.5.

5.4.2 Discontinuation of Entire Study

AbbVie may terminate this study, either in its entirety or at a study site provided that written notice is submitted at a reasonable time in advance of the intended termination. The following procedures for discontinuation will be followed:

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

5.5 Treatments

5.5.1 Treatments Administered

Subjects will self-administer ABT-263 orally once daily (QD). Each dose will be taken with approximately 240 mL of water. On days that pre-dose pharmacokinetic sampling is required, dosing will occur in the morning (approximately 8 AM) in the clinic to facilitate pharmacokinetic sampling. All subjects will self-administer ABT-263 within 30 minutes after the completion of breakfast. The effect of food on pharmacokinetics will be evaluated outside of this study protocol and changes will be initiated if fasting conditions are superior.

On dosing days with PK collection (per Table 4 through Table 6), the time of each drug administration will be recorded to the nearest minute. On all other days, subjects will be

instructed to record the date and time they take study drug. Subject diaries will be provided by AbbVie.

During the Study Drug Dosing Period, a subject with confirmed (viral test positive) or suspected COVID-19 infection can only be dosed with study drug if the following COVID-19 viral clearance criteria are met:

- Symptomatic subjects: At least 2 negative viral tests in a row, ≥ 24 hours apart after at least 10 days have passed since recovery, defined as resolution of fever without use of antipyretics and improvement in respiratory symptoms (e.g., cough, shortness of breath)
- Asymptomatic subjects: At least 2 negative viral tests in a row, ≥ 24 hours apart after at least 10 days have passed since prior positive result (note: subjects who develop symptoms will follow guidance above for symptomatic subjects)

Delays in study drug dosing due to the above COVID-19 testing guidance for subjects must be discussed with the AbbVie medical contact, along with the possibility of premature discontinuation from the study drug dosing period. Frequency or timing of COVID-19 testing and intervals between testing for the above viral clearance criteria may be adjusted to account for epidemiologic trends, updated information regarding infectivity, and local/institutional guidelines.

5.5.2 Identity of Investigational Product

The individual study drug information is presented in Table 12.

Table 12. Identity of Investigational Products

Study Drug	Trademark*	Formulation	Route of Administration	Manufacturer
ABT-263 (Navitoclax)	N/A	ABT-263 Stabilized Oral Solution (25 mg/mL, 90 mL/bottle)	Oral	AbbVie/Abbott
ABT-263 (Navitoclax)	N/A	Tablets (25 mg)	Oral	AbbVie/Abbott
ABT-263 (Navitoclax)	N/A	Tablets (100 mg)	Oral	AbbVie/Abbott

* N/A = Not Applicable

ABT-263 Stabilized Oral Solution

AbbVie (or designee) will supply, at a minimum:

- ABT-263 Stabilized Oral Solution packaged in amber glass bottles containing a solution of 25 mg/mL concentration of ABT-263 per bottle. Each bottle will be supplied in a carton.
- Written instructions for dosing and handling of drug supplies for the subject.
- Written instructions for preparation and dispensing of prefilled syringes by the site pharmacist (or designee).

Ancillary Materials:

- Amber oral syringes with caps.
- Child-resistant syringe cartons.
- Adapt-a-Caps (for bottles of stabilized oral solution).
- Dispensing labels for prefilled syringes and corresponding child-resistant cartons.
- Insulated cooler bags with freezable gel packs, to allow subject to transport of syringe cartons under recommended cold storage conditions.

ABT-263 Tablets

ABT-263 tablets and any applicable ancillary materials will be provided by AbbVie.

5.5.2.1 Packaging and Labeling

ABT-263 Stabilized Oral Solution (25 mg/mL) will be packaged in amber glass bottles containing 90 mL solution per bottle. Each bottle will be supplied in a carton.

ABT-263 tablets will be packaged in HDPE (high density polyethylene) plastic bottles.

Each bottle and carton will be labeled as required per country requirement. Labels must remain affixed to the bottles and cartons. Blank spaces on the label will be completed by the site.

ABT-263 Stabilized Oral Solution

The pharmacist (or designee) will prepare (prefill) the appropriate size oral syringes according to the dosing schedule and instructions provided. Prefilled syringes will be placed in a child resistant carton for the subject to take home. All prefilled syringes and child resistant cartons provided to the subject will also contain a label (completed by the site pharmacist or designee). Each syringe and child resistant carton will be labeled as required per country requirements. Labels must remain affixed to the syringes and child resistant cartons. AbbVie will provide detailed instructions and training for the handling of study supplies to the study site.

5.5.2.2 Storage and Disposition of Study Drug

The investigational products supplied in this study are for investigational use only, and are to be used only within the context of this study. All clinical supplies must be maintained under adequate security until dispensed for subject use, destroyed or returned to AbbVie. All clinical supplies must be stored per the conditions specified on the label.

ABT-263 Stabilized Oral Solution

ABT-263 Stabilized Oral Solution (25 mg/mL) must be stored at 15° to 25°C (59° to 77°F). For additional oral solution storage information, please refer to labeled storage conditions. Prefilled syringes must be stored at 2° to 8°C (36° to 46°F) and protected from light.

ABT-263 Tablets

ABT-263 tablets must be stored at 15° to 25°C (59° to 77°F) and protected from moisture and light.

5.5.2.3 Preparation/Reconstitution of Dosage Form

Written instructions for the preparation of ABT-263 oral solution and syringes will be provided to the site pharmacists as separate documents outside of this protocol.

5.5.3 Method of Assigning Subjects to Treatment Groups

As they are enrolled in the Phase 1 portion of the study, subjects will be assigned a dose and unique consecutive subject number, beginning with 501. A detailed description for the methodology of allocating subjects to treatment groups according to the continual assessment methodology is provided in Section 8.1.1. As the study progresses, subjects may progressively escalate to the highest dose level tolerated through 2 cycles of ABT-263 administration. These decisions will be based on the judgment of the investigator in coordination with the AbbVie Medical Monitor. As they are enrolled in the Phase 2a portion of the study, subjects will be assigned a unique consecutive subject number, beginning with 601. The site, in conjunction with the sponsor, will be responsible for assignment of all unique subject numbers and dose assignments. Subjects who continue in the Extension Study will retain the subject number that was assigned in the Phase 1 or Phase 2a portion of the study.

5.5.4 Selection and Timing of Dose for Each Subject

Selection of the dose for this study is discussed in Section 5.6.4. The same dose will be administered to all subjects in each dose level. All subjects will receive ABT-263 within 30 minutes following the completion of breakfast, unless specified otherwise.

COVID-19 Pandemic-Related Acceptable Protocol Modifications

Study drug may be shipped from the study site directly to the study subject's home if all the following criteria are met:

- Direct-to-patient (DTP) shipment of study drug is allowed by local regulations and the relevant ethics committee
- Study drug can be administered by the subject (or subject's caregiver) at home
- Subject agrees to have the study drug shipped directly to their home
- Shipments may also include other study supplies (e.g., drug dosing diaries). Instructions will be provided by AbbVie as to how a study site can initiate a DTP shipment using Marken, a global vendor selected by AbbVie to provide this service when necessary. Shipments of study drugs from the study site to a subject's home will be appropriately temperature controlled (qualified shipper or temperature monitoring) within the labeled storage conditions. Signature is required upon delivery; due to COVID-19 related social distancing, this may be provided by the courier after delivery. Documentation of the shipment is to be retained by the clinical site.
- AbbVie will not receive subject identifying information related to these shipments, as the site will work directly with the courier.

The study site is responsible for meeting IRB/IEC reporting requirements related to DTP shipments of study drug, and for obtaining consent to provide delivery information to the courier and documenting this consent in source documents.

5.5.5 Blinding

This is an open-label study.

5.5.6 Treatment Compliance

To document compliance with the treatment regimen, subjects will be instructed to return all prefilled drug syringes or bottles, even if empty, and any other study related items as necessary, to the appropriate study site personnel at scheduled clinic visit. Compliance will be monitored and documented by the study site personnel on the appropriate form. The study site personnel will question the subject regarding adherence to the dosing regimen, record either the number of prefilled syringes returned in the carton or the number of bottles returned, the date returned and determine treatment compliance before dispensing new medication to the study subject. Compliance below 80% will require counseling of the subject by study site personnel.

5.5.7 Drug Accountability

The investigator or his/her designated representatives will administer study drug only to subjects enrolled in the study. Documentation of the receipt of supplies will be supported by a signed and dated Proof of Receipt or similar document. A current (running) and accurate inventory of ABT-263 will be kept by the site and will include lot number, Proof of Receipt number(s), bottle numbers, number of prefilled syringes or bottles dispensed, and the date on which study drug is administered or dispensed to the subject. An overall accountability of the study drug will be performed and verified by the AbbVie designated monitors throughout the study and at the study site closeout visit. Subjects will be instructed to return all prefilled syringes or bottles at each study visit, used or unused. The site will maintain a current and accurate inventory of supplies returned by the subject, whether used or unused. Upon completion or termination of the study, all original containers (containing unused study drug) will be returned to AbbVie according to instructions from AbbVie. If pre-arranged between AbbVie and the site, destruction of used and unused study drug bottles and syringes will be performed at the site. Empty bottles will be destroyed at the site per the site's destruction policy. Labels must remain attached to the containers.

5.6 Discussion and Justification of Study Design

5.6.1 Discussion of Study Design and Choice of Control Groups

Phase 1

For the Phase 1 portion of the study, the experimental design is an adaptation of the continual reassessment method (CRM). The CRM is expected to locate the MTD efficiently. The MTD is defined as the dose at which 30% of subjects experience a DLT during the first cycle. The CRM attempts to estimate the target MTD from a continuum of doses, whereas a fixed design merely selects a dose from a discrete set. If the true target dose is not among the choices set out in advance by fixed designs, they can only approximate it. A CRM based design uses a statistical model for dose and toxicity by including the accumulating data to guide selection of the next dose. Simulations and literature have shown that compared to the conventional fixed 3+3 design, the CRM typically requires fewer subjects to find the MTD, does not greatly overshoot the MTD (that is, subjects are not expected to be treated with dangerously high doses), and does not greatly underestimate the MTD.

During Phase 1, this study will employ a CRM design.[32,33] Dosing with ABT-263 will begin at 10 mg with a cohort of three subjects. The study drug dose will be escalated to the CRM estimated MTD, not to exceed an increase of more than 100 mg or 40% increase from the current dose level. A minimum of three subjects will be treated per dose level to account for potential inter-subject variability. The study design will be based on the concept of entering every subject at the best current statistical estimation of the MTD given the previous observations. The dose escalation strategy will be based on a dose and probability of DLT response model. The model will be adjusted using all of the available data and a new estimate of MTD will be projected from the updated model. There are no control groups in this study.

Phase 2a

The Phase 2a portion of the study will be open-label at the recommended Phase 2 dose (RPTD) and dosing schedule. The RPTD will be defined by observed DLTs and/or determination of MTD from the Phase 1 portion of the study.

5.6.2 Appropriateness of Measurements

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

5.6.3 Suitability of Subject Population

Subjects with relapsed or refractory CLL will be selected to participate in this study. Pre-clinical findings support the possibility of efficacy in this patient population. Due to the expected mechanism based, potentially dose-limiting thrombocytopenia, the study eligibility requirements take into consideration a potential subject's baseline platelet count, history of bleeding or active bleeding, coagulation parameters, CNS metastasis, ongoing immune thrombocytopenic purpura, and transplant history.

5.6.4 Selection of Doses in the Study

The starting dose in this Phase 1/2a trial is derived from the results obtained in the ABT-263 1-month rat and dog toxicity studies. The initial starting dose of 10 mg was obtained by applying a safety factor of 10 to the lowest dosage used in the 1-month rat study (10 mg/kg/day) and the second-lowest dosage used in the 1-month dog study (3 mg/kg/day). Although mild changes in platelets were noted in the rats and mild to moderate changes in platelets and lymphocytes were noted in dogs at these doses, the degree of platelet and lymphocyte decrease was well tolerated. At all dosages, the decrease in platelets was readily reversible upon discontinuation of ABT-263. Additionally, at the dosages of 10 mg/kg/day in the rat or 3 mg/kg/day in the dog, platelets returned to baseline or near baseline values in the face of continued dosing. Given the ability to monitor the anticipated dose-limiting toxicity (thrombocytopenia) and the intended subject population, the safety factor of 10 provides an appropriate margin of

safety and safeguard against variability when extrapolating between species. The conversion of the 10 mg/kg dose in rats and the 3 mg/kg dose in dogs to the human equivalent dose of approximately 10 mg was made using body surface area scaling for a 60 kg human. Projections of human pharmacokinetic data suggest that the proposed dose of 10 mg taken once daily to a 60 kg human would be expected to produce at steady state a C_{max} in plasma of 0.2 µg/mL and an AUC over a dosing interval (AUC_{24}) of 2.6 µg•hr/mL. These predicted values are below those concentrations that resulted in a No-Observed-Adverse-Effect-Level (NOAEL) in the dog or a tolerated dose in the rat. An AUC value of at least 53 µg•hr/mL-88 µg•hr/mL is projected to provide an efficacious concentration. Subsequent to the 10 mg dose, the study drug dose will be escalated to the estimated MTD not to exceed an increase of 100 mg or a 40% increase from the current dose level, whichever is greater.

Phase 1

Selection of doses will be based on CRM by using a dose and probability of DLT response model. A prior model will be employed based on preclinical and clinical data. Estimates of the model parameters and the probability of toxicity will be updated at each dose level. The methodology for fitting the dose-toxicity response model is described in Section 8.1.1. Subjects will be assigned to the dose level that estimates the targeted MTD, defined as the dose to reflect 30% rate of DLT according to the model. The design is adaptive because at each dose level, the model will be updated using all of the previous available data and a new estimate of MTD will be projected from the updated model. A minimum of three subjects will be enrolled to warrant reasonable accuracy for the estimates. The modeling process provides flexibility so that the new estimated MTD may be escalated or decreased from the previous dose. The design continues in this fashion by assigning subjects to the MTD as estimated from current results. When the next predicted MTD is within 10% of the current dose, the model is considered to have converged and MTD will be declared. However, dose-determination will stop if the predetermined sample size of subjects is reached, based on operational considerations.

Once either the MTD is defined or dosing in the 4th dose level is completed for the 14/21 day dosing schedule, whichever occurs first, a continuous dosing schedule will be assessed. Dosing with ABT-263 under the continuous dosing schedule (21/21 day) will begin at the dose estimated to provide exposure equivalent to the highest dosing level cleared (4^{th} dose level) or the MTD from the 14/21 day schedule.

The starting dose for continuous dosing will be determined by calculating a dose of equivalent exposure from a 14/21 day schedule to a 21/21 day schedule (MTD × 14)/21. For example if the highest tolerated dose is determined to be 375 mg then ABT-263 will be dosed at 250 mg once daily (375 mg × 14/21 = 250 mg).

A 7 day period of dosing with a lead-in dose of ABT-263 will be explored with the 21/21 day dosing schedule in order to interrogate whether higher doses may then be given with overall less reduction in platelet counts. Subjects will begin dosing at 100 mg on Lead-in Day 1 (LD1). This is the dose level at which a mean maximal platelet drop of approximately 60% from baseline with recovery during 14 days of continued dosing is expected based on observations in this study to date. The lead-in titration dose may be adjusted if the defined dose level fails to significantly mitigate ABT-263-induced thrombocytopenia following the lead-in period or the defined dose level results in significant occurrence of DLT in the lead-in period.

Phase 2a

Once the MTD and/or RPTD is declared on the Phase 1-21/21 day continuous dosing schedule, a safety analysis will be performed as described in Section 8.1.4. The results of the safety analysis as well as the recommended Phase 2 dose and dosing schedule will be communicated to all participating research sites prior to the start of enrollment in the Phase 2a portion of the study.

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, outcome, relationship of the adverse event to study drug, and any action(s) taken. For serious adverse events not considered "probably related" to study drug, the investigator will provide an Other cause of the event. For adverse events to be considered intermittent, the events must be of similar nature and severity. Adverse events, whether in response to a query, observed by site personnel, or reported spontaneously by the subject will be recorded.

All adverse events will be followed to a satisfactory conclusion.

6.1 Definitions

6.1.1 Adverse 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. 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 6.7 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 preexisting condition and the surgery/procedure has been pre planned prior to study entry. However, if the pre-existing condition deteriorates unexpectedly during the study (e.g., surgery performed

earlier than planned), then the deterioration of the condition for which the elective surgery/procedure is being done will be considered an adverse event.

Hospitalization for the purpose of TLS prophylaxis (e.g., for I.V. hydration) will not be captured as a serious adverse event (SAE), unless there is an additional reason for hospitalization or an additional criterion for seriousness other than hospitalization.

A treatment-emergent adverse event is defined as any adverse event with onset or worsening reported by a subject from the time that the first dose of study drug is administered until 30 days have elapsed following discontinuation of study drug administration.

6.1.2 Serious Adverse Events

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

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

Important Medical Event Requiring Medical or Surgical Intervention to Prevent Serious Outcome	An important medical event that may not be immediately life-threatening or result in death or hospitalization, but based on medical judgment may jeopardize the subject and may require medical or surgical intervention to prevent any of the outcomes listed above (i.e., death of subject, life-threatening, hospitalization, prolongation of hospitalization, congenital anomaly, or persistent or significant disability/incapacity). 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.
Spontaneous Abortion	Miscarriage experienced by study subject.
Elective Abortion	Elective abortion performed on study subject.

6.2 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, Version 3.0 (NCI CTCAE).[34]

If a reported adverse event increases in severity the initial adverse event should be given an outcome date and a new adverse event reported to reflect the change in severity. For all reported serious adverse events that increase in severity, the supplemental eCRFs (paper CRFs for the Extension Study) also need to be updated to reflect the change in severity.

For adverse events not captured by the Common Terminology Criteria, the following should be used:

Grade 1 (Mild)	The adverse event is transient and easily tolerated by the subject.
Grade 2 (Moderate)	The adverse event causes the subject discomfort and interrupts the subject's usual activities.

Grade 3/4 (Severe)	The adverse event causes considerable interference with the subject's usual activities and may be incapacitating or life-threatening.
Grade 5	The adverse event resulted in death of the subject.

6.3 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:

Probably Related	An adverse event has a strong temporal relationship to study drug or recurs on re-challenge and an Other cause of event is unlikely or significantly less likely.
Possibly Related	An adverse event has a strong temporal relationship to the study drug and an Other cause of event is equally or less likely compared to the potential relationship to study drug.
Probably Not Related	An adverse event has little or no temporal relationship to the study drug and/or a more likely Other cause of event exists.
Not Related	An adverse event is due to an underlying or concurrent illness or effect of another drug and is not related to the study drug (e.g., has no temporal relationship to study drug or has a much more likely Other cause of event).

For causality assessments, events meeting the categories of probably or possibly will be considered "associated." Events that are probably not or not related will be considered "not associated." In addition, when the investigator has not reported a causality or deemed it not assessable, AbbVie will consider the event associated.

If an investigator's opinion of possibly, probably not, or not related to study drug is given, an Other cause of event must be provided by the investigator for the serious adverse event.

6.4 Adverse Event Collection Period

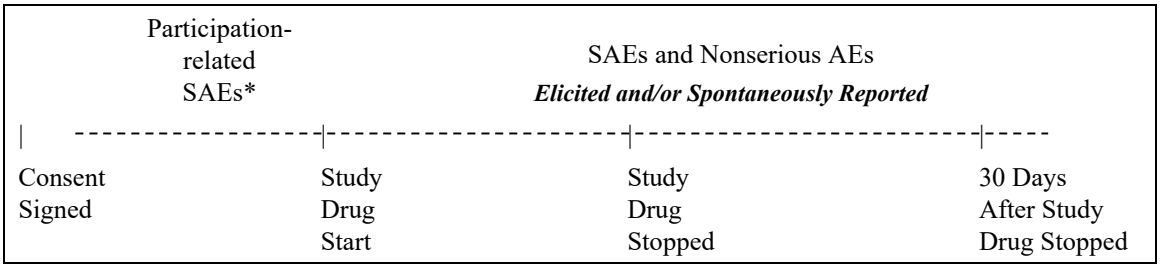
All serious and non-serious adverse events reported from the time of study drug administration until 30 days following discontinuation of study drug administration will be collected, whether elicited or spontaneously reported by the subject.

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

For subjects in the Extension Study, all adverse events that occur after Day 1 visit in the Extension Study should be captured in the Extension Study paper Case Report Forms.

Adverse event information will be collected as shown in Figure 5.

Figure 5. Adverse Event Collection



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

6.5 Adverse Event Reporting

In the event of a serious adverse event, whether related to study drug or not, the investigator will notify Oncology Safety Management within 24 hours of the site being made aware of the serious adverse event by faxing the appropriate serious adverse event forms to the AbbVie Oncology Safety Management Team.

FAX to: +1 (847) 785-8224

Email: SafetyManagement_Oncology@abbvie.com

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

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

Safety Phone: (847) 935-2609
Safety Fax: (847) 785-8224
Safety Email: SafetyManagement_Oncology@abbvie.com

For any subject safety concerns, please contact the AbbVie Medical Monitor listed below:

AbbVie Medical Monitor:
[redacted]
Executive Medical Director
1 North Waukegan Rd
North Chicago, IL

Phone: [redacted]
EMAIL: [redacted]

In emergency situations involving the study subjects when the primary Medical Monitor is not available by phone, please contact the 24-hour AbbVie Medical Escalation Hotline where your call will be re-directed to a designated backup AbbVie Medical Monitor:

Phone: +1 (973) 784-6402

COVID-19 Pandemic-Related Acceptable Protocol Modifications

Supplemental study case report forms should be completed in the event of COVID-19 related missed/virtual visits, study drug interruptions or discontinuations, or adverse events (including capture of specific signs/symptoms of infection and testing results).

COVID-19 infections should be captured as adverse events. If the event meets the criteria for a serious adverse event (SAE), then follow the SAE reporting directions per the protocol and above. The following COVID-19 related supplemental eCRFs should be completed:

- COVID-19 Supplemental Signs/symptoms
- COVID-19 Status Form

6.6 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 6.5 within 1 working day of the site becoming aware of the pregnancy.

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.

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.

6.7 Toxicity Management

6.7.1 Definition - Dose Limiting Toxicity

Dose-limiting toxicities for dose-escalation purposes will be determined during the first cycle. Adverse events occurring following the first cycle will also be evaluated by

the investigator and the AbbVie Medical Monitor and may be considered as dose limiting. Any of the following events, which are considered possibly or probably related to the administration of ABT-263, will be considered a dose limiting toxicity (DLT).

- Thrombocytopenia:
  - Grade 4 thrombocytopenia (< 25,000/mm^3)
- Platelet counts < 25,000/mm^3 should be confirmed the same day by manual reading and a separate peripheral draw. If the repeat platelet count is ≥ 25,000/mm^3, this will not be considered a DLT. If the repeat platelet count cannot be obtained within the same day as the initial measurement of < 25,000/mm^3, then the initial measurement will constitute a DLT.
- Grade 2 or higher bleeding associated with thrombocytopenia
- All other Grade 3, 4 or 5 adverse events will be considered a DLT. Exceptions include:
  - Grade 3, 4 Afebrile Neutropenia less than 7 days
  - Grade 3, 4 Leukopenia
  - Grade 3, 4 Lymphopenia
  - Grade 3 nausea, vomiting and/or diarrhea unless unresponsive to treatment
  - Grade 2 toxicity that requires dose modification or delay of > 1 week, will be considered a DLT (e.g., peripheral neuropathy)

Any DLT will require an interruption and possible discontinuation of ABT-263. ABT-263 may be reintroduced, but only at a reduced dose, if the toxicity grade returns to ≤ Grade 1 or to baseline if Grade 2 at study entry. Following a DLT of thrombocytopenia, ABT-263 may be reintroduced, but only at a reduced dose, if the platelet toxicity grade returns to ≤ Grade 2 (≥ 50,000/mm^3). Any reduced dose level will be jointly defined by the investigator and the AbbVie Medical Monitor. The dose may be increased thereafter upon joint determination of the investigator and the AbbVie Medical Monitor. This dose is not to exceed the highest tolerated dose level.

For the Phase 1 portion of the study, all decisions regarding continued dosing for individual subjects will be medically managed by the investigator, in conjunction with the

AbbVie Medical Monitor, as appropriate. These decisions will be driven by the definition of DLTs as described above.

6.7.2 Management of Thrombocytopenia

ABT-263 induces apoptosis, rather than lysis, of circulating platelets, which differs from typical chemotherapy induced thrombocytopenia related to myelosuppression.

All decisions regarding continued ABT-263 dosing for individual subjects will be determined by the investigator, in conjunction with the AbbVie Medical Monitor, as appropriate. These decisions should be guided by the following:

Administration of ABT-263 will be interrupted or discontinued for:

- Any pre-dose platelet count < 25,000/mm^3
- Any clinically significant bleeding, defined as Grade 2 or higher hemorrhage

If ABT-263 is held, it may be restarted, but only at a reduced dose to be jointly defined by the investigator and the AbbVie Medical Monitor, once the subject's platelet count is ≥ 50,000/mm^3. The dose may be increased (not to exceed the highest tolerated dose) thereafter upon joint determination of the AbbVie Medical Monitor and the investigator.

After any Grade 4 platelet count < 25,000/ mm^3 is observed for the first time in a subject, serial PK samples will be collected. PK samples will be collected as soon as possible after the Grade 4 platelet count is determined and then 24 and 48 hours after the event. Starting with Protocol Amendment 13, PK samples will NOT be collected.

Limited human clinical data are available to understand the response to infusion of exogenous platelets in the presence of circulating drug levels. Platelet transfusion studies conducted in beagle dogs demonstrated that transfusion of one-day old platelets administered near the time of ABT-263 C_{max}, resulted in higher platelet levels than dogs not receiving supplemental platelets. Platelet concentrations remained higher after 24 hours with declining ABT-263 concentrations. This study suggests that infusion of

platelets may have beneficial effects in treating acute thrombocytopenia following oral dosing with ABT-263.

If platelet transfusions are required in response to active bleeding, dosing of ABT-263 should be suspended. It should be noted that platelet response with transfusions may not follow typical platelet kinetics of thrombocytopenia as with typical chemotherapy induced myelosuppression. Procedures consistent with local institutional blood banking guidelines regarding platelet transfusions should be followed.

Platelet Transfusion Recommendations:

If a platelet transfusion is deemed necessary, the treating physician should be aware of the following:

- Due to the rapid apoptotic effect of ABT-263 on mature platelets, the initial increase in platelets post-transfusion may be smaller and the duration of response may be shorter. For this reason, donor platelets collected as recently as possible prior to transfusion should be considered.
- A post-transfusion platelet count should be obtained within 10 to 60 minutes.
- Additional transfusions may be necessary to achieve the desired platelet response.

6.7.3 Management of Lymphopenia

There is a potential for clinically significant lymphopenia in this study. If clinically indicated, anti-infective prophylaxis should be implemented at the investigator's discretion, including appropriate prophylaxis for viral, fungal, bacterial or Pneumocystis carinii pneumonia (PCP) infections. Potential for drug-drug interactions should be considered. See Appendix E for a description of excluded and cautionary medications.

6.7.4 Management of Tumor Lysis Syndrome

There is a potential for tumor lysis in subjects with various tumor types in the presence of the following risk factors: bulky disease, elevated pre-treatment LDH levels, elevated

leukocyte count and dehydration. Adequate hydration, careful monitoring of laboratory values and an agent to reduce the uric acid level should be considered for subjects at high risk during the Lead-in and subsequent cycles. Please discuss with the AbbVie Medical Monitor, as appropriate.

6.7.5 Determination of the MTD

The MTD is defined as the dose at which 30% of subjects experience a DLT during the first cycle. At each dose level, MTD will be estimated based on actual observations from subjects to construct a dose and toxicity rate model using the maximum likelihood method. As data accumulate and the reassessment continues, the MTD will be determined based on the convergence criteria described in Section 5.6.4. The recommended Phase 2 dose (RPTD) will be defined by observed DLTs and/or determination of MTD.

7.0 Protocol Deviations

AbbVie does not allow intentional/prospective deviations from the protocol except when necessary to eliminate an immediate hazard to study subjects. The investigator is responsible for complying with all protocol requirements, written instructions, and applicable laws regarding protocol deviations. If a protocol deviation occurs (or is identified, including those that may be due to the COVID-19 pandemic), the investigator is responsible for notifying independent ethics committee (IEC)/independent review board (IRB), regulatory authorities (as applicable), and AbbVie.

Primary Contact:

[redacted]
Study Management Associate
AbbVie
1 North Waukegan Rd.
North Chicago, IL 60064

Contact Information:
Office: [redacted]
Email: [redacted]

Medical Monitor:

[redacted]
Executive Medical Director
1 North Waukegan Rd
North Chicago, IL 60064

Contact Information:
Phone: [redacted]
Email: [redacted]

Program Lead:

[redacted]
Program Lead II
Clinical Program Development
[redacted]
AbbVie
1 North Waukegan Road
North Chicago, IL 60064

Contact Information:
Office: [redacted]
Email: [redacted]

Such contact must be made as soon as possible to permit a decision as to whether or not the subject is allowed to enter or continue in the study. The deviation from the protocol will be authorized only for that subject. In addition, any significant protocol deviations affecting subject eligibility and/or safety must also be reviewed and approved prior to implementation by the Independent Ethics Committee (IEC)/Institutional Review Board (IRB) and regulatory authorities, as applicable, except when necessary to eliminate an immediate hazard to study subjects.

8.0 Statistical Methods and Determination of Sample Size

8.1 Statistical and Analytical Plans

Unless otherwise noted, for all statistical analyses, statistical significance will be determined by a two-sided p-value < 0.05.

8.1.1 Demographics and Treatment Allocation

Demographics

Descriptive statistics will be provided for baseline demographic variables for the Phase 1 and the Phase 2a portion of the study separately. Age, height and weight will be summarized with means, medians, standard errors, standard deviations and ranges. Frequencies and percentages will be provided for gender and race.

Treatment Allocation

One of the objectives of the Phase 1 portion of this study is to determine the MTD, and the dose allocation process will be conducted according to a continual reassessment method (CRM).[35,36,37] A two-parameter logistic regression model will be employed to characterize dose and toxicity rate relationship. A prior model based on preclinical and clinical data will be employed to estimate doses with approximately 30% and 90% probability of inducing a DLT. The MTD is the dose that reflects a 30% rate of DLT. The dose associated with 90% DLT rate will be incorporated for future model fitting to stabilize the high dose-toxicity portion of the model. For each subject, the response will be defined as 0 (no DLT event) or 1 (DLT). Along with the actual observed data, 10 imputed subjects will be added with 9 subjects having DLT and 1 without DLT at the dose associated with 90% DLT rate. A small weight of 0.025 will be assigned to these imputed data to reflect a small degree of certainty, and at the same time to stabilize the model fitting process as shown in the simulations. To estimate the dose corresponding to approximately 30% probability of inducing DLT, one out of the three subjects in the 160 mg dosing cohort from the M06-814 study will be utilized with a small weight of

0.083 assigned to these prior data. For the actual observations, a unity weight will be assigned. The maximum likelihood method will be employed to estimate the parameters and probability of DLT within the framework of the logistic regression analysis. The fitted model will be inverted to estimate the target dose associated with 30% chance of DLT, or the MTD. The next cohort of subjects will then be assigned to the projected MTD and evaluated. The outcome will be incorporated to update the logistic regression model using all the cumulative information. The design will continue to adapt data from current results and assign subjects to the projected MTD until the target dose changes by less than 10%, or a sample size of 40 subjects is reached. Simulations to compare the conventional fixed 3+3 design and the CRM based design are provided in Appendix F.

8.1.2 Pharmacokinetics

8.1.2.1 Tabulations and Summary Statistics

Plasma concentrations of ABT-263 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.

8.1.2.2 Model and Tests

Dose Proportionality

For subjects who participate in the Phase 1 14/21 day dosing portion of the study, an analysis will be performed on pharmacokinetic variables for C1D1 dose to simultaneously explore for demographic variables that explain some of the variability in pharmacokinetics and to address questions of dose proportionality and linear kinetics. An analysis will be performed for dose-normalized C_{max}, T_{max}, and dose-normalized AUC_t (AUC_{0-24}), provided that they can be adequately determined from the data. The model used for the statistical analyses will include dose level. This may be done by classifying subjects by dose level or, if appropriate, using dose level as a continuous variable. Covariates such as age, body weight, body surface area, gender, and potentially formulation (if applicable), as well as others that might explain some of the variability in

the population will be included in the model initially. However, a covariate may be dropped from the model if the regression coefficient is not significant at level 0.10. The natural logarithmic transformation will be employed for C_{max} and AUC_t 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. Within the framework of the model, tests that have good power for a trend with dose will be performed on the effect of dose level.

A corresponding analysis will also be performed on pharmacokinetic variables of the dose on C1D14 for both the Phase 1 14/21 and 21/21 day dosing schedules. The variables will include dose-normalized C_{max}, T_{max}, and dose-normalized AUC_t (AUC_{0-8}).

Additional analyses will be performed if useful and appropriate.

8.1.2.3 Missing Values and Model Violations

The possibility of bias from missing data of subjects who prematurely discontinue will be addressed. 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, missing concentration values for isolated individual blood samples may be replaced (imputed) if such might affect study conclusions or meaningfully affect point estimates.

8.1.3 Exploratory Efficacy

The following exploratory efficacy analyses will be performed on the data collected from the Phase 2a portion of the study.

8.1.3.1 Progression-Free Survival

The distribution of PFS will be estimated using Kaplan-Meier methodology. Median time to PFS and the corresponding 95% confidence interval will be estimated.

For a given subject, PFS will be defined as the number of days from the date the subject started study drug to the date the subject experiences an event of disease progression, as defined in Section 5.3.3, or to the date of death if disease progression is not reached. All events of disease progression will be included, regardless of whether the event occurred while the subject was still taking study drug or had previously discontinued study drug. Events of death will be included for subjects who had not experienced disease progression provided the death occurred within 2 cycles (42 days) of the date of the last available tumor evaluation. If a subject has not experienced an event of disease progression or death as defined above, then the subject's data will be censored at the date of the last available evaluation for disease progression. The date of the last available evaluation will be the date of the last study visit at which a tumor assessment was performed.

8.1.3.2 Objective Response Rate

The proportion of subjects with a complete remission (CR), complete remission with incomplete bone marrow recovery (CRi) or partial remission (PR) based on the NCI-WG criteria in Section 5.3.3.1 will be estimated and the corresponding 95% confidence interval for the proportion will be constructed. The exact binomial distribution will be used to construct this confidence interval.

A subject will be classified as a complete remission (CR), complete remission with incomplete bone marrow recovery (CRi), partial remission (PR) or as having PD based on the definition in Section 5.3.3.1. The objective response rate (CR, CRi, PR) will be computed for all subjects with active disease at baseline (in the opinion of the investigator).

8.1.3.3 Time to Tumor Progression

Time to tumor progression for a given subject will be defined as the number of days from the date the subject started study drug to the date of the subject's tumor progression. Time to tumor progression may be collected up to 2 cycles (42 days) following the date of the last available tumor evaluation. All events of tumor progression will be included,

regardless of whether the event occurred while the subject was still taking study drug, or after the subject discontinued study drug. If a subject has not progressed, then the data will be censored at the date of the last study visit at which a tumor assessment was performed.

The distribution of the time to tumor progression will be estimated using Kaplan-Meier methodology. Median time to tumor progression and the corresponding 95% confidence interval will be estimated.

8.1.3.4 Overall Survival

Time to death for a given subject will be defined as the number of days from the date the subject started study drug to the date of the subject's death. All events of death will be included, regardless of whether the event occurred while the subject was still taking study drug, or after the subject discontinued study drug. If a subject has not died, then the data will be censored at the date of the last study visit, the last contact date, or the date the subject was last known to be alive, whichever is last. The date of the last study visit will be determined by selecting the last available date of the following study procedures for a subject: physical examination, vital signs assessment, blood chemistry, hematology, and urinalysis collection.

The distribution of the time to death will be estimated using Kaplan-Meier methodology. Median survival time and the corresponding 95% confidence interval will be estimated.

8.1.3.5 Duration of Overall Response

The duration of overall response for a given subject will be defined as the number of days from the day the criteria are met for CR, CRi or PR (whichever is recorded first) to the date that PD is objectively documented. The reference for PD will be the smallest measurements recorded since the treatment started. If a subject is still responding then the subject's data will be censored at the last study visit at which a tumor assessment was performed.

The distribution of the duration of overall response will be estimated using Kaplan-Meier Methodology.

8.1.3.6 ECOG Performance Status

For the ECOG performance scale, descriptive statistics will be summarized for each assessment. In addition, a mean change from baseline to each assessment will be summarized.

8.1.3.7 Reporting of Results

All subjects enrolled will be assessed for response to treatment based on the NCI-WG criteria in Section 5.3.3.1. Each subject will be assigned to one of the following categories: 1) complete remission, 2) complete remission with incomplete bone marrow recovery, 3) partial remission, 4) stable disease, 5) progressive disease, 6) early death from malignant disease, 7) early death from toxicity, 8) early death because of other cause, or 9) unknown (not assessable, insufficient data).

Subjects in response categories 5-8 will be considered as failing to respond to treatment (disease progression). Thus, an incorrect treatment schedule or drug administration will not result in exclusion from the analysis of a response.

Sub-analyses may be performed on the subset of subjects for whom major protocol deviations have not been reported (e.g., early discontinuation of treatment, major protocol violations, etc.). The reasons for excluding subjects from the analysis will be clearly reported.

8.1.4 Safety

Safety summaries will include all subjects participating in the study unless otherwise indicated. A safety analysis will be performed for all subjects in the Phase 1 portion of the study once the MTD is reached and/or RPTD is determined, after the last enrolled subject completes one cycle of drug, and prior to enrollment of subjects into the Phase 2a portion of the study. A second safety analysis will be performed for all subjects in the

Phase 1 and Phase 2a portions of the study upon completion of the study. The following will be included in these analyses:

Adverse Events

The number and percentage of subjects having treatment-emergent adverse events will be tabulated by MedDRA system organ class and preferred term.[38] The tabulations will also be provided with further breakdowns by NCI CTCAE toxicity grade and relationship to study drug. Serious adverse events, events leading to discontinuation of treatment, and events leading to death, will be summarized. For subjects who participate in Cycle 1 of Phase 1 of the study, all summaries will be done by dose. For the study as a whole, summaries will be provided with a breakdown as appropriate.

Platelet Counts

Platelet counts will be explored for trends with dose and time and summarized as appropriate. The baseline value (last measurement before the beginning of study drug administration) will be included in the statistical analysis and changes from baseline will be addressed.

A repeated measures model with dose level as a classification variable will be performed for values in Cycle 1 of the platelet counts for which multiple measurements will be taken. A transformation of a variable will be used if it clearly provides more nearly symmetric probability distribution and/or more nearly homogenous variances across dose levels.

The relationship between drug concentration variables and platelet counts will be explored. The dependence of observations from the same subject will be appropriately taken into account in all of the above analyses.

Other Safety Measurements

Laboratory test results, lymphocyte enumeration results, vital signs, echocardiogram results, and ECG interval measurements results will be explored for trends with dose and

time and summarized as appropriate. The baseline values (Screening values) will be included in the statistical analysis and changes from baseline will be addressed. Changes from baseline at the recommended Phase 2a dose will be analyzed with a *t*-test at each scheduled visit. Where applicable, blood chemistry and hematology determinations will be categorized according to NCI CTCAE (Version 3.0) grades, and shifts from baseline NCI CTCAE grades to maximum and final post-baseline grades for each treatment group will be assessed. Vital signs values will be evaluated for possible clinical significance using criteria developed at AbbVie. Additional analyses will be performed if useful and appropriate.

8.2 Determination of Sample Size

The sample size was based on simulations for CRM, clinical justification and subject enrollment numbers historically used for the testing of new oncology compounds.

During the dose-toxicity modeling process, a minimum of three subjects per cohort will be included to warrant reasonable accuracy for the estimates. The total number of subjects required for the Phase 1 portion of this study will depend upon the toxicities observed as the trial progresses. The total number of subjects for Phase 1 is not likely to exceed 40 based on operational considerations. For the Phase 2a portion of the study, approximately 32 subjects with relapsed disease was chosen to further characterize safety and assess preliminary evidence of efficacy with the RPTD in this population.

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. 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. A list of the documents required prior to initiation of the study can be found in Appendix C.

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.

In the event of a state of emergency due to the COVID-19 pandemic leading to difficulties in performing protocol-specified procedures, AbbVie will engage with study site personnel in efforts to ensure the safety of subjects, maintain protocol compliance, and minimize risks to the integrity of the study while trying to best manage subject continuity of care. This may include alternative methods for assessments (e.g., phone contacts or virtual site visits), alternative locations for data collection (e.g., use of a local lab instead of a central lab), and shipping investigational product and/or supplies direct to subjects to ensure continuity of treatment where allowed.

In all cases, these alternative measures must be allowed by local regulations and permitted by IRB/IEC. Investigators should notify AbbVie if any urgent safety measures are taken to protect the subjects against any immediate hazard.

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. The investigator must ensure that the study is conducted in accordance with the

provisions as stated in the FDA regulations and complies with prevailing local laws and customs. Responsibilities of the clinical investigator are specified in Appendix D.

9.3 Subject Information and Consent

Prior to the initiation of any screening or study-specific procedures, the investigator or his/her representative will explain the nature of the study to the subject and answer all questions regarding this study. Subjects who provide blood or tissue samples for pharmacogenetic or pharmacodynamic analyses will also sign an informed consent regarding the collection of these samples. Each informed consent will be reviewed, signed and dated by the subject or his/her legal representative and the person who administered the informed consent. A copy of each informed consent will be given to the subject and each 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.

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.

During the COVID-19 pandemic, remote monitoring of data may be employed if allowed by the local regulatory authority, IRB/IEC, and the study site.

10.2 Case Report Forms

Case report forms must be completed for each subject 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 will be collected with an Electronic Data Capture (EDC) tool called InForm provided by the technology vendor Phase Forward of Waltham, MA, USA. In addition, this study will use the Central Coding tool provided by Phase Forward to code event and medication terms. The EDC system and the study-specific eCRFs will be in compliance with Title 21 CFR Part 11. The documentation related to the validation of the EDC tool is available through the vendor, Phase Forward, while the validation of the study-specific eCRFs will be conducted by AbbVie and be maintained in the Trial Master File at AbbVie.

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

If eCRF corrections are necessary they will be made by the investigator or by an authorized member of the investigator's staff to the eCRFs. 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 CRFs 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/her electronic signature and date to eCRFs as evidence thereof.

Access to the EDC system will be provided by Phase Forward 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 tool will be archived on appropriate data media (CD-ROM, etc.) and provided to the investigator at that time as a durable record of his eCRF entries. It will be possible for the investigator to make paper printouts from that media.

10.3 Extension Study Case Report Forms

Case report forms must be completed for each subject enrolled in this study. These forms will be used to transmit information collected during the study to AbbVie and regulatory authorities, as applicable. Each CRF will be printed on 2-part NCR paper: the white copy will be retrieved by AbbVie or its designee, and the pink copy will be retained by the site.

All information written on the CRFs must also be reflected in the subject source documents. All CRFs must be legible and completed in indelible ballpoint ink. Any necessary corrections are to be made by drawing a single line through the incorrect entry and writing in the revision, which must be initialed and dated by the investigator or designee. Data are not to be obliterated by blacking out, correction fluid, or by erasing the original entry. If the reason for the correction is not obvious, a brief explanation (e.g., "transcription error") should accompany the change. Once a CRF has been separated, all changes must be made via addenda. All addenda must be signed and dated by the investigator.

The principal investigator will review the case report forms for completeness and accuracy and sign and date the set of case report forms where indicated.

Case report forms will be reviewed periodically against source documents for completeness, legibility, and acceptability by AbbVie Laboratories personnel or its designee.

11.0 Data Quality Assurance

Prior to enrolling any subject in the study, an initiation meeting will be held with AbbVie personnel, the investigator(s), and the study coordinators/project manager(s). This meeting will include a detailed discussion and review of the protocol and essential

documents, performance of study procedures, case report form completion and specimen collection methods. The personnel at the study site will be trained on the study procedures, when applicable, by AbbVie (or designee).

The AbbVie designated monitor will monitor the study site throughout the study. A 100% source document review will be made against entries on the case report forms and a quality assurance check will be performed to ensure that the investigator is complying with the protocol and regulations. In addition, continuous review of the data will be conducted by a physician or representative at AbbVie.

Computer logic checks will be run to identify such items as inconsistent study dates. Any necessary corrections will be made to the electronic CRF.

Routine hematology, serum chemistry and urinalysis tests will be conducted using a certified clinical laboratory. Laboratory reference ranges will be obtained prior to the initiation of the study. The AbbVie designated monitor, the investigator and other appropriate personnel from AbbVie will conduct a review of all laboratory results.

12.0 Use of Information

All information concerning ABT-263 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 ABT-263. This information may be disclosed as deemed necessary by AbbVie to other clinical investigators, other pharmaceutical companies, to the FDA and to other 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, including each subject's name, subject number, address, phone number and emergency contact information. This list will be maintained at the study site with other study records under adequate security and restricted access, 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. 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 also 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.

AbbVie agrees that before it publishes any results of this study, it shall provide the investigator a pre-publication manuscript for review prior to the submission of the manuscript to the publisher.

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.

AbbVie may terminate this study either in its entirety or at a study site provided that written notice is submitted at a reasonable time in advance of the intended termination. The investigator may also terminate the study at his/her study site after providing written notice to AbbVie at a reasonable time 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, it will immediately notify the investigator by telephone and subsequently provide written instructions for study termination.

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

The end of study is defined as the date of the last subject's last scheduled visit or the actual date of follow-up contact, whichever is longer.

14.0 Investigator's Agreement

1. I have received and reviewed the Investigator Brochure for ABT-263.
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.

Protocol Title: A Phase 1/2a Study Evaluating the Safety, Pharmacokinetics, and Efficacy of ABT-263 in Subjects with Relapsed or Refractory Chronic Lymphocytic Leukemia

Protocol Date: 03 September 2020

Signature of Principal Investigator	Date

Name of Principal Investigator (printed or typed)

15.0 Reference List

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Appendix A. List of Abbreviations and Definitions of Terms

Abbreviations

ACD	Acid Citrate Dextrose
AE	Adverse Event
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
AST	Aspartate Aminotransferase
aPTT	Activated Partial Thromboplastin Time
Bcl	B-Cell Lymphoma
BH	Bcl-2 Homology
BSA	Body Surface Area
BUN	Blood Urea Nitrogen
^{14}C	Carbon-14 (Radiocarbon)
CGH	Comparative Genomic Hybridization
CLL	Chronic Lymphocytic Leukemia
CNS	Central Nervous System
COVID-19	Coronavirus Disease-2019
CR	Complete Remission
CRi	Complete Remission with Incomplete Bone Marrow Recovery
CRM	Continual Reassessment Method
CRF	Case Report Form or Electronic Case Report Form
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP2C8	Cytochrome P450 2C8
CYP2C9	Cytochrome P450 2C9
CYP3A	Cytochrome P450 3A
DLT	Dose Limiting Toxicity
DNA	Deoxyribonucleic acid
DTP	Direct To Patient
EC_{50}	50% Effective Concentration
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form

EDC	Electronic Data Capture
EDTA	Edetic Acid (ethylenediaminetetraacetic acid)
EMEA	European Agency for the Evaluation of Medical Products
ERT	Estrogen Replacement Therapy
FCR	Fludarabine, cyclophosphamide, rituximab
FDA	U.S. Food and Drug Administration
FISH	Fluorescence *in situ* Hybridization
GCP	Good Clinical Practice
G-CSF	Granulocyte-Colony Stimulating Factor
GM-CSF	Granulocyte Macrophage-Colony Stimulating Factor
HDPE	High Density Polyethylene
HIV	Human Immunodeficiency Virus
hr	Hour
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IQR	Interquartile Range
IRB	Institutional Review Board
ITP	Immune Thrombocytopenia Purpura
IWCLL	International Workshop for Chronic Lymphocytic Leukemia
JP	Japanese Pharmacopoeia
K/μL	Thousand per Microliter
kg	kilogram
K_i	Inhibition Constant
LDH	Lactate Dehydrogenase
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
mcl	microliter
MCT	Medium Chain Triglyceride
MCV	Mean Corpuscular Volume
MedDRA	Medical Dictionary for Regulatory Activities
μg	Microgram
mg	Milligram
min	Minute
mL	Milliliter

µM	Micromolar
MPV	Mean Platelet Volume
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
NCI-WG	National Cancer Institute-Working Group
nM	Nanomolar
NOAEL	No Observed Adverse Effect Level
nPR	Nodular Partial Remission
ORR	Objective Response Rate
OS	Overall Survival
PCP	Pneumocystis Pneumonia
PD	Pharmacodynamic or Progressive Disease
PFS	Progression-free Survival
PG	Pharmacogenetic
Ph. Eur.	European Pharmacopoeia
PK	Pharmacokinetic
PLL	Prolymphocytic Leukemia
PR	Partial Remission
PT	Prothrombin Time
QD	Once daily
QTc	QT interval corrected for heart rate
RBC	Red Blood Cell
RPTD	Recommended Phase Two Dose
SAE	Serious Adverse Event
SCLC	Small Cell Lung Cancer
SD	Stable Disease
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic-Pyruvic Transaminase
SSRI	Selective Serotonin Reuptake Inhibitor
STAT	statim (immediately)
TLS	Tumor Lysis Syndrome
TTP	Time-to-Tumor Progression
ULN	Upper Limit of Normal

US	Ultrasound
USP	United States Pharmacopoeia
WBC	White Blood Cell

Pharmacokinetic and Statistical Abbreviations

AUC	Area under the plasma concentration-time curve
AUC_t	Area under the plasma concentration-time curve from time zero to time of last measurable concentration
AUC_∞	Area under the plasma concentration-time curve from time zero to infinity
C_{max}	Maximum observed plasma concentration
C_{min}	Minimum observed plasma concentration
$t_{1/2}$	Terminal phase elimination half-life
T_{max}	Time to maximum observed plasma concentration

Appendix B. List of Protocol Signatories

Name	Title	Functional Area
[redacted]	Sr. Scientist II	Biomarkers
[redacted]	Program Lead II	Clinical Program Development
[redacted]	Study Project Manager II	Clinical Program Development
[redacted]	Director	Statistics
[redacted]	Executive Medical Director, TA MD	Clinical Program Development

Appendix C. Documents Required Prior to Initiation of the Study

As sponsor of a clinical study, AbbVie has an obligation to ensure that the study will be conducted by a qualified investigator with sufficient resources (of time, personnel, and physical facilities) to conduct the study and to ensure that the investigator understands and agrees to comply with Good Clinical Practices and applicable regulations, policies, and procedures. Prior to the beginning of any clinical study, the investigator will be asked to provide the following documentation.

1. A signed and dated Investigator's agreement page for the study.
2. A signed and dated Form FDA 1572 certifying the investigator's agreement to comply with the appropriate regulations governing the conduct of the study. A signed and dated Investigator Information and Agreement Form certifying the investigator's agreement to comply with the appropriate (e.g., ICH GCP) regulations governing the conduct of the study.
3. Current curriculum vitae for the investigator. If subinvestigators will participate in the study, curriculum vitae for each.
4. Requirements for the Independent Ethics Committee (IEC)/Institutional Review Board (IRB).
    - A copy of the signed and dated letter of approval of the IEC/IRB. The letter must specify that both the protocol and informed consent form were approved (unless separate documentation that the informed consent was approved is provided).
    - A dated list containing the names and affiliations of the members of the IEC/IRB, or the institution's General Assurance Number.
    - If the investigator and/or subinvestigator is a member of the IEC/IRB, a letter stating that he/she did not participate in the review or approval of the protocol or informed consent form.
5. A specimen copy of the IEC/IRB-approved informed consent document to be used in the study.

6. A list of reference ranges of values for all laboratory tests specified by the protocol for all laboratories utilized.
7. A copy of the laboratory(ies) certification(s) or the authorization number of the certification(s), the name of the certifying authority, and the period of certification.
8. Financial Disclosure Certification forms must be completed by each investigator and all subinvestigators identified on the Form FDA 1572 or Investigator Information and Agreement Form. A Financial Disclosure, EU Consent, is required to be completed for each investigator and/or subinvestigator who is a resident of the European Union.

Appendix D. 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(s) and only make changes in a protocol 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. Inform all subjects, or any 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 committees [IEC] or institutional review board [IRB]) review and approval of the protocol 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.
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 and make 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, coordinating investigator, institutional 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 E. Sample List of Excluded and Cautionary Medications

SSRI's (Cautionary)

citralopram (Celexa)

escitalopram (Lexapro)

fluoxetine (Prozac)

paroxetine (Paxil)

sertraline (Zoloft)

Anticoagulation Therapy (Excluded)

coumadin (Warfarin)+

dalteparin (Fragmin)

enoxaparin (Lovenox)

fondaparinux (Arixtra)

heparin++

melagatran/ximelagatran

tinzaparin (Innohep)

Anti-platelet (Excluded)

acetylsalicylic acid (Aspirin)

aspirin/extended-release dipyridamole (Aggrenox)

clopidogrel (Plavix)

dipyridamole (Persantine)

ticlopidine (Ticlid)

Tirofiban (Aggrastat)

NSAIDS+ (Excluded)

aspirin

celecoxib

diclofenac

diflunisal

etodolac

ibuprofen

indomethacin

ketoprofen

CYP3A Inhibitors (Excluded)

atanazavir

clarithromycin

fluconazole

fluvoxamine (Luvox)

indinavir

itraconazole

ketoconazole

nefazodone

nelfinavir

ritonavir

saquinavir

telithromycin

voriconazole

CYP3A Inducers (Cautionary)

barbiturates

carbamazepine (Tegretol®)

efavirenz

nevirapine

oxcarbazepine

phenobarbital

phenytoin (Dilantin®)

rifampin (Rifadin®)

rifapentine

St. John's wort

CYP2C9 Substrates (Cautionary)

fluvastatin

glipizide

irbesarten

losartan

phenytoin

nabumetone
naproxen
oxaprozin
salsalate
sulindac
tolmetin

Ethanol (Excluded)**

Aldehyde Dehydrogenase Inhibitor (Excluded)**
disulfiram (Antabuse)

sulfamethoxazole
sulfinpyrazone
tolbutamide
tosomide

CYP2C8 Substrates[#] (Cautionary)
aminodarone
amodiaquine
cerivastatin
chloroquine
lovastatin*
paclitaxel (Taxol)
pioglitazone
repaglinide
rosiglitazone
simvastatin (Zocor)*
troglitazone

\+ Warfarin and many NSAIDS are also CYP2C9 substrates.
++ Heparin may be used for patency of a central venous catheter.
* Significant increase in AUC by co-administration of gemfibrozile, a potent CYP2C8 inhibitor. However, the involvement of CYP2C8 is unclear.
** This does not apply if the subject is taking Meltrex tablets.
\# Only certain statins qualify as CYP2C8 substrates.

Appendix F. Simulations Comparing Fixed 3+3 Design Versus CRM-based Design

Introduction

Simulations were conducted to compare a fixed 3+3 design to a design based on a specific continual reassessment method (CRM). Designs were compared with respect to total sample size required, closeness of the design-determined MTD to the true MTD, and number of subjects treated at doses that are potentially 'too high' (e.g., doses with a > 90% chance of resulting in a DLT). Two families of dose-toxicity curves were considered, one representing a "steep" dose-toxicity response curve and another representing a "shallow" dose-toxicity curve.

The CRM-based method provided essentially uniformly better results than the fixed 3+3 design. That is, for each simulated dose-toxicity relationship, the CRM design generally required fewer total subjects, resulted in an estimated MTD closer to the true MTD, and treated fewer subjects at potentially toxic doses, compared to the fixed 3+3 design.

The following sections describe the study designs, the simulations, and the performance of each design in the simulations.

Methods

Abbreviations

CRM	continual reassessment method
D30	dose with a 30% probability of a DLT
D90	dose with a 90% probability of a DLT
DLT	dose-limiting toxicity
MTD	maximum tolerated dose (defined as D30 for this protocol)

Fixed 3+3 Design

The following steps describe the dose allocation scheme for the simulated fixed 3+3 designs.

- Three simulated subjects treated at the initial dose (10 mg).
- If no DLTs, double the dose.
- Proceed similarly until the first DLT is observed.
- If 1/3 DLT, enroll 3 more subjects at the same dose.
- If 1/6 DLT, increase dose by 33%.
- If > 1/6 DLTs decrease dose by 25%.
- If 2/3 or 3/3 DLTs, decrease dose by 25%.
- Upon dose decrease:
- If 0/3 or 1/6 DLTs, this is the MTD
- If > 1 DLT, dose decrease by 25% and repeat.
- If 0/3 or 1/6 DLTs, this is the MTD.
- If > 1 DLT, the MTD is the next highest dose with 0/3 or 1/6 DLTs

CRM Design

Three simulated subjects are treated at a dose of 10 mg. Data from these 3 subjects (for each subject, DLT or no DLT) are combined with 13 imputed values. Ten values are imputed at a very high dose (2000 mg): 9 observations with a DLT and 1 observation without a DLT. These 10 values represent a dose with a probability of a DLT of at least 90%, and they were assigned a weight of 0.025, so that they collectively represent one-fourth of one subject. Three values are imputed at a dose of 160 mg: 1 observation with a DLT and two observations without a DLT. These 3 values represent data borrowed from Study M06-814, in which 1/3 subjects who received a dose of 160 mg experienced a DLT. The 3 imputed values are assigned a weight of 0.083, so that they collectively represent one-fourth of one subject. The use of the imputed data is essential to allow the model fit to converge. Without the imputed data, the logistic regression model fit is

essentially a step function, which generally does not allow the CRM to converge to the MTD.

A 2-parameter logistic regression model is fitted to the data as described above, and the next dose is chosen to be at the model-estimated MTD (the dose predicted to result in a 30% probability of DLT, "D30"). If the predicted dose is more than 100 mg above the current dose, the new dose is escalated by 100 mg or less.

When the next predicted D30 value is within 5% of the current dose, the model is considered to have converged and the MTD is declared.

Simulation Details

Two families of dose-toxicity relationships were considered: one with a steep slope Figure 1) and one with a shallow slope (Figure 2). Parameters were chosen so that a total of 7 dose-toxicity curves for each family were assessed, spanning the expected dynamic range of ABT-263 doses. Thus, the fixed 3+3 design was compared to the CRM-based design in 14 different scenarios. In each scenario, 1000 simulations of each design were conducted and the following characteristics were summarized:

- Estimated MTD (median, IQR)
- True DLT probabilities associated with the estimated MTD (median, IQR)
- Sample size (median, interquartile range [IQR])
- Subjects dosed above D90 (median)

Figure 1. Steep Dose-toxicity Relationships

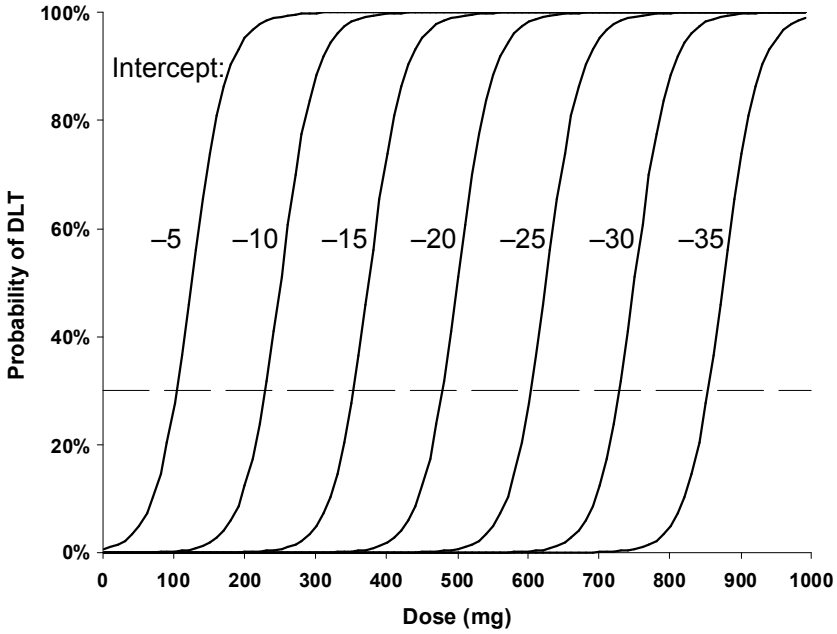
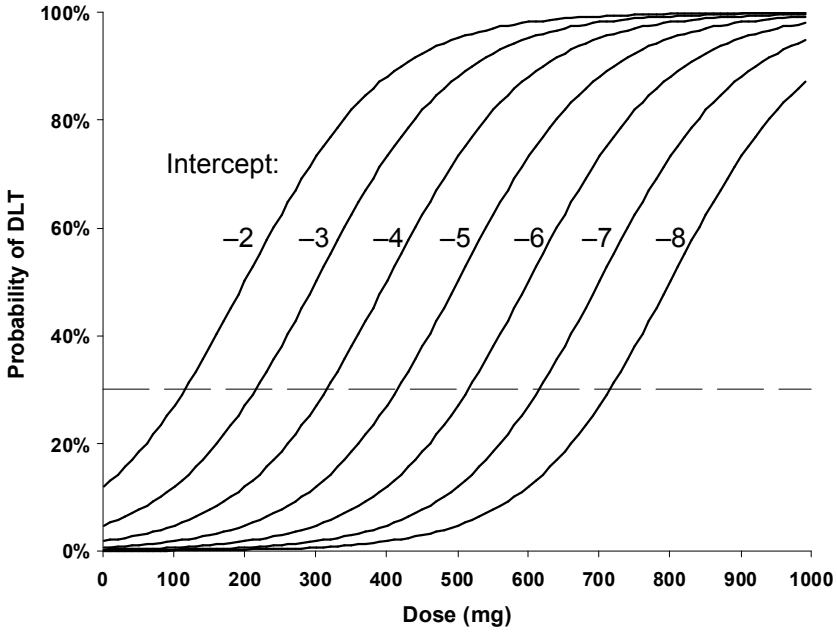


Figure 2. Shallow Dose-toxicity Relationships



Results

Results for simulations of the steep dose-toxicity relationships are summarized in Table 1. The CRM design consistently resulted in better estimates of the MTD. The median estimated MTD ranged from D12 to D35, whereas the fixed design consistently underestimated the true MTD (median estimated MTD values ranged from < D01 to D25). The CRM design also had an advantage in total number of subjects required, especially for dose-toxicity relationships with a lower true MTD. For higher true MTDs, the sample size advantage disappeared due to the restriction on the maximum dose increase (100 mg, see Methods). Finally, the CRM design generally dosed a smaller number of subjects above the D90.

Table 1. Simulation Results for Steep Dose-toxicity Curves (Slope = 0.04)

Intercept	True MTD (mg)	Design	Estimated MTD (median, IQR)	True DLT probabilities assoc. with est. MTD (median, IQR)	Sample size (median, IQR)	No. dosed above D90 (median)
–5	104	Fixed	90 (80, 90)	.20 (.14, .20)	27 (21, 27)	0
		CRM	99 (93, 117)	.26 (.22, .42)	15 (12, 21)	0
–10	229	Fixed	181 (181, 213)	.06 (.06, .19)	30 (30, 30)	3
		CRM	234 (212, 240)	.35 (.18, .40)	18 (15, 21)	0
–15	354	Fixed	320 (320, 320)	.10 (.10, .10)	30 (30, 30)	6
		CRM	364 (332, 359)	.30 (.15, .35)	21 (18, 24)	0
–20	479	Fixed	362 (362, 481)	.00 (.00, .32)	33 (27, 33)	3
		CRM	461 (452, 485)	.17 (.13, .35)	24 (24, 24)	0
–25	604	Fixed	481 (481, 481)	.00 (.00, .00)	27 (27, 30)	0
		CRM	592 (574, 628)	.21 (.12, .53)	27 (27, 27)	0
–30	729	Fixed	723 (640, 723)	.25 (.01, .25)	33 (33, 33)	6
		CRM	726 (699, 726)	.28 (.12, .28)	30 (30, 30)	0
–35	854	Fixed	723 (723, 723)	.02 (.02, .02)	33 (33, 33)	6
		CRM	825 (825, 862)	.12 (.12, .37)	33 (33, 36)	0

Both designs performed better for shallow dose-toxicity curves (Table 2) than they did for steep curves, but the CRM design retained advantages over the fixed design, both in the accuracy of the estimates (median estimated MTDs ranged from D26 to D30, versus D10 to D23 for the fixed design) and in total sample size (median of 3 to 11 fewer subjects).

Table 2. Simulation Results for Shallow Dose-toxicity Curves (Slope = 0.01)

Intercept	True MTD (mg)	Design	Estimated MTD (median, IQR)	True DLT probabilities assoc. with est. MTD (median, IQR)	Sample size (median, IQR)	No. dosed above D90 (median)
–2	115	Fixed	40 (15, 80)	.17 (.14, .23)	21 (15, 30)	0
		CRM	116 (88, 149)	.30 (.24, .38)	18 (15, 24)	0
–3	215	Fixed	159 (90, 199)	.20 (.11, .27)	30 (24, 36)	0
		CRM	213 (177, 252)	.30 (.23, .38)	18 (15, 24)	0
–4	315	Fixed	241 (213, 320)	.17 (.13, .31)	33 (27, 36)	0
		CRM	314 (262, 346)	.30 (.30, .37)	21 (15, 24)	0
–5	415	Fixed	325 (319, 462)	.15 (.14, .20)	33 (30, 33)	0
		CRM	404 (354, 448)	.28 (.19, .37)	21 (18, 24)	0
–6	515	Fixed	481 (362, 481)	.23 (.08, .23)	33 (27, 33)	0
		CRM	495 (450, 556)	.26 (.18, .39)	24 (21, 27)	0
–7	615	Fixed	481 (481, 640)	.10 (.10, .35)	30 (30, 33)	0
		CRM	596 (556, 660)	.26 (.19, .40)	27 (24, 30)	0
–8	715	Fixed	640 (481, 641)	.17 (.04, .17)	36 (33, 36)	3
		CRM	699 (662, 762)	.27 (.20, .41)	27 (27, 33)	0

Example Simulations

Figure 3 and Figure 4 show typical simulation runs for a steep dose-toxicity curve (slope = 0.04, intercept = –10) for the fixed 3+3 design and the CRM design, respectively. The true MTD for this example is 229 mg.

Figure 3. **Typical Fixed 3+3 Design Simulation Result for Steep Dose-toxicity Relationship**

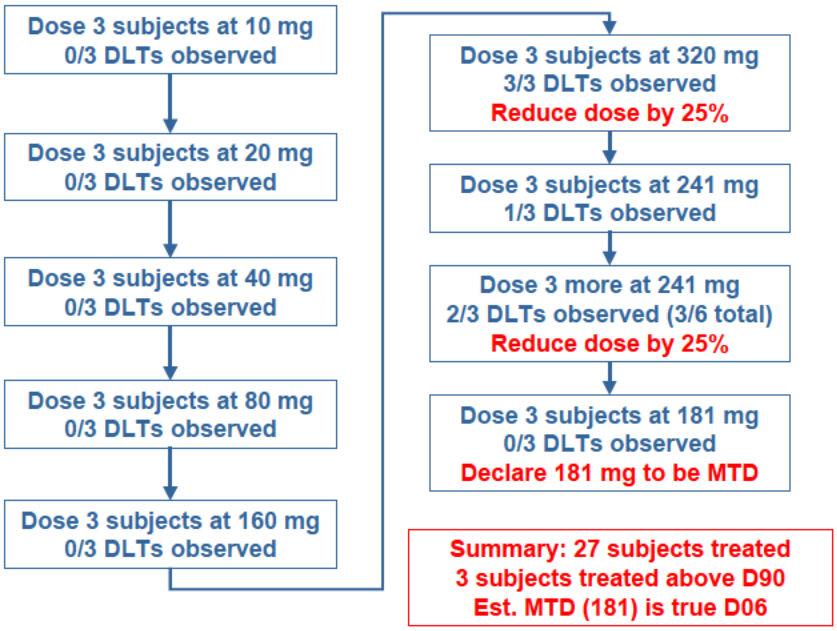


Figure 4. Typical CRM Design Simulation Result for Steep Dose-toxicity Relationship

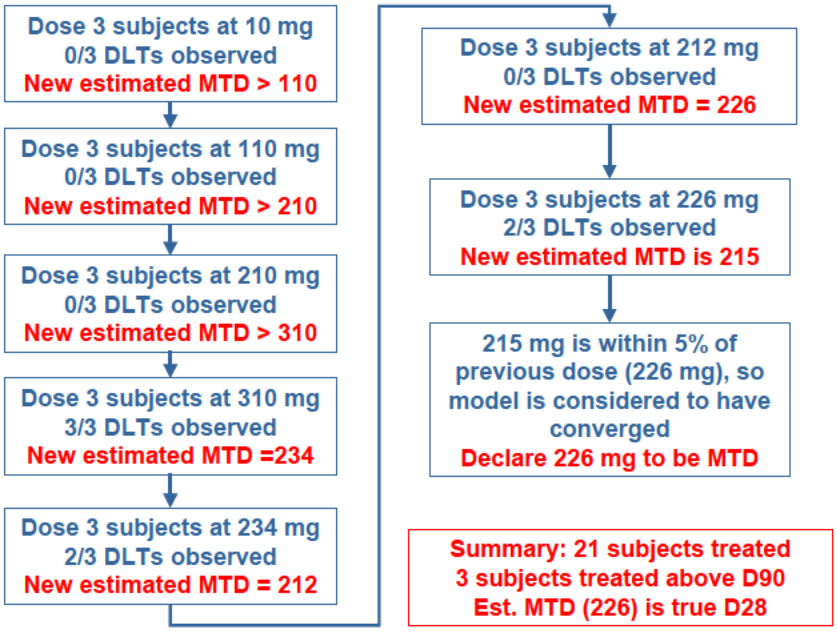


Figure 5 and Figure 6 show typical simulation runs for a shallow dose-toxicity curve (slope = 0.01, intercept = –5) for the fixed 3+3 design and the CRM design, respectively. The true MTD for this example is 415 mg.

Figure 5. Typical Fixed 3+3 Design Simulation Result for Shallow Dose-toxicity Relationship

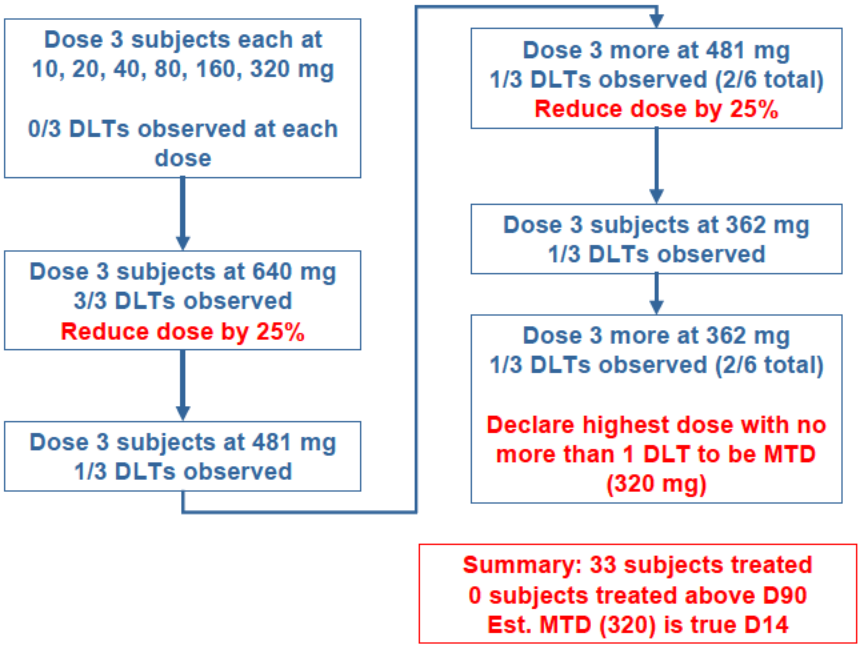
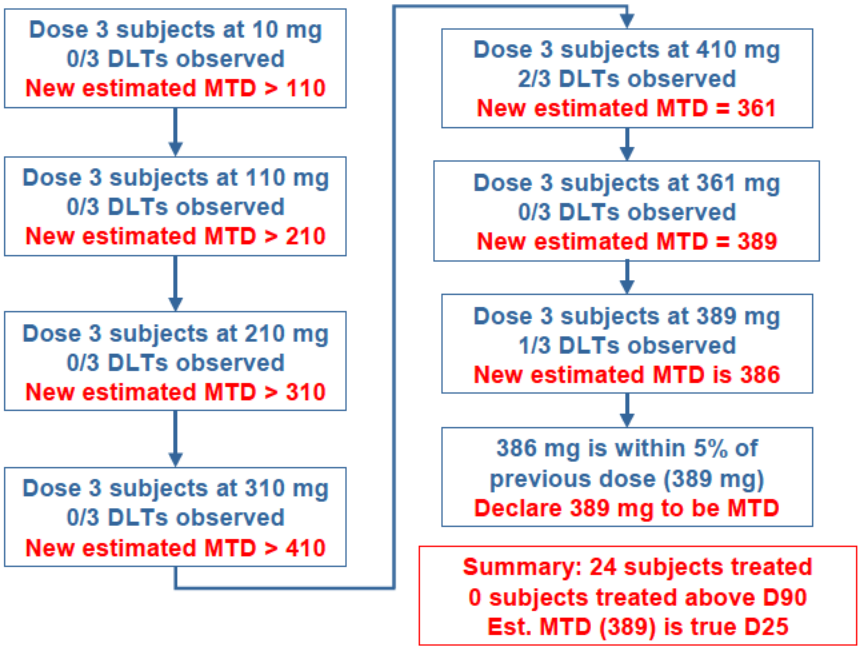


Figure 6. Typical CRM Design Simulation Result for Shallow Dose-toxicity Relationship



Conclusions

The CRM design provided estimated MTD values that were both more accurate (median simulated estimated MTDs closer to D30) and more precise (interquartile range of simulated estimated MTDs clustered nearer D30), compared to the fixed 3+3 design. The CRM design also provided an advantage over the fixed 3+3 design in overall sample size, especially for models with MTDs below 600 mg, typically treating in such scenarios approximately 20 subjects compared to approximately 30 subjects for the fixed 3+3 design. Finally, for steep dose-toxicity relationships, the CRM design generally had a lower risk of treating subjects at potentially toxic doses (above D90).

Appendix G. Extension Study - Assessments

Table 1. Extension Study: Schedule of Assessments

Procedures	Day 1[#]	Every 4 Cycles[#]	Final Visit[#]	30 Day Safety Follow-up Visit[#]
Informed Consent	X			
Physical Exam (including weight)	X[a]	X[a]	X	X
Vital Signs	X	X	X	X
12-lead ECG			X	
2D Echocardiogram with Doppler			X	
Platelet Count[b,#]	X	X	X	X
Lymphocyte Enumeration[c,#]			X	
Chemistry[d,#]	X	X	X	X
Hematology[d,#]	X	X	X	X
Urinalysis[d,#]			X	X
Performance Status (ECOG)[#]			X	X
Tumor Assessments[e,#]			X	
Disease Progression Assessment	X	X	X	
Adverse Event/Concomitant Medications Assessment	X	X	X	X[f]
Dispense/Collect ABT-263[g]	X	X	X	
Dispense/Collect Subject Dosing Log	X	X	X	

Visits and activities may be conducted in the subject's home residence or by phone/virtually.

a. Symptom directed.

b. Platelet Counts will be performed and assessed by the investigator or subinvestigator prior to study drug administration. Any platelet count less than 25,000/mm^3 should be confirmed the same day by manual reading and separate peripheral draw. Additional platelet counts will be obtained if ABT-263 is held or interrupted. If a platelet count is less than or equal to 50,000/mm^3, additional platelet counts will be performed every day at the discretion of the investigator. Platelet counts should be obtained 10 to 60 minutes after the completion of any platelet transfusion.

c. Perform Lymphocyte Enumeration at the Final Visit and as needed for subjects if deemed necessary by the investigator.

Table 1. Extension Study: Schedule of Assessments (Continued)

d. The specific laboratory tests required for chemistry, hematology and urinalysis are listed in Table 7. Triglycerides, amylase and lipase will only be collected at the Final Visit. For any subjects who are at high risk for tumor lysis syndrome (TLS), additional samples for hematology and chemistry may be collected as per the management guidelines in Section 6.7.4. ANC ≥ 500/μL and < 1,000/μL should be monitored at an increased frequency at the discretion of the investigator. Grade 2 chemistry labs should be monitored at an increased frequency at the discretion of the investigator.

e. If additional tumor assessments are collected by the site per standard of care, the data should be recorded on the appropriate paper CRF.

f. Adverse events will be followed until satisfactory clinical resolution of the adverse event is achieved.

g. A bottle's expiration date and pill count should be taken into account when dispensing 4 cycles of drug.

Appendix H. Protocol Amendment: List of Changes

The summary of changes is listed in Section 1.1.

Specific Protocol Changes

Section 1.0 Title Page
"Sponsor/Emergency Contact:," "Title" previously read:

Group Medical Director

Has been changed to read:

Executive Medical Director

Section 3.0 Introduction
Subsection ABT-263 Clinical Data
Add: new fourth paragraph

Considering the coronavirus (COVID-19) pandemic, the benefit and risk to subjects participating in this study has been re-evaluated. Subjects receiving ABT-263 may be at an increased risk for COVID-19 infection or experience serious illness if infected. Management of these adverse events will be made on a case-by-case basis with consideration of benefit/risk. However, based on the population and disease being studied, and the anticipation that COVID-19 related risks are not expected to differ substantially between study subjects and the broader population of subjects receiving treatment for CLL, no change to the benefit/risk balance for subjects in this study is expected.

Section 5.3.1.1 Study Procedures
Add: new last paragraph

Study visits may be impacted due to the COVID-19 pandemic. This may include changes such as phone or virtual visits, visits at alternative locations, or changes in the visit frequency and timing of study procedures, among others. Additional details are provided in the subsequent section. Every effort should be made to ensure the safety of subjects

and site staff, while maintaining the integrity of the study. If visits cannot be conducted onsite due to travel restrictions or other pandemic-related reasons, follow the updates below how to proceed.

Section 5.3.1.1 Study Procedures
Subsection COVID-19 Pandemic-Related Acceptable Protocol Modifications
Add: new subsection title and text

COVID-19 Pandemic-Related Acceptable Protocol Modifications

During the COVID-19 pandemic, if it is not possible for all study procedures to be performed as specified due to travel restrictions or other reasons, the following modifications are allowed:

- If permitted by local regulations, the IRB/IEC and the subject, the subject visits may be conducted in the subject's home residence.
- Some study visits and/or activities may be performed by phone/virtually. These are indicated by a hashtag (#) in the activity table (Appendix G)
  - During a virtual visit, activities that do not need to be performed are indicated by a (#) in the activity table (Appendix G).
- Study visits and/or activities may be performed by a local clinic/hospital/laboratory. All procedures performed at local facilities must be performed by appropriately qualified personnel.
- Study Visits and/or activities should be performed as scheduled whenever possible. If it is not possible to do so due to the pandemic, perform the activity at the earliest feasible opportunity. Laboratory draws must be obtained within 24 hours from the scheduled visit.

Section 5.3.1.1 Study Procedures
Subsection Informed Consent
Add: new last paragraph

Due to the COVID-19 pandemic, it is possible that additional protocol modifications not outlined in this protocol may become necessary. If this situation arises, in addition to the

study informed consent, additional verbal consent may be obtained prior to these adaptations or substantial changes in study conduct in accordance with local regulations.

Section 5.3.1.1 Study Procedures
Subsection Vital Signs
Heading "COVID-19 Pandemic-Related Acceptable Protocol Modifications"
Add: new heading title and text

COVID-19 Pandemic-Related Acceptable Protocol Modifications

Due to the COVID-19 pandemic, subject visits may be conducted via phone or video conference. In these situations, weight, and vital signs measurements may be performed by the subject or caregiver as needed.

Section 5.3.1.1 Study Procedures
Subsection Platelet Count
Heading "COVID-19 Pandemic-Related Acceptable Protocol Modifications"
Add: new heading title and text

COVID-19 Pandemic-Related Acceptable Protocol Modifications

If travel restrictions or other changes in local regulations in light of the COVID-19 pandemic prevent the subject from having blood drawn for laboratory testing at the study site, if possible, arrange for subjects to have laboratory work done at a local lab, hospital, or other facility. Local lab results should be obtained along with reference ranges and kept within the subjects' source documentation. Local lab results should be reviewed by the investigator as soon as possible. If laboratory samples cannot be obtained, study drug administration may be continued provided the investigator has reviewed all prior laboratory results and confirms and discusses with the subject that there is no safety concern for the subject to continue use of the study drug in the absence of current labs. The subject should be scheduled for laboratory draws as soon as feasible within 14 days from the scheduled visit.

Section 5.4.1 Discontinuation of Individual Subjects
Add: new fourth and fifth paragraph

During the COVID-19 pandemic, it has been necessary to employ mitigation strategies to enable the investigator to ensure subject safety and continuity of care.

The investigator should contact the sponsor medical contact before discontinuing a subject from the study for a reason other than "planned per protocol," to ensure all acceptable mitigation steps have been explored.

Section 5.5.1 Treatments Administered
Add: new third and fourth paragraph

During the Study Drug Dosing Period, a subject with confirmed (viral test positive) or suspected COVID-19 infection can only be dosed with study drug if the following COVID-19 viral clearance criteria are met:

- Symptomatic subjects: At least 2 negative viral tests in a row, ≥ 24 hours apart after at least 10 days have passed since recovery, defined as resolution of fever without use of antipyretics and improvement in respiratory symptoms (e.g., cough, shortness of breath)
- Asymptomatic subjects: At least 2 negative viral tests in a row, ≥ 24 hours apart after at least 10 days have passed since prior positive result (note: subjects who develop symptoms will follow guidance above for symptomatic subjects)

Delays in study drug dosing due to the above COVID-19 testing guidance for subjects must be discussed with the AbbVie medical contact, along with the possibility of premature discontinuation from the study drug dosing period. Frequency or timing of COVID-19 testing and intervals between testing for the above viral clearance criteria may be adjusted to account for epidemiologic trends, updated information regarding infectivity, and local/institutional guidelines.

Section 5.5.4 Selection and Timing of Dose for Each Subject
Subsection COVID-19 Pandemic-Related Acceptable Protocol Modifications
Add: new subsection title and text

COVID-19 Pandemic-Related Acceptable Protocol Modifications

Study drug may be shipped from the study site directly to the study subject's home if all the following criteria are met:

- Direct-to-patient (DTP) shipment of study drug is allowed by local regulations and the relevant ethics committee
- Study drug can be administered by the subject (or subject's caregiver) at home
- Subject agrees to have the study drug shipped directly to their home
- Shipments may also include other study supplies (e.g., drug dosing diaries). Instructions will be provided by AbbVie as to how a study site can initiate a DTP shipment using Marken, a global vendor selected by AbbVie to provide this service when necessary. Shipments of study drugs from the study site to a subject's home will be appropriately temperature controlled (qualified shipper or temperature monitoring) within the labeled storage conditions. Signature is required upon delivery; due to COVID-19 related social distancing, this may be provided by the courier after delivery. Documentation of the shipment is to be retained by the clinical site.
- AbbVie will not receive subject identifying information related to these shipments, as the site will work directly with the courier.

The study site is responsible for meeting IRB/IEC reporting requirements related to DTP shipments of study drug, and for obtaining consent to provide delivery information to the courier and documenting this consent in source documents.

Section 6.5 Adverse Event Reporting
"AbbVie Medical Monitor," "Title" previously read:

Group Medical Director

Has been changed to read:

Executive Medical Director

Section 6.5 Adverse Event Reporting
Subsection COVID-19 Pandemic-Related Acceptable Protocol Modifications
Add: new subsection title and text

COVID-19 Pandemic-Related Acceptable Protocol Modifications

Supplemental study case report forms should be completed in the event of COVID-19 related missed/virtual visits, study drug interruptions or discontinuations, or adverse events (including capture of specific signs/symptoms of infection and testing results).

COVID-19 infections should be captured as adverse events. If the event meets the criteria for a serious adverse event (SAE), then follow the SAE reporting directions per the protocol and above. The following COVID-19 related supplemental eCRFs should be completed:

- COVID-19 Supplemental Signs/symptoms
- COVID-19 Status Form

Section 7.0 Protocol Deviations
First paragraph previously read:

Protocol deviations should be avoided. When a deviation from the protocol is deemed necessary for an individual subject, the investigator or other physician in attendance must contact one of the following AbbVie representatives prior to implementation:

Has been changed to read:

AbbVie does not allow intentional/prospective deviations from the protocol except when necessary to eliminate an immediate hazard to study subjects. The investigator is responsible for complying with all protocol requirements, written instructions, and applicable laws regarding protocol deviations. If a protocol deviation occurs (or is identified, including those that may be due to the COVID-19 pandemic), the investigator

is responsible for notifying independent ethics committee (IEC)/independent review board (IRB), regulatory authorities (as applicable), and AbbVie.

Section 7.0 Protocol Deviations
Contact Information previously read:

Primary Contact:

[redacted]
SPM II
Clinical Program Development
1 North Waukegan Road
North Chicago, IL 60064

Contact Information:
Office: [redacted]
Email: [redacted]

Medical Monitor:

[redacted]
Group Medical Director
1 North Waukegan Rd
North Chicago, IL 60064

Contact Information:
Phone: [redacted]
Email: [redacted]

Has been changed to read:

Primary Contact:

[redacted]
Study Management Associate
AbbVie
1 North Waukegan Rd.
North Chicago, IL 60064

Contact Information:
Office: [redacted]
Email: [redacted]

Medical Monitor:

[redacted]
Executive Medical Director
1 North Waukegan Rd
North Chicago, IL 60064

Contact Information:
Phone: [redacted]
Email: [redacted]

Program Lead:

[redacted]
Program Lead II
Clinical Program Development
[redacted]
AbbVie
1 North Waukegan Road
North Chicago, IL 60064

Contact Information:
Office: [redacted]
Email: [redacted]

Section 9.1 Independent Ethics Committee (IEC) or Institutional Review Board (IRB)
Add: new fourth and fifth paragraph

In the event of a state of emergency due to the COVID-19 pandemic leading to difficulties in performing protocol-specified procedures, AbbVie will engage with study site personnel in efforts to ensure the safety of subjects, maintain protocol compliance, and minimize risks to the integrity of the study while trying to best manage subject continuity of care. This may include alternative methods for assessments (e.g., phone contacts or virtual site visits), alternative locations for data collection (e.g., use of a local lab instead

of a central lab), and shipping investigational product and/or supplies direct to subjects to ensure continuity of treatment where allowed.

In all cases, these alternative measures must be allowed by local regulations and permitted by IRB/IEC. Investigators should notify AbbVie if any urgent safety measures are taken to protect the subjects against any immediate hazard.

Section 10.1 Source Documents
Add: new last paragraph

During the COVID-19 pandemic, remote monitoring of data may be employed if allowed by the local regulatory authority, IRB/IEC, and the study site.

Appendix A. List of Abbreviations and Definitions of Terms
Subsection <u>Abbreviations</u>
Add:

COVID-19	Coronavirus Disease-2019
DTP	Direct To Patient

Appendix B. List of Protocol Signatories
Previously read:

Name	Title	Functional Area
[redacted]	Sr. Scientist II	Biomarkers
[redacted]	Program Lead II	Clinical
[redacted]	Study Project Manager II	Clinical
[redacted]	Director, Biometrics	Statistics
[redacted]	Group Medical Director	Clinical

Has been changed to read:

Name	Title	Functional Area
[redacted]	Sr. Scientist II	Biomarkers
[redacted]	Program Lead II	Clinical Program Development
[redacted]	Study Project Manager II	Clinical Program Development
[redacted]	Director	Statistics
[redacted]	Executive Medical Director, TA MD	Clinical Program Development

Appendix G. Extension Study - Assessments

Table 1. Extension Study: Schedule of Assessments

Previously read:

Procedures	Day 1	Every 4 Cycles	Final Visit	30 Day Safety Follow-up Visit
Informed Consent	X			
Physical Exam (including weight)	X[a]	X[a]	X	X
Vital Signs	X	X	X	X
12-lead ECG			X	
2D Echocardiogram with Doppler			X	
Platelet Count[b]	X	X	X	X
Lymphocyte Enumeration[c]			X	
Chemistry[d]	X	X	X	X
Hematology[d]	X	X	X	X
Urinalysis[d]			X	X
Performance Status (ECOG)			X	X
Tumor Assessments[e]			X	
Disease Progression Assessment	X	X	X	
Adverse Event/Concomitant Medications Assessment	X	X	X	X[f]
Dispense/Collect ABT-263[g]	X	X	X	
Dispense/Collect Subject Dosing Log	X	X	X	

a. Symptom directed.

b. Platelet Counts will be performed and assessed by the investigator or subinvestigator prior to study drug administration. Any platelet count less than 25,000/mm^3 should be confirmed the same day by manual reading and separate peripheral draw. Additional platelet counts will be obtained if ABT-263 is held or interrupted. If a platelet count is less than or equal to 50,000/mm^3, additional platelet counts will be performed every day at the discretion of the investigator. Platelet counts should be obtained 10 to 60 minutes after the completion of any platelet transfusion.

c. Perform Lymphocyte Enumeration at the Final Visit and as needed for subjects if deemed necessary by the investigator.

d. The specific laboratory tests required for chemistry, hematology and urinalysis are listed in Table 7. Triglycerides, amylase and lipase will only be collected at the Final Visit. For any subjects who are at high risk for tumor lysis syndrome (TLS), additional samples for hematology and chemistry may be collected as per the management guidelines in Section 6.7.4. ANC ≥ 500/μL and < 1,000/μL should be monitored at an increased frequency at the discretion of the investigator. Grade 2 chemistry labs should be monitored at an increased frequency at the discretion of the investigator.

e. If additional tumor assessments are collected by the site per standard of care, the data should be recorded on the appropriate paper CRF.

f. Adverse events will be followed until satisfactory clinical resolution of the adverse event is achieved.

g. A bottle's expiration date and pill count should be taken into account when dispensing 4 cycles of drug.

Has been changed to read:

Procedures	Day 1[#]	Every 4 Cycles[#]	Final Visit[#]	30 Day Safety Follow-up Visit[#]
Informed Consent	X			
Physical Exam (including weight)	X[a]	X[a]	X	X
Vital Signs	X	X	X	X
12-lead ECG			X	
2D Echocardiogram with Doppler			X	
Platelet Count[b,#]	X	X	X	X
Lymphocyte Enumeration[c,#]			X	
Chemistry[d,#]	X	X	X	X
Hematology[d,#]	X	X	X	X
Urinalysis[d,#]			X	X
Performance Status (ECOG)[#]			X	X
Tumor Assessments[e,#]			X	
Disease Progression Assessment	X	X	X	
Adverse Event/Concomitant Medications Assessment	X	X	X	X[f]
Dispense/Collect ABT-263[g]	X	X	X	
Dispense/Collect Subject Dosing Log	X	X	X	

Visits and activities may be conducted in the subject's home residence or by phone/virtually.

a. Symptom directed.

b. Platelet Counts will be performed and assessed by the investigator or subinvestigator prior to study drug administration. Any platelet count less than 25,000/mm^3 should be confirmed the same day by manual reading and separate peripheral draw. Additional platelet counts will be obtained if ABT-263 is held or interrupted. If a platelet count is less than or equal to 50,000/mm^3, additional platelet counts will be performed every day at the discretion of the investigator. Platelet counts should be obtained 10 to 60 minutes after the completion of any platelet transfusion.

c. Perform Lymphocyte Enumeration at the Final Visit and as needed for subjects if deemed necessary by the investigator.

d. The specific laboratory tests required for chemistry, hematology and urinalysis are listed in Table 7. Triglycerides, amylase and lipase will only be collected at the Final Visit. For any subjects who are at high risk for tumor lysis syndrome (TLS), additional samples for hematology and chemistry may be collected as per the management guidelines in Section 6.7.4. ANC ≥ 500/µL and < 1,000/µL should be monitored at an increased frequency at the discretion of the investigator. Grade 2 chemistry labs should be monitored at an increased frequency at the discretion of the investigator.

e. If additional tumor assessments are collected by the site per standard of care, the data should be recorded on the appropriate paper CRF.

f. Adverse events will be followed until satisfactory clinical resolution of the adverse event is achieved.

g. A bottle's expiration date and pill count should be taken into account when dispensing 4 cycles of drug.