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Protocol for Study M16-085

Relapsed or Refractory Multiple Myeloma: Venetoclax and Pomalidomide

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FULL TITLE: A Phase 2, Open-Label, Multicenter, Dose-Escalation and Expansion Study of Venetoclax in Combination with Pomalidomide and Dexamethasone in Subjects with Relapsed or Refractory Multiple Myeloma

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PRINCIPAL INVESTIGATOR(S): Investigator information on file at AbbVie.

EMERGENCY MEDICAL CONTACT:*

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

Office:
Mobile:
Email: [redacted]

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

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1 SYNOPSIS

Title: A Phase 2, Open-Label, Multicenter, Dose-Escalation and Expansion Study of Venetoclax in Combination with Pomalidomide and Dexamethasone in Subjects with Relapsed or Refractory Multiple Myeloma	
Background and Rationale:	Overexpression of BCL-2 is a major contributor to the pathogenesis of some lymphoid malignancies including multiple myeloma (MM). Current treatment paradigms for relapsed or refractory (R/R) MM clearly demonstrate that new treatments are needed for patients with MM. Plasma cells are typically geared towards long-term survival and have low apoptotic rates associated with high levels of anti-apoptotic proteins such as BCL-2 and myeloid-cell leukemia (MCL)-1. Dysregulation of apoptotic pathways in these cells, often from aberrant BCL-2 and/or MCL-1 overexpression, is thought to play a major role in the development and progression of MM. AbbVie is developing a potent, selective, and orally bioavailable small molecule inhibitor of BCL-2, venetoclax, that restores programmed cell death (apoptosis) in cancer cells and that may address the current needs for patients with (R/R) MM. Pomalidomide, a thalidomide analog, is a potent immunomodulatory drug (IMiD) that displays antiangiogenic, antiproliferative, and immunomodulatory activity. In addition, dexamethasone promotes BCL-2-dependence in MM through increased expression of BCL-2 and BIM potentially increasing sensitivity to venetoclax. Venetoclax, dexamethasone, and pomalidomide have all demonstrated significant activity in MM. Therefore, the combination of a potent BCL-2 inhibitor (venetoclax) with a potent IMiD (pomalidomide), and low-dose dexamethasone in subjects with R/R MM may lead to additive antitumor effects because of multiple complementary mechanisms of action.
Objectives and Endpoints:	The primary objective of this study is: • To characterize the safety and tolerability profiles of venetoclax combined with pomalidomide and dexamethasone when co-administered in subjects with R/R MM The secondary objectives of this study are: • To evaluate the anti-MM activity of co-administered venetoclax combined with pomalidomide and dexamethasone therapy • To characterize the plasma pharmacokinetics (PK) of venetoclax and pomalidomide when co-administered in subjects with R/R MM The exploratory objectives of this study are: • To evaluate correlative biomarkers of co-administered venetoclax combined with pomalidomide and dexamethasone therapy including, but not limited to, BCL-2 family member expression and chromosomal abnormalities • To assess minimal residual disease (MRD) negativity in the bone marrow by next generation sequencing

	The primary efficacy endpoint is the overall response rate (ORR) which is defined as all responses greater than or equal to partial response (PR). The secondary efficacy endpoints are as follows: progression-free survival (PFS); duration of response (DOR); and time-to-progression (TTP). Safety evaluations include adverse event (AE) monitoring, physical examinations, vital sign measurements, electrocardiograms (ECGs), and clinical laboratory testing (hematology and chemistry) as a measure of safety and tolerability for the entire study duration. PK samples will be collected and analyzed for venetoclax and pomalidomide concentrations. The PK parameters of maximum observed plasma concentration (C_{max}), the time to C_{max} (T_{max}), and the area under the plasma concentration versus time curve (AUC) will be determined. Biospecimens (blood, serum, plasma, bone marrow aspirate, and bone marrow core biopsy tissue) will be collected at specified time points throughout the study to evaluate known and/or novel disease-related or drug-related biomarkers. Types of biomarkers analyzed may include nucleic acids, proteins, lipids, and/or metabolites. The analyses may include BCL-2 family member expression, immune cell phenotyping and quantification, T-cell clonality, chromosomal abnormalities, and/or MRD negativity. Baseline t(11;14) status will be determined for all subjects and guide subject enrollment in the dose-expansion phase (Part 2).
Investigators:	Investigator information on file at AbbVie.
Study Sites:	Approximately 15 sites in approximately 3 countries
Study Population and Number of Subjects to be Enrolled:	The patient population consists of subjects with R/R MM. The study will enroll approximately 6 to 12 subjects in the dose-escalation phase (Part 1) and approximately 50 subjects in an expansion phase (Part 2).
Investigational Plan:	This is an open-label, multicenter study designed to evaluate the safety and preliminary efficacy of venetoclax combined with pomalidomide and dexamethasone in subjects with R/R MM who have received at least 1 prior line of therapy. The study will consist of 2 parts: Part 1 (dose escalation) and Part 2 (dose expansion). The dose-escalation phase of the study will evaluate the safety, tolerability, and PK profile of combination therapy with venetoclax, pomalidomide, and dexamethasone in 6 to 12 subjects who will be enrolled in 2 cohorts of at least 3 subjects per cohort. In the first cohort, a low dose of venetoclax (400 mg oral [PO], once daily [QD]) will be administered with the approved dose of pomalidomide (4 mg PO, QD) and dexamethasone (40 mg once weekly [qw]). If acceptable safety and tolerability are observed at the completion of Cycle 1 with at least 3 dose-limiting toxicity (DLT)-evaluable subjects, the dose of venetoclax will be escalated to 800 mg QD, which has been identified as the target dose; the dose of pomalidomide and dexamethasone will not change. The decision to escalate to the higher dose of venetoclax will be made according to the Bayesian optimal interval (BOIN) design and based on

	the cumulative number of subjects who experience a DLT at the current combination dose. The dose-expansion phase of the study will consist of 2 arms. Arm A will further evaluate the safety and efficacy profile of the combination therapy with venetoclax, pomalidomide, and dexamethasone in approximately 23 subjects positive for t(11;14) translocation. Arm B further evaluate the safety and efficacy profile of the combination therapy with venetoclax, pomalidomide, and dexamethasone in approximately 27 subjects negative for t(11;14) translocation. Subjects will receive venetoclax (800 mg PO, QD) + pomalidomide (4 mg PO, QD) + dexamethasone (40 mg qw). All subjects who participate in the dose-expansion phase of the study are required to undergo bone marrow aspirate collection at screening for determination of t(11;14) status before enrollment.

Key Eligibility Criteria:	Male or female subjects, at least 18 years old, with a diagnosis of R/R MM. Subjects should meet the following disease activity criteria:
	• R/R MM with documented evidence of progression during or after the subject's last treatment regimen based on the investigator's determination of the International Myeloma Working Group (IMWG) criteria.
	• Measurable disease, defined by at least 1 of the following disease activity criteria:
	  • serum M-protein ≥ 1.0 g/dL (≥ 10 g/L) for immunoglobulin (Ig)G MM
	  • serum M-protein ≥ 0.5 g/dL (≥ 5 g/L) for IgA, IgD, IgE, and IgM MM
	  • urine M-protein ≥ 200 mg/24 hours
	  • serum free-light chain (FLC) ≥ 10 mg/dL provided serum FLC ratio is abnormal
	• Has received at least 1 prior line of therapy
	• Must meet all of the following prior antimyeloma treatment parameters:
	  • subject must have received at least 2 consecutive cycles of lenalidomide or a lenalidomide-containing regimen
	  • subject must be refractory to lenalidomide
	  • subject must have documented evidence of progressive disease based on the investigator's determination of response as defined by the modified IMWG criteria on or after the last regimen
	  • subject who received only 1 line of prior treatment must have demonstrated progressive disease on or within 60 days of completion of the lenalidomide-containing regimen

	• subject must have been exposed to a proteasome inhibitor alone or in combination with another agent • subject must have had a response of PR or better to prior therapy based on the investigator's determination of response as defined by IMWG criteria • Has t(11;14) status determined by an analytically validated fluorescent in situ hybridization (FISH) assay per central laboratory testing of a bone marrow aspirate sample and meets the following criteria: • For Part 1: MM subjects independent of cytogenetic profile • For Part 2, Arm A: subject must be t(11;14) positive • For Part 2, Arm B: subject must be t(11;14) negative • An Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2. Subjects should have laboratory values meeting the following criteria: • serum alanine aminotransferase (ALT) ≤ 3 × the upper limit of normal (ULN) • aspartate aminotransferase (AST) ≤ 3 × ULN • total bilirubin ≤ 1.5 × ULN (subject with documented Gilbert's syndrome may be allowed total bilirubin > 1.5 × ULN) • creatinine clearance ≥ 30 mL/min, measured by 24-hour urine collection or calculated using the Cockcroft-Gault formula • prothrombin/international normalized ratio and/or activated partial thromboplastin time ≤ 1.5 × normal limits • absolute neutrophil count (ANC) > 1,000/µL (growth factor support is allowed to achieve eligibility criteria) • platelet count • ≥ 75,000/mm^3 for subjects with ≤ 50% myeloma involvement in the bone marrow • ≥ 50,000/mm^3 for subjects with > 50% myeloma involvement in the bone marrow • no platelet transfusion ≤ 72 hours before screening platelet count • hemoglobin ≥ 8.0 g/dL (subject must not receive a blood transfusion within 72 hours before screening hemoglobin) Subjects should also meet the following criterion: • No previous treatment with venetoclax or other BCL-2 inhibitors, or previous treatment with pomalidomide. • No acute infections within 14 days before first dose of study drug requiring antibiotic, antifungal, or antiviral therapy.

Study Drug and Duration of Treatment:	**Venetoclax** will be administered PO, QD for each 28-day cycle beginning on Day 1. For Part 1, Cohort 1, venetoclax will be administered as 400-mg doses. For Part 1, Cohort 2, venetoclax will be administered as 800-mg doses. For Part 2, venetoclax will be administered a dose that is determined to be safe in Part 1. **Pomalidomide** will be administered PO, QD for all 28-day cycles (Parts 1 and 2) on Days 1 to 21 as 4-mg doses. **Dexamethasone** will be administered qw for all 28-day cycles (Parts 1 and 2) as 40-mg doses. For subjects older than 75 years, the dexamethasone dose may be administered at a 20-mg dose (qw). Subjects will receive venetoclax and pomalidomide until documented disease progression, documented unacceptable toxicity, withdrawal of consent, or the subject meets other criteria for discontinuation. Subjects will remain on study treatment as long as venetoclax or pomalidomide/dexamethasone is being administered. Subjects may discontinue pomalidomide/dexamethasone but may continue receiving venetoclax QD as monotherapy for up to 2 years following the date of the last subject enrolled on study provided the subject completed venetoclax plus pomalidomide and dexamethasone dosing in Cycle 1, continue to tolerate venetoclax, have no evidence of disease progression, and do not meet any criteria for treatment discontinuation.
Date of Protocol Synopsis:	24 June 2020

2 INTRODUCTION

2.1 Background and Rationale

Why Is This Study Being Conducted

Venetoclax, an inhibitor of the anti-apoptotic protein B-cell lymphoma (BCL)-2, is currently being evaluated for the treatment of patients with chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), acute myeloid leukemia (AML), multiple myeloma (MM), and non-Hodgkin's lymphoma (NHL).

Overexpression of BCL-2 is a major contributor to the pathogenesis of some lymphoid malignancies including MM. Current treatment paradigms for relapsed or refractory (R/R) MM clearly demonstrate that new treatments are needed for patients with MM. Plasma cells are typically geared towards long-term survival and have low apoptotic rates associated with high levels of anti-apoptotic proteins such as BCL-2 and myeloid-cell leukemia (MCL)-1. Dysregulation of apoptotic pathways in these cells, often from aberrant BCL-2 and/or MCL-1 overexpression, is thought to play a major role in the development and progression of MM. Antagonizing BCL-2 and MCL-1 function to induce apoptosis is a compelling therapeutic approach in MM.

Venetoclax (also referred to as ABT-199, A-1195425.0, GDC-0199, RO5537382, Venclexta,® and Venclyxto®) is a selective, potent, orally bioavailable, small molecule, BCL-2 inhibitor that restores programmed cell death (apoptosis) in cancer cells. Venetoclax binds with high affinity (inhibition rate constant [K_i] < 0.010 nM) to antiapoptotic protein BCL-2 and with lower affinity to other antiapoptotic BCL-2 family proteins, like BCL-extra large (BCL-X_L) and BCL-Walter and Eliza Hall Institute (BCL-w) (> 4,000-fold and > 2,000- to > 20,000-fold lower affinity than to BCL-2, respectively). The anticipated and observed venetoclax-associated toxicities are also mechanism based; in particular, BCL-2-mediated effects on lymphocytes.[1,2] Venetoclax, as a BCL-2-selective (BCL-X_L-sparing) inhibitor, is projected to yield an improved therapeutic profile compared to dual BCL-2/BCL-X_L inhibitors. Because the survival of platelets depends on BCL-X_L,[3] thrombocytopenia, a major dose-limiting toxicity (DLT) caused by inhibition of BCL-X_L in the clinic,[4] is not expected to be dose limiting for venetoclax.

Venetoclax has demonstrated potent killing of MM cell lines and primary tumor samples bearing the t(11;14) translocation, which tend to express high levels of BCL-2 relative to MCL-1. Additionally, in Study M12-901, subjects with tumor cells determined to express high levels of BCL-2 had better reduction in M-protein and overall clinical response to venetoclax in combination with bortezomib, a proteasome inhibitor that upregulates expression of the MCL-1 inhibitor, Noxa, and dexamethasone.

Pomalidomide, a thalidomide analog, is a potent immunomodulatory drug (IMiD) that displays antiangiogenic, antiproliferative, and immunomodulatory activity. Pomalidomide is also shown to stimulate antibody-dependent cytotoxic T-cell activity. In addition, dexamethasone promotes BCL-2-dependence in MM through increased expression of BCL-2 and BIM potentially increasing sensitivity to venetoclax. Venetoclax, dexamethasone, and pomalidomide have all demonstrated significant activity in MM. Therefore, the combination of a potent BCL-2 inhibitor (venetoclax) with a potent IMiD (pomalidomide), and low-dose dexamethasone in subjects with R/R MM may lead to additive antitumor effects because of multiple complementary mechanisms of action.

As of 28 November 2016, 4 Phase 1/2 studies are ongoing in the MM indication with venetoclax. Overall for MM, when treated with venetoclax as a single agent or in combination with other therapies, most subjects experience at least 1 adverse event (AE) with the most common being nausea, diarrhea, and fatigue in monotherapy studies; and diarrhea, constipation, thrombocytopenia, neuropathy peripheral, and insomnia in combination studies. Approximately half of the subjects in MM clinical trials experience ≥ Grade 3 AEs with the most common being anemia, platelet count decreased, neutrophil count decreased, and thrombocytopenia. Approximately 30% of subjects experienced serious adverse events (SAEs). All of the AEs reported in the current MM studies are consistent with underlying disease or concomitant medical conditions, as well as other combination agents used to treat MM patients. Neutropenia and infections are consistent with the expected safety profile of venetoclax based on expected on-target effects of BCL-2 inhibition.

The BELLINI study (Study M14-031), a global, Phase 3, multicenter, randomized, double-blind study of bortezomib and dexamethasone in combination with either venetoclax or placebo in subjects with R/R MM who are sensitive or naïve to proteasome inhibitors, was unblinded as per protocol for the final analysis of the primary efficacy endpoint. As of the data cutoff date of 26 November 2018, 194 subjects were randomized to the venetoclax arm and 97 subjects to the placebo arm (2:1 randomization). The BELLINI study met its primary endpoint of progression-free survival (PFS; 22.4 versus 11.5 months, hazard ratio [HR] 0.63, 95% confidence interval [CI]: 0.44 - 0.90) and showed statistically significant improvements in overall response rate (ORR; 82% versus 68%) and very good partial response (VGPR) or better (59% versus 36%) in the venetoclax arm compared to the control arm. However, there were 51 deaths in the safety analysis set, 40 (20.7%) in the venetoclax arm and 11 (11.5%) in the placebo arm (the median overall survival [OS] has not been reached in either arm). The imbalance was predominantly seen in the treatment-emergent deaths which are those occurring on-therapy or within 30 days after the last dose of therapy. Among the 14 treatment-emergent deaths reported, 13 (6.7%) were in the venetoclax arm and 1 (1.0 %) in placebo arm. Of the 13 treatment-emergent deaths in the venetoclax arm, 8 were attributed by investigator to an event of infection; more than half of the deaths were also in the setting of refractory or progressive disease (PD). Although the majority of infection-related deaths occurred within 180 days of starting study treatment, some have occurred later, even after a year or more on treatment. A higher rate of Grade 3 or 4 neutropenia was seen in the venetoclax arm compared to placebo but an association of infection-related deaths with neutropenia has not been established at this point. Among the 37 nontreatment-emergent deaths (those occurring more than 30 days after the last dose of study treatment), 27 (14.0%) were in the venetoclax arm (6 deaths attributed to infection, 3.1%), and 10 (10.4%) in the placebo arm (2 deaths attributed to infection, 2.1%). After the data cutoff of 26 November 2018, additional deaths were reported in the BELLINI trial. As of 01 March 2019, there were 65 deaths in the safety analysis set, 48 (24.7%) in venetoclax arm and 17 (17.5%) in the placebo arm.

This is the first study of venetoclax in combination with pomalidomide and dexamethasone. This study will determine if venetoclax and pomalidomide can be safely combined for treatment of subjects with R/R MM and produce potentially meaningful clinical activity.

Clinical Hypothesis

Overall, MM accounts for more than 10% of all hematologic malignancies and 1% of all malignancies. It is the most prevalent hematologic malignancy in patients older than 65 years of age. Approximately 114,000 new cases of MM were diagnosed worldwide in 2012.[5]

The treatment paradigms and outcomes for patients with MM have markedly changed in the past decade with the introduction of several new, more effective, and less toxic therapies, doubling the median OS from 3 years to 6 years.[6,7] Nevertheless, significant unmet needs remain for the treatment of MM, as this disease has no cure to date and current therapies can only slow disease progression, prolong survival, and minimize symptoms. In fact, the majority of patients with MM will relapse or become refractory, regardless of the line of therapy, which is associated with high morbidity and mortality. Additionally, the remission duration in relapsed myeloma decreases with each regimen.

Various treatment options are available in case of relapse ranging from conventional cytostatic agents such as melphalan or cyclophosphamide and steroids to novel classes of drugs, including IMiDs, proteasome inhibitors (PIs), histone deacetylase (HDAC) inhibitors, and monoclonal antibodies (anti-CS1, anti-CD38) with and without corticosteroids. Most recommended treatment protocols comprise variable combinations of these drugs.

The mechanisms of action of venetoclax (BCL-2 inhibitor) and pomalidomide (IMiD) are independent and have the potential to provide additive clinical benefit relative to the individual agents alone in subjects with R/R MM.

2.2 Benefits and Risks to Patients

Despite recent therapeutic advances, MM remains incurable and is associated with high morbidity and mortality; even with the best available approved agents, all subjects will eventually relapse. Furthermore, the remission duration in R/R MM decreases with each subsequent regimen.[8]

Based on supportive safety and efficacy data from ongoing Phase 1/2 studies of venetoclax as a single agent or in combination with other therapies (see above), subjects enrolled in this study are anticipated to benefit from the combined treatment with pomalidomide based on the pro-apoptotic effects in myeloma cells.

Since the antitumorigenic effects of venetoclax and pomalidomide on myeloma cells are via distinctive mechanisms of action, the combination of these 2 drugs is anticipated to result in an enhanced therapeutic effect that could potentially benefit patients with relapsed MM. The goal of this study is to determine the safety profile, tolerability, and the potential efficacy of venetoclax combined with pomalidomide and dexamethasone in patients with R/R MM.

Following the analysis of the BELLINI study (see Section 2.1), guidance for dose interruption/reduction following a Grade ≥ 3 infection or any serious infection in subjects receiving venetoclax have been implemented (see Section 6.4 and Appendix I).

For further details, please see findings from completed studies including safety data in the venetoclax Investigator Brochure[9] and the pomalidomide package insert.[10]

3 STUDY OBJECTIVES AND ENDPOINTS

3.1 Objectives

Primary

The primary objective of this study is:

- To characterize the safety and tolerability profiles of venetoclax combined with pomalidomide and dexamethasone when co-administered in subjects with R/R MM

Secondary

The secondary objectives of this study are:

- To evaluate the anti-MM activity of co-administered venetoclax combined with pomalidomide and dexamethasone therapy
- To characterize the plasma pharmacokinetics (PK) of venetoclax and pomalidomide when co-administered in subjects with R/R MM

Exploratory

The exploratory objectives of this study are:

- To evaluate correlative biomarkers of co-administered venetoclax combined with pomalidomide and dexamethasone therapy including, but not limited to, BCL-2 family member expression and chromosomal abnormalities
- To assess minimal residual disease (MRD) negativity in the bone marrow by next generation sequencing

3.2 Primary Efficacy Endpoint

The primary efficacy endpoint is the ORR which is defined as all responses greater than or equal to partial response (PR).

3.3 Secondary Efficacy Endpoints

Key Secondary Endpoints

The secondary endpoints are as follows:

- PFS
- Duration of response (DOR)

- Time-to-progression (TTP)

The definitions of key secondary endpoints are specified in the Statistical Analysis Plan (SAP).

3.4 Safety Endpoints

Safety evaluations include AE monitoring, physical examinations, vital sign measurements, electrocardiograms (ECGs), and clinical laboratory testing (hematology and chemistry) as a measure of safety and tolerability for the entire study duration.

3.5 Pharmacokinetic Endpoints

PK samples will be collected and analyzed for venetoclax and pomalidomide concentrations. The PK parameters of maximum observed plasma concentration (C_{max}), the time to C_{max} (T_{max}), and the area under the plasma concentration versus time curve (AUC) from time 0 to 24 hours postdose (AUC_{0-24}) will be determined, as appropriate, using noncompartmental methods. Additional parameters may also be calculated if appropriate.

3.6 Biomarker Research Endpoints

Biospecimens (blood, serum, plasma, bone marrow aspirate, and bone marrow core biopsy tissue) will be collected at specified time points (Appendix D) throughout the study to evaluate known and/or novel disease-related or drug-related biomarkers. Types of biomarkers analyzed may include nucleic acids, proteins, lipids, and/or metabolites. The analyses may include BCL-2 family member expression, immune cell phenotyping and quantification, T-cell clonality, chromosomal abnormalities (immunoglobulin [Ig]H translocations, amplifications, or deletions), and/or MRD negativity. Baseline t(11;14) status will be determined for all subjects and guide subject enrollment in the dose-expansion phase (Part 2), as detailed in Section 5.1. The biomarker research may be exploratory in nature and results may not be included with the clinical study report. Further details regarding the biomarker research rationale and collection time points are located in Appendix D and Appendix E.

4 INVESTIGATIONAL PLAN

4.1 Overall Study Design and Plan

The schematic of the study is shown in Figure 1. Further details regarding study procedures are located in Appendix E.

This is an open-label, multicenter study designed to evaluate the safety and preliminary efficacy of venetoclax combined with pomalidomide and dexamethasone in subjects with R/R MM who have received at least 1 prior line of therapy. The study will consist of 2 parts: Part 1 (dose escalation) and Part 2 (dose expansion).

Part 1: Dose Escalation

The dose-escalation phase of the study will evaluate the safety, tolerability, and PK profile of combination therapy with venetoclax, pomalidomide, and dexamethasone in 6 to 12 subjects who will be enrolled in 2 cohorts of at least 3 subjects per cohort. In the first cohort, a low dose of venetoclax (400 mg oral [PO], once daily [QD]) will be administered with the approved dose of pomalidomide (4 mg PO, QD) and dexamethasone (40 mg once weekly [qw]). If acceptable safety and tolerability are observed at the completion of Cycle 1 with at least 3 dose-limiting toxicity (DLT)-evaluable subjects, the dose of venetoclax will be escalated to 800 mg QD (Cohort 2), which has been identified as the target dose; the dose of pomalidomide and dexamethasone will not change. The decision to escalate to the higher dose of venetoclax will be made according to the Bayesian optimal interval (BOIN) design and based on the cumulative number of subjects who experience a DLT at the current combination dose.

Table 1 displays the dose-escalation decision rule for the BOIN design with target toxicity rate of 30% and optimal interval of (23.6%, 35.9%).

Table 1. Dose-Escalation Decision Rule

	Number of DLT-Evaluable Subjects Treated at Current Combination							
Action	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Escalate if number of subjects with DLT ≤	0	0	1	1	1	1	2	2
Stay at current combination if number of subjects with DLT =	1	1	-	2	2	2	3	3
De-escalate if number of subjects with DLT ≥	2	2	2	3	3	3	4	4
Eliminate[a] if number of subjects with DLT ≥	3	3	4	4	5	5	5	6

DLT = dose-limiting toxicity

a. Eliminate current combination and higher combinations (i.e., venetoclax dose and pomalidomide dose ≥ current dose level).

Subjects must complete at least 80% of pomalidomide dosing and at least 80% of venetoclax dosing in Cycle 1 or experience a DLT to be considered evaluable for dose-escalation decisions. Subjects not DLT-evaluable may be replaced as necessary to meet minimum requirement for dose escalation. DLTs are defined in Section 6.5.

Additional information regarding the BOIN design will be provided in the SAP.

During Part 1, dose review meetings will be conducted at the completion of Cycle 1 in at least 3 evaluable subjects in each cohort.

All subjects who participate in the dose-escalation phase of the study will undergo bone marrow aspirate collection for cytogenetic determination at baseline.

Part 2: Dose Expansion

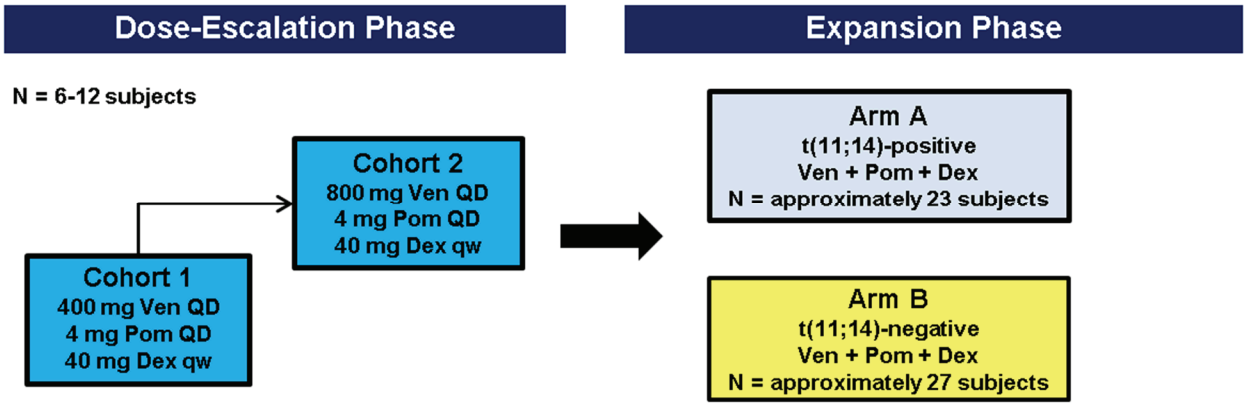
The dose-expansion phase of the study will consist of 2 arms. Arm A will further evaluate the safety and efficacy profile of the combination therapy with venetoclax, pomalidomide, and dexamethasone in approximately 23 subjects positive for t(11;14) translocation. Arm B will further evaluate the safety and

efficacy profile of the combination therapy with venetoclax, pomalidomide, and dexamethasone in approximately 27 subjects negative for t(11;14) translocation. Subjects will receive the venetoclax dose that is determined to be safe in Part 1 + pomalidomide (4 mg PO, QD) + dexamethasone (40 mg qw). All subjects who participate in the dose-expansion phase of the study are required to undergo bone marrow aspirate collection at screening for determination of t(11;14) status before enrollment.

See Section 5.1 for information regarding eligibility criteria.

Review of the efficacy and safety data will be completed on an ongoing basis. During Part 1, dose review meetings will be conducted at the completion of Cycle 1 with at least 3 evaluable subjects in each cohort. Additional reviews will be held as deemed necessary based on study events or data.

Figure 1. Study Design



Dex = dexamethasone; Pom = pomalidomide; QD = once daily; qw = once weekly; Ven = venetoclax

Note: Venetoclax will be administered once daily from Day 1 through Day 28 of each cycle. Pomalidomide will be administered once daily from Day 1 through Day 21 of each cycle.

Hematology must be completed before the initiation of each subsequent cycle of combination therapy. Subjects must meet the following minimum criteria to continue combination therapy:

- absolute neutrophil count (ANC) ≥ 500/µL; growth factor support is allowed after Cycle 1
- platelets ≥ 50,000/mm^3
- all other AEs should resolve to ≤ Grade 2

Subjects will receive venetoclax and pomalidomide until documented disease progression, documented unacceptable toxicity, withdrawal of consent, or the subject meets other criteria for discontinuation per study protocol (Section 5.5). Subjects will remain on study treatment as long as venetoclax or pomalidomide/dexamethasone is being administered. Subjects may discontinue pomalidomide/dexamethasone but may continue receiving venetoclax QD as monotherapy for up to 2 years following the date of the last subject enrolled on study provided the subject completed venetoclax plus pomalidomide and dexamethasone dosing in Cycle 1, continue to tolerate venetoclax, have no evidence of disease progression, and do not meet any criteria for treatment discontinuation. For subjects that

continue to derive benefit after 2 years of treatment following the date of the last subject enrolled, AbbVie will work with the investigator to evaluate options for continuation of venetoclax therapy.

4.2 Discussion of Study Design

Choice of Control Group

Not applicable.

Appropriateness of Measurements

Standard statistical, clinical, and laboratory procedures will be utilized in this study. All efficacy measurements in this study are standard for assessing disease activity in subjects with R/R MM. All clinical and laboratory procedures in this study are standard and generally accepted.

Suitability of Subject Population

Venetoclax has demonstrated potent killing of MM cell lines and primary tumor samples bearing the t(11;14) translocation, which tend to express high levels of BCL-2 relative to MCL-1. Pomalidomide is a potent IMiD that displays antiangiogenic, antiproliferative, and immunomodulatory activity. Additionally, dexamethasone promotes BCL-2-depenedence in MM through increased expression of BCL-2 and BIM potentially increasing sensitivity to venetoclax. Venetoclax, dexamethasone, and pomalidomide have all demonstrated significant activity in MM. Therefore, a potent BCL-2 inhibitor (venetoclax) with a potent IMiD (pomalidomide), and low-dose dexamethasone in subjects with R/R MM might be combined safely and with potentially meaningful clinical activity in this subject population.

Selection of Doses in the Study

The selected dosage regimen of pomalidomide (4 mg QD on Days 1 to 21 of each 28-day cycle) and dexamethasone (40 mg, qw) is the approved dosage regimen for this combination therapy in subjects with MM that have received at least 2 prior therapies, as specified on the US package insert.[10]

The selected dosage regimen of venetoclax is based on the results from a Phase 1b study (Study M12-901) of venetoclax plus bortezomib and dexamethasone in R/R MM subjects. An exposure-response analysis of the efficacy (best response) and safety (Grade ≥ 3 anemia, thrombocytopenia, and neutropenia) from the study indicated that a venetoclax dosage regimen of 600 mg QD or higher in combination with bortezomib and dexamethasone would likely result in a substantial VGPR or better response rate with these response rates increasing through 1200 mg QD. No relationship was observed between venetoclax exposure and anemia or thrombocytopenia but the neutropenia (Grade ≥ 3) rates began to increase at doses greater than 800 mg QD. Based on these efficacy and safety results and treatment compliance considerations, a (maximum) venetoclax dose of 800 mg QD was selected. The first subjects (Cohort 1) who administer the combination of venetoclax with pomalidomide and dexamethasone will receive a lower dose of venetoclax (400 mg) to evaluate safety of this specific combination before escalation to the 800 mg dose of venetoclax (if appropriate).

5 STUDY ACTIVITIES

5.1 Eligibility Criteria

Subjects must meet all of the following criteria to be included in the study. Anything other than a positive response to the questions below will result in exclusion from study participation.

Consent

- 1. Subjects must voluntarily **sign and date an informed consent**, approved by an Independent Ethics Committee (IEC)/Institutional Review Board (IRB), before the initiation of any screening or study-specific procedures.
- 2. All subjects enrolled in this trial must be registered and must comply with all requirements of the pomalidomide risk evaluation and mitigation strategies (REMS) program or local equivalent.

Demographic and Laboratory Assessments

- 3. Adult **male or female**, at least 18 years old.
- 4. **Laboratory values** meeting the following criteria within the screening period before the first dose of study drug:
  - serum alanine aminotransferase (ALT) ≤ 3 × the upper limit of normal (ULN)
  - aspartate aminotransferase (AST) ≤ 3 × ULN
  - total bilirubin ≤ 1.5 × ULN (subject with documented Gilbert's syndrome may be allowed total bilirubin > 1.5 × ULN)
  - creatinine clearance (CrCL) ≥ 30 mL/min, measured by 24-hour urine collection or calculated using the Cockcroft-Gault formula
  - prothrombin/international normalized ratio (INR) and/or activated partial thromboplastin time (aPTT) ≤ 1.5 × normal limits
  - ANC > 1,000/µL (growth factor support is allowed to achieve eligibility criteria)
  - platelet count
    - ≥ 75,000/mm^3 for subjects with ≤ 50% myeloma involvement in the bone marrow
    - ≥ 50,000/mm^3 for subjects with > 50% myeloma involvement in the bone marrow
    - no platelet transfusion ≤ 72 hours before screening platelet count
  - hemoglobin ≥ 8.0 g/dL (subject must not receive a blood transfusion within 72 hours before screening hemoglobin)
- 5. Are willing or able to comply with procedures required in this protocol.

Disease Activity

- 6. R/R MM with documented evidence of progression during or after the subject's last treatment regimen based on the investigator's determination of the International Myeloma Working Group (IMWG) criteria.
- 7. Measurable disease, defined by at least 1 of the following disease activity criteria:
  - serum M-protein ≥ 1.0 g/dL (≥ 10 g/L) for IgG MM
  - serum M-protein ≥ 0.5 g/dL (≥ 5 g/L) for IgA, IgD, IgE, and IgM MM
  - urine M-protein ≥ 200 mg/24 hours
  - serum free-light chain (FLC) ≥ 10 mg/dL provided serum FLC ratio is abnormal
- 8. Has received at least 1 prior line of therapy.
  - A line of therapy consists of > 1 complete cycle of a single agent, a regimen consisting of a combination of several drugs, or a planned sequential therapy of various regimens
- 9. Must meet all of the following prior antimyeloma treatment parameters:
  - subject must have received at least 2 consecutive cycles of lenalidomide or a lenalidomide-containing regimen
  - subject must be refractory to lenalidomide
    - subject must have documented evidence of PD based on the investigator's determination of response as defined by the modified IMWG criteria on or after the last regimen
    - subject who received only 1 line of prior treatment must have demonstrated PD on or within 60 days of completion of the lenalidomide-containing regimen
  - subject must have been exposed to a PI alone or in combination with another agent
  - subject must have had a response of PR or better to prior therapy based on the investigator's determination of response as defined by IMWG criteria
- 10. Has t(11;14) status determined by an analytically validated fluorescent in situ hybridization (FISH) assay per central laboratory testing of a bone marrow aspirate sample and meets the following criteria:
  - For Part 1: MM subjects independent of cytogenetic profile
  - For Part 2, Arm A: subject must be t(11;14) positive
  - For Part 2, Arm B: subject must be t(11;14) negative
- 11. An Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2.

Subject History

- 12. No history of clinically significant medical conditions within the last 6 months that, in the investigator's opinion, would adversely affect the subject's participation in the study.

- 13. No history of **any active malignancies**, including myelodysplastic syndromes, within the past 3 years except for the following:
  - adequately treated in situ carcinoma of the cervix uteri or the breast;
  - basal cell carcinoma of the skin or localized squamous cell carcinoma of the skin;
  - prostate cancer Gleason Grade 6 or lower AND with stable prostate-specific antigen levels off treatment; or
  - previous malignancy with no current evidence of disease, and which was confined and surgically resected (or treated with other modalities) with curative intent and unlikely to impact survival during the duration of the study.
- 14. None of the following conditions:
  - Nonsecretory myeloma, active plasma cell leukemia, Waldenström's macroglobulinemia, primary amyloidosis, central nervous syndrome myeloma, and POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes [POEMS])
  - positive human immunodeficiency virus infection or active hepatitis B or C infection
  - major surgery within 4 weeks before first dose of study drug or planned during study participation
  - acute infections within 14 days before first dose of study drug requiring antibiotic, antifungal, or antiviral therapy
  - significant cardiovascular disease, including uncontrolled angina, arrhythmia, recent myocardial infarction (within 6 months of first dose), and congestive heart failure (New York Heart Association Functional Class ≥ 3)
  - uncontrolled diabetes or hypertension within 14 days before first dose of study drug
  - peripheral neuropathy ≥ Grade 3 or ≥ Grade 2 with pain within 2 weeks before the first dose of study drug
- 15. No known sensitivity to any IMiDs.
- 16. No allogenic or syngeneic stem cell transplant within 6 months before the first dose of study drug or active ongoing graft versus host disease.
- 17. No autologous stem cell transplant within 12 weeks before the first dose of study drug.
- 18. No known meningeal involvement of MM.
- 19. No previous treatment with venetoclax or other BCL-2 inhibitors, or previous treatment with pomalidomide.

Contraception

- 20. A **negative serum pregnancy test** for all female subjects of childbearing potential during the screening period (within 10 to 14 days before initiating treatment with study drugs) and a negative urine pregnancy test for all female subjects within 24 hours before the first dose of study drugs.

- 21. **If female**, subject must be either **postmenopausal** OR permanently **surgically sterile** OR for women of childbearing potential practicing at least 2 protocol-specified **methods of birth control** that are effective from at least 30 days before starting study drugs through at least 30 days after the last dose of any study drug (refer to Section 5.2).
- 22. **If male**, and subject is **sexually active with female partner(s) of childbearing potential**, he must agree, from Study Day 1 through 30 days after the last dose of pomalidomide, to practice the protocol-specified contraception (refer to Section 5.2).
- 23. Female who is not **pregnant, breastfeeding, or considering becoming pregnant** during the study and for approximately 30 days after the last dose of any study drug.
- 24. Male who is not considering **fathering a child or donating sperm** during the study and for approximately 30 days after the last dose of pomalidomide.

Concomitant Medications

- 25. Subject must not have been treated with anti-myeloma therapy (other than monoclonal antibodies) including: chemotherapy, radiotherapy, biological therapy, immunotherapy, targeted small molecule therapy, or investigational therapy within 5 half-lives (or 2 weeks if half-life is unknown or not applicable) before the first dose of study drugs and through the last dose of any study drug.
- 26. Subject must not have been treated with anti-myeloma monoclonal antibodies within 6 weeks before the first dose of study drugs and through the last dose of any study drug.
- 27. Subject must not have received corticosteroid therapy at a cumulative dose equivalent of ≥ 140 mg of prednisone or a single-dose equivalent to ≥ 40 mg/day of dexamethasone within 2 weeks before the first dose of study drug.
- 28. Subject must not have used systemic strong or moderate inhibitor or inducer of cytochrome P450 (CYP)3A within 1 week before the first dose of study drugs.
- 29. Subject must not have used systemic strong inhibitor of CYP1A2 within 1 week before the first dose of study drugs.
- 30. Subject must not have consumed grapefruit, grapefruit products, Seville oranges (including marmalade containing Seville oranges), or star fruit within 3 days before the first dose of study drugs administrations and through the last dose of any study drug.
- 31. Subject must not have received **any live vaccines** within 8 weeks before the first dose of study drugs, or have an expected need of live vaccination during study participation including at least 4 weeks after the last dose of any study drug.
- 32. Subject must not anticipate the use of prohibited medications or foods during study participation (see Section 5.3 for additional prohibited medications or foods).

5.2 Contraception Recommendations

Subjects must follow the contraceptive guidelines as specified below (minimum requirements for venetoclax and pomalidomide; local guidelines and pomalidomide REMS program may differ and should be followed, when applicable).

If female, subject must be either:

- Postmenopausal defined as:
  - age > 55 years with no menses for at least 24 or more consecutive months without an alternative medical cause; or
  - age ≤ 55 years with no menses for 24 or more consecutive months without an alternative medical cause and a follicle-stimulating hormone level > 40 IU/L

or

- Permanently surgically sterile (bilateral oophorectomy, bilateral salpingectomy, or hysterectomy)

or

- Women of childbearing potential must use 2 reliable forms of contraception simultaneously from at least 30 days before initiating treatment with study drugs through at least 30 days after the last dose of any study drug. The 2 methods of reliable contraception must include 1 highly effective method and 1 additional effective (barrier) method. The following are examples of highly effective and additional effective methods of contraception:
  - Highly Effective Methods
    - hormonal (birth control pills, injections, levonorgesterel-releasing intrauterine system, medroxyprogesterone acetate depot injections, ovulation inhibitory progesterone-only pill [e.g., desogestrel])
    - bilateral tubal occlusion/ligation at least 1 month before study Day 1
    - bilateral tubal occlusion via hysteroscopy (i.e., Essure), provided a hysterosalpingogram confirms success of the procedure at least 1 month before study Day 1
    - vasectomized partner, provided the vasectomized partner verbally confirms receipt of medical assessment of the surgical success and is the sole sexual partner of the female subject;
    - intrauterine device
  - Additional Effective Methods
    - male condom
    - diaphragm
    - cervical cap

or

- true abstinence which is defined as refraining from heterosexual intercourse if this is in line with the preferred and usual lifestyle of the subject (periodic abstinence [e.g., calendar, ovulation, symptothermal, postovulation methods] and withdrawal are not acceptable)

There is an increased risk of venous thromboembolism in subjects with MM taking pomalidomide and dexamethasone; combined oral contraceptive pills are not recommended. If a subject is currently using combined oral contraception, the subject should switch to another highly effective method. The risk of venous thromboembolism continues for 4 to 6 weeks after discontinuing combined oral contraception. The efficacy of contraceptive steroids may be reduced during co-treatment with dexamethasone.

Implants and levonorgestrel-releasing intrauterine systems are associated with an increased risk of infection at the time of insertion and irregular vaginal bleeding. Prophylactic antibiotics should be considered, particularly in subjects with neutropenia.

For male subjects, pomalidomide is present in the semen of subjects receiving the drug. Therefore, male subjects must practice complete abstinence or always use a latex or synthetic condom during any sexual contact with females of reproductive potential while taking pomalidomide and for up to 4 weeks after discontinuing pomalidomide, even if they have undergone a successful vasectomy. Male subjects taking pomalidomide must not donate sperm during study participation and for up to 30 days after discontinuing any study drug.

5.3 Prohibited Medications and Therapy

In addition to the medications and therapy listed in the eligibility criteria (Section 5.1, **Concomitant Medications**), the following medications are **prohibited** during Part 1, Cycle 1:

- Strong and moderate CYP3A inhibitors
- Strong CYP1A2 inhibitors
- Strong and moderate CYP3A inducers

Subjects must be consented for the study before discontinuing any prohibited medications for the purpose of meeting study eligibility. A sample list of prohibited and cautionary medications is listed in Appendix J.

5.4 Prior and Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the subject is receiving from 30 days before and throughout screening or receives during the study and up to 30 days after last dose of study drug must be recorded in the electronic case report form (eCRF). Any prior transfusions (blood or platelet) must be recorded in the eCRF and the investigator must ensure that this data is consistent with the subject's medical history.

The following medications are allowed **after Part 1, Cycle 1** and for Part 2 (dose expansion) to **use with caution** if no appropriate therapeutic alternative exists (additional guidance noted):

- Strong and moderate CYP3A inhibitors (venetoclax dose reductions)
- Strong CYP1A2 inhibitors (pomalidomide dose reductions)
- Strong and moderate CYP3A inducers (avoid)

Recommended venetoclax and pomalidomide dose modifications when administered concomitantly with strong or moderate CYP3A inhibitors and strong CYP1A2 inhibitors are provided in Appendix I.

The following medications to **use with caution** include:

- warfarin (closely monitor international normalized ratio)
- P-glycoprotein (P-gp) substrates
- breast cancer resistance protein (BCRP) substrates
- organic anion-transporting polypeptide (OATP)1B1/1B3 substrates
- P-gp inhibitors
- BCRP inhibitors
- high-dose corticosteroids

Specific examples of prohibited and cautionary medications that fall into these categories can be found in Appendix J.

Subjects should be advised that cigarette smoking reduces pomalidomide exposure because of CYP1A2 induction and therefore may reduce efficacy.

Herbal and natural remedies are to be avoided while on study drug.

Any questions regarding prior or concomitant therapy should be raised to the AbbVie emergency contact. Information regarding potential drug interactions with venetoclax or pomalidomide can be located in the Investigator's Brochure or package insert, respectively.

While on study, unless prohibited by the protocol, subjects should receive best supportive care per investigator discretion. Supportive care and medications that may be required for venetoclax and/or pomalidomide during the study include the following:

- allopurinol or other appropriate tumor lysis syndrome (TLS) risk-reducing agent
- adequate fluids to ensure dehydration prevention (note: per institutional standards while using medical judgment)
- enteric-coated aspirin 81 mg PO, QD or low molecular weight heparin if history of prior thrombotic disease according to local practice

Allowed Concomitant Therapies

The following concomitant medications are allowed during the study:

- Bisphosphonates intravenous or PO as indicated per institutional guidelines. Note: institution of bisphosphonates after Cycle 2 if not already in use is prohibited.
- Only low-dose corticosteroids (e.g., prednisone ≤ 10 mg PO, QD or its equivalent), inhaled steroids, and topical preparations for reasons other than MM (e.g., asthma) are allowed during the study. Systemic corticosteroids > 10 mg PO QD of prednisone (or its equivalent) should not be given on the same day as dexamethasone administration. Systemic corticosteroids > 10 mg PO QD of prednisone (or its equivalent) are allowed when the dose of prednisone (or its equivalent) is given for less than 7 days and the cumulative dose is < 120 mg. For additional guidance and to determine the equivalent dose of systemic corticosteroid, refer to Appendix K.
- Surgery and radiation:
    - Localized radiation therapy to a site of pre-existing disease may be permitted while on study. Following approval by the AbbVie Therapeutic Area Medical Director (TA MD) or designee, the subject may initiate or continue with protocol therapy without interruption during the course of palliative radiation therapy if the risk of excessive bone marrow suppression or other toxicity is acceptable, per the investigator's opinion, and the treatment is in the best interest of the subject.
    - If the subject develops a definite increase in the size of existing bone lesions or soft tissue plasmacytomas that meet the criteria for PD, treatment must be discontinued for PD regardless of whether radiation therapy is initiated.
    - Kyphoplasty, vertebroplasty, or emergency orthopedic surgery is permitted.
    - Use of radiotherapy or surgical intervention must be recorded on the eCRF.

Pretreatment Guidance

Anti-Infective Prophylaxis

It is recommended that subjects should receive anti-infective prophylaxis (e.g., amoxicillin/clavulanic acid, levofloxacin, or equivalent per institutional guidelines) at least during the first 90 days of study, when Grade 4 neutropenia develops (ANC < 500 cells/µL) and continued until the neutropenia improves to Grade 3 or better (ANC > 500 cells/µL), and upon disease progression for at least 30 days, unless contraindicated per investigator discretion. Furthermore, it is recommended that subjects deemed at high risk of infection receive immunoglobulin replacement therapy (i.e., intravenous immunoglobulin [IVIG]) per institutional guidelines or at the Investigator's discretion. Pneumocystis prophylaxis is allowed per institutional guidelines or at the investigator's discretion.

- The use of antibiotics that are moderate or strong CYP3A4 inhibitors should be avoided or used with caution and with the appropriate venetoclax dose modification (Appendix I) as per protocol.

Pneumococcal and Influenza Vaccination

Pneumococcal vaccination may be considered during the initiation of screening procedures for all subjects who have not previously received the vaccine. At the investigator's discretion, influenza vaccination may also be considered (live attenuated vaccines are not allowed) during the initiation of screening procedures and while on study treatment.

Tumor Lysis Syndrome Prophylaxis

There is a potential for TLS in subjects affected by hematologic malignancies. Refer to Section 6.4 for required TLS prophylaxis.

5.5 Withdrawal of Subjects and Discontinuation of Study

A subject may voluntarily withdraw or be withdrawn from the study at any time for reasons including, but not limited to, the following:

- clinically significant abnormal laboratory results or AEs, which rule out continuation of the study drug, as determined by the investigator or the AbbVie TA MD;
- investigator's opinion that discontinuation is in the best interest of the subject;
- subject requests withdrawal from the study;
- eligibility criteria violation was noted after the subject started study drug and continuation of the study drug would place the subject at risk;
- introduction of prohibited medications or dosages and continuation of the study drug would place the subject at risk;
- subject becomes pregnant while on study drug;
- subject is significantly noncompliant with study procedures which would put the subject at risk for continued participation in the trial.

Each subject must be withdrawn if any of the following occur:

- disease progression confirmed with IMWG criteria
- drug-related toxicities that lead to dose interruption of > 28 days (subjects may remain in the study if only 1 treatment is discontinued)
- use of antimyeloma treatment not specified in the protocol or operations manual and before documented disease progression

For subjects to be considered lost to follow-up, reasonable attempts must be made to obtain information on the final status of the subject. At a minimum, 2 telephone calls must be made and 1 certified letter must be sent and documented in the subject's source documentation.

AbbVie may terminate this study prematurely, either in its entirety or at any site. The investigator may also stop the study at his/her site if he/she has safety concerns. If AbbVie terminates the study for safety reasons, AbbVie will promptly notify the investigator.

In the event a subject withdraws consent to participate in the clinical study and AbbVie is notified in writing, no new biomarker data will be collected from the withdrawn subject or added to the existing data or database(s). A subject may withdraw consent for optional research at any time and remain in the clinical study. Data generated from biomarker research samples collected before subject withdrawal of consent will remain part of the study results.

5.6 Follow-Up for Subject Withdrawal from Study

To minimize missing data for efficacy and safety assessments, subjects who prematurely discontinue study drug treatment should continue to be followed for all regularly scheduled visits, unless subjects have decided to discontinue the study participation entirely (withdrawal of informed consent). Subjects should be advised on the continued scientific importance of their data even if they discontinue treatment early.

If a subject discontinues study participation (withdrawal of informed consent), the procedures outlined for the end-of-treatment visit should be completed as soon as possible, preferably within 2 weeks. In addition, if subject is willing, a 30-day follow-up phone call after the last dose of study drug may be completed to ensure all treatment-emergent AEs/SAEs have been resolved to a ≤ Grade 1 or baseline level or, in the opinion of the investigator, the event is unlikely to resolve.

All attempts must be made to determine the date of the last study drug dose and the primary reason for the discontinuation of the study drugs or study participation. The information will be recorded on the appropriate eCRF page. However, these procedures should not interfere with the initiation of any new treatments or therapeutic modalities that the investigator feels are necessary to treat the subject's condition. Following the discontinuation of the study drugs, the subject will be treated in accordance with the investigator's clinical judgment, irrespective of whether or not the subject decides to continue participation in the study.

5.7 Study Drugs

Venetoclax manufactured by AbbVie will be administered PO, QD for each 28-day cycle beginning on Day 1 and should be taken at approximately the same time each day. Subjects will be trained to self-administer venetoclax (refer to Operations Manual Section 4.1).

Pomalidomide will be administered PO, QD on Days 1 to 21 for each repeated 28-day cycle. Subjects will be trained to self-administer pomalidomide (refer to Operations Manual Section 4.1).

Subject dosing will be recorded in a subject dosing diary. The subject will be instructed to return all drug containers (even if empty) to the study site personnel at each study visit. The study site personnel will document compliance.

AbbVie will not supply drugs other than venetoclax and pomalidomide, if applicable. Dexamethasone and any other noninvestigational medicinal products (standard of care) must be obtained commercially.

Pomalidomide will be dispensed as noninvestigational medical product in the US under the Pomalyst REMS program. Further information can be found at: www.CelgeneRiskManagement.com.

Study drug information is presented in Table 2.

Table 2. Study Drug Information

Investigational Product	Manufacturer	Mode of Administration	Dosage Form	Strength
Venetoclax	AbbVie	Oral	Film-coated tablet	100 mg
Pomalidomide	Celgene	Oral	Capsules	1, 3, and/or 4 mg

Venetoclax will be packaged in bottles with quantities sufficient to accommodate study design. Pomalidomide will be packaged in bottles or blisters in cartons (local marketed product or overlabeled product with a clinical study label). Each kit will be labeled per local requirements and this label must remain affixed to the kit. Upon receipt, study drugs should be stored as specified on the label and kept in a secure location. Each kit will contain a unique kit number. This kit number is assigned to a subject via Interactive Response Technology (IRT) and encodes the appropriate study drugs to be dispensed at the subject's corresponding study visit. Study drugs must not be dispensed without contacting the IRT system. Study drugs will only be used for the conduct of this study.

Information on the investigational products is provided in Operations Manual Section 4.

5.8 Randomization/Drug Assignment

This is an open-label study. There is no randomization for this study. All subjects will be assigned a unique identification number by the IRT at the screening visit following signed consent and completion of at least 1 study-required procedure. For subjects who rescreen, the screening number assigned by the IRT at the initial screening visit should be used.

5.9 Protocol Deviations

The investigator is responsible for complying with all protocol requirements, written instructions, and applicable laws regarding protocol deviations. Protocol deviations are prohibited except when necessary to eliminate an immediate hazard to study subjects. If a protocol deviation occurs (or is identified), the investigator is responsible for notifying IEC/IRB, regulatory authorities (as applicable), and AbbVie.

6 SAFETY CONSIDERATIONS

6.1 Complaints and Adverse Events

Complaints

A complaint is any written, electronic, or oral communication that alleges deficiencies related to the physical characteristics, identity, quality, purity, potency, durability, reliability, safety, effectiveness, or performance of a product. Complaints associated with any component of this investigational product must be reported to AbbVie.

Medical Complaints/Adverse Events and Serious Adverse Events

An AE is defined as any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE 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.

An AE 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 AE. Worsening in severity of an AE should be reported as a new AE. Laboratory abnormalities and changes in vital signs are considered to be AEs only if they result in discontinuation from the study, necessitate therapeutic medical intervention, meet protocol-specified criteria (see Section 6.4 regarding toxicity management), and/or if the investigator considers them to be AEs.

The investigators will monitor each subject for clinical and laboratory evidence of AEs on a routine basis throughout the study. The investigator will assess and record any AE in detail including the date of onset, event diagnosis (if known), or sign/symptom, severity, time course (end date, ongoing, intermittent), relationship of the AE to study drug, and any action(s) taken. For SAEs considered as having "no reasonable possibility" of being associated with study drug, the investigator will assign "other" as the cause of the event. For AEs to be considered intermittent, the events must be of similar nature and severity. AEs, whether in response to a query, observed by site personnel, or reported spontaneously by the subject, will be recorded.

All AEs will be followed to a satisfactory conclusion.

An elective surgery/procedure scheduled to occur during a study will not be considered an AE if the surgery/procedure is being performed for a pre-existing condition and the surgery/procedure was preplanned before 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 being done will be considered an AE.

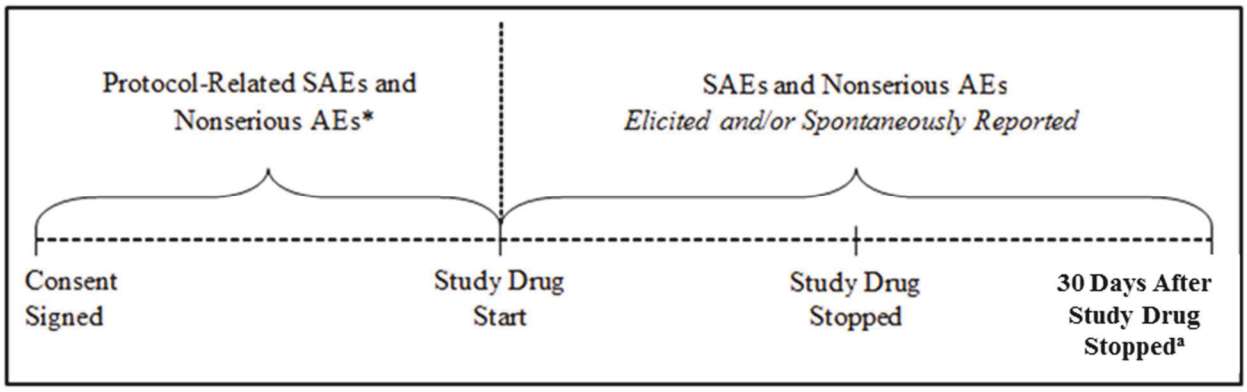
If an AE meets any of the following criteria, it is to be reported to AbbVie or contract research organization (as appropriate) as an SAE within 24 hours of the site being made aware of the SAE:

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 subject. Disability is not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle).
Important Medical Event Requiring Medical or Surgical Intervention to Prevent Serious Outcome	An important medical event that may not be immediately life-threatening or result in death or hospitalization but, based on medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent any of the outcomes listed above (i.e., death of subject, life threatening, hospitalization, prolongation of hospitalization, congenital anomaly, or persistent or significant disability/incapacity). Additionally, any elective or spontaneous abortion or stillbirth is considered an important medical event. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Hospitalization of a subject to allow observation and management (e.g., intravenous [IV] hydration) for the purpose of TLS prophylaxis will not be captured as an SAE unless there is an additional reason for hospitalization or an additional criterion for seriousness other than hospitalization (e.g., abnormal postdose TLS laboratories that necessitate therapeutic medical intervention, etc.).

All AEs reported from the time the study drugs are administered until 30 days after discontinuation of any study drug will be collected whether solicited or spontaneously reported by the subject. In addition, protocol-related SAEs and nonserious AEs will be collected from the time the subject signed the study-specific informed consent.

All AEs should be followed until resolution, return to baseline, or determined to be stable per the investigator.



AE = adverse event; SAE = serious adverse event

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

a. 30 Days after the last dose of venetoclax.

Adverse Event Severity and Relationship to the Study Drugs

The investigators will rate the severity of each AE according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. If a reported AE increases in severity, the initial AE should be given an outcome date and a new AE must be reported on a different onset date than the end date of the previous AE to reflect the change in severity. The dates on the AEs cannot overlap. For all reported SAEs that increase in severity, the supplemental eCRFs also need to be updated to reflect any changes due to the increase in severity.

For AEs not captured by the NCI CTCAE, the following should be used:

Grade 1	The AE is transient and easily tolerated by the subject (mild).
Grade 2	The AE causes the subject discomfort and interrupts the subject's usual activities (moderate).
Grade 3	The AE causes considerable interference with the subject's usual activities and may be incapacitating (moderate to severe).
Grade 4	The AE is life-threatening and requires urgent intervention (severe).
Grade 5	The AE resulted in death of the subject (severe).

The investigators will use the following definition to assess the relationship of each AE to the use of the study drugs:

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

For causality assessments, events assessed as having a reasonable possibility of being related to the study drug will be considered "associated." Events assessed as having no reasonable possibility of being related to study drug will be considered "not associated." In addition, when the investigator has not reported causality or deemed it not assessable, AbbVie will consider the event associated.

If an SAE is assessed as having no reasonable possibility of being related to study drug per the investigator's opinion, an "other" cause of event must be provided by the investigator for the SAE.

Adverse Events of Special Interest

AEs will be monitored throughout the study to identify any of special interest that may indicate a trend or risk to subjects. The following AEs of special interest (serious and nonserious) are to be entered into the electronic data capture system immediately (i.e., no more than 24 hours after the site becoming aware of the event):

- TLS

Dose-Limiting Toxicity

DLTs (as defined Section 6.5) will be assessed during the first cycle of venetoclax and pomalidomide dosing. Toxicities occurring after the first cycle of dosing will also be evaluated by the investigator and the AbbVie TA MD and taken into consideration for dose-escalation decisions.

Pregnancy

While not an AE, pregnancy in a study subject must be reported to AbbVie within 1 working day of the site becoming aware of the pregnancy. If a pregnancy occurs in a study subject or in the partner of a study subject, information regarding the pregnancy and the outcome will be collected. In the event of pregnancy occurring in a subject's partner during the study, written informed consent from the partner must be obtained before collection of any such information. A separate consent will be provided by AbbVie for this purpose. Pregnancies in study subject's partners will be collected from the date of the first dose through 30 days following the last dose of study drug.

The pregnancy outcome of an elective or spontaneous abortion, stillbirth, or congenital anomaly is considered an SAE and must be reported to AbbVie within 24 hours of the site becoming aware of the event.

Deaths

Deaths that occur during the protocol-specified AE reporting period that are attributed by the investigator solely to progression of MM should be recorded only on the study completion eCRF with

disease progression as the reason for discontinuation and not on the AE eCRF. All other on-study deaths, regardless of relationship to study drug, must be recorded on the AE eCRF and immediately reported to the sponsor.

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

Lack of Efficacy or Worsening of Disease

Events that are clearly consistent with the expected pattern of progression of the underlying disease, including transformation to a more aggressive histology, are also considered an expected outcome for this study and will NOT be recorded as AEs. These data will be captured as efficacy assessment data only. If there is any uncertainty as to whether an event is due to disease progression, the event should be reported as an AE.

6.2 Recording Data and Analyses of Safety Findings

AEs will be coded using the Medical Dictionary for Regulatory Activities. Details on the statistical analyses for safety will be provided in the SAP.

6.3 Reporting Adverse Events and Intercurrent Illnesses

In the event of an SAE, whether associated with study drug or not, the investigator will notify clinical pharmacovigilance within 24 hours of the site being made aware of the SAE by entering the SAE data into the electronic data capture system. SAEs that occur before the site has access to the RAVE® system, or if RAVE is not operable, should be documented on the SAE nonCRF forms and emailed (preferred route) or faxed to clinical pharmacovigilance within 24 hours of the site being made aware of the SAE (refer to Appendix L for safety reporting contact information).

6.4 Toxicity Management

Venetoclax: Venetoclax could lead to suppression of lymphocytes. In addition, clinically significant neutropenia may also be observed. Both lymphopenia and neutropenia could increase the risk for infections, including opportunistic infections. Venetoclax treatment can also lead to TLS. Subjects will be managed based on their TLS risk factors as detailed below.

Pomalidomide: Pomalidomide could lead to neutropenia, anemia, and thrombocytopenia. Among the nonhematologic toxicities, venous and arterial thromboembolism, hepatotoxicity, hypersensitivity reactions, dizziness and confusional state, and neuropathy have been reported with pomalidomide.

Dexamethasone: Dose modifications or discontinuation may be necessary for gastrointestinal events, acute pancreatitis, neurologic disorders or muscle weakness, and edema or hyperglycemia.

Subjects will be monitored for these events throughout the study and treatment may be discontinued or adjusted as appropriate. Dose modifications and treatment guidelines for drug-related toxicities (venetoclax, pomalidomide, or dexamethasone) are provided in Appendix I. If an investigator considers it necessary, subjects who interrupt study therapy for longer than 28 days may be discontinued from further study therapy.

Prophylaxis and Management of Tumor Lysis Syndrome

Venetoclax and pomalidomide can cause rapid reduction in tumor and thus poses a risk for TLS. Changes in electrolytes consistent with TLS that require prompt management can occur as early as 6 to 8 hours following the first dose of venetoclax (Appendix H). Definitions of laboratory TLS and clinical TLS are provided in the Appendix G (Howard grading classification).

There is a potential for TLS in subjects affected by hematologic malignancies. Depending on the specific tumor type, risk factors may include one or more of the following: bulky disease or high tumor burden, elevated pretreatment lactate dehydrogenase levels, elevated leukocyte count, renal insufficiency, and dehydration.

MM subjects with high tumor burden (e.g., high bone marrow plasma cell infiltration, plasma cell leukemia, or bulky plasmacytomas), rapidly increasing M-protein or light chains or high proliferative activity, plasmablastic morphology, or compromised renal function (CrCL < 50 mL/minute) may be at higher risk of developing TLS.[11] Additionally, subjects with t(11;14) and high bone marrow plasma cell infiltration or a significant number of circulating plasma cells appear to have an increased risk for TLS when treated with venetoclax.

Consider TLS prophylaxis with oral hydration (at least 1 to 2 L, as tolerable) in all subjects at least 72 hours before the first day of dosing with venetoclax and pomalidomide. Prophylaxis with uric acid reducing agents may be required for subjects with high uric acid levels. Monitor for clinical and laboratory evidence of TLS during treatment (Appendix G) and manage abnormalities in serum creatinine, uric acid, and electrolytes promptly according to institutional guidelines (guidance also available in Appendix H).

For subjects with t(11;14) and > 50% bone marrow plasma cell infiltration or CrCL < 50 mL/minute, oral hydration as aforementioned is required and chemistry laboratory tests (phosphate, potassium, calcium, uric acid, creatinine, lactate dehydrogenase, and AST at a minimum) should be done at approximately 6 hours after the first dose with venetoclax. Consider uric acid-lowering drugs in subjects at higher risk for TLS. More intensive measures (e.g., IV hydration, frequent monitoring of laboratory values, hospitalization, etc.) should be considered at the investigator's discretion or in accordance with institutional guidelines. All TLS prophylaxis measures should be appropriately recorded in the eCRF.

In case of evidence of TLS, dosing with venetoclax should be interrupted. Drug interruption for up to 72 hours following transient (i.e., lasting < 48 hours) chemical changes and laboratory TLS will not require a dose reduction. If the TLS has not resolved within 72 hours, then a dose reduction should be considered. The subject may be allowed to re-escalate to the final dose based on a risk assessment (including tumor burden status). If active correction of electrolytes was performed, the first dose of

venetoclax should only be given when electrolytes have been stable without additional treatment for at least 24 hours.

If a subject meets criteria for clinically significant laboratory or clinical TLS, the subject must dose reduce (refer to the Appendix I, as applicable). The subject may be allowed to re-escalate to the intended cohort dose based on a risk assessment (including tumor burden status) after discussion between the investigator and the TA MD.

Additional TLS prophylaxis and monitoring (more frequent laboratory sample collection, IV hydration, dose ramp-up requirements, etc.) can be implemented as needed based upon review of safety data (e.g., if a higher than expected rate of laboratory TLS is observed or cases of clinical TLS are identified).

Management of Neutropenia and Other Cytopenias

Venetoclax and pomalidomide can cause cytopenias including clinically significant neutropenia and lymphopenia that can increase risk for serious infection including opportunistic infections. Subjects with a history of neutropenia who have received multiple prior therapies and/or have significant bone marrow involvement may be at a particularly high risk. Grade 3 or 4 neutropenia has been reported in subjects treated with venetoclax and pomalidomide.

Complete blood counts should be monitored throughout the treatment period. Anti-infective prophylaxis and granulocyte-colony stimulating factor (G-CSF) for management of neutropenia should be considered per institutional guidelines. Subjects should receive anti-infective prophylaxis (e.g., amoxicillin/clavulanic acid or levofloxacin or equivalent per institutional guidelines) when Grade 4 neutropenia develops (ANC < 500 cells/µL) and continued until the neutropenia improves to Grade 3 or better (ANC > 500 cells/µL). Please refer to the Appendix I for guidance on dose reductions or interruptions related to venetoclax or pomalidomide toxicities.

Management of Decrease in Spermatogenesis

Venetoclax may cause a decrease in spermatogenesis. Male subjects considering preservation of fertility should bank sperm before initiating treatment with venetoclax.

Embryo-Fetal Toxicity

Pomalidomide is contraindicated in pregnancy. Pomalidomide is a thalidomide analog; thalidomide is a known human teratogen that causes severe life-threatening birth defects. Refer to the pomalidomide package insert for details.[10]

Venous and Arterial Thromboembolism

Deep venous thrombosis, pulmonary embolism, myocardial infarction, and stroke occur in subjects with multiple myeloma treated with pomalidomide. Antithrombotic prophylaxis is recommended for subjects with a history of cardiovascular disease or per investigator discretion. Refer to the pomalidomide package insert for details.[10]

Management of Infection

Subjects should receive anti-infective prophylaxis (e.g., amoxicillin/clavulanic acid or levofloxacin or equivalent per institutional guidelines) at least during the first 90 days of study and upon disease

progression for at least 30 days unless contraindicated per investigator discretion. Furthermore, subjects deemed at high risk of infection should receive immunoglobulin replacement therapy (i.e., IVIG) per institutional guidelines or at the investigator's discretion.

The use of antibiotics that are moderate or strong CYP3A inhibitors should be avoided or used with caution and with appropriate venetoclax dose modification (refer to Appendix I) as per protocol.

All subjects receiving venetoclax should be closely monitored for infections and in the event of a Grade ≥ 3 or serious infection, treatment with venetoclax should be interrupted and upon resolution, treatment can be either resumed at a reduced dose or discontinued, depending on investigator's clinical judgment.

Please refer to Table 9 and Table 10 for guidance on dose interruptions and/or reductions related to venetoclax toxicities.

Potential for drug-drug interactions should be considered. Please refer to Appendix J for a description of prohibited and cautionary medications.

Management of Other Toxicities

If other events occur that are related to venetoclax or pomalidomide, the investigator may interrupt or dose reduce venetoclax and/or pomalidomide, as appropriate (refer to Appendix I).

Pomalidomide must be permanently discontinued for angioedema, skin exfoliation, bullae, or any other severe dermatologic reaction.

All subjects should be monitored for new onset hematologic, hepatic, and renal toxicities with dose delay or reduction as appropriate. Please follow local, approved product label or applicable summary of product characteristics[12] for monitoring guidelines for pomalidomide or Appendix I for venetoclax.

Dexamethasone dose modifications or discontinuation may be necessary for Grades 1 to 2 gastrointestinal disorders that do not respond to appropriate treatment, > Grade 3 gastrointestinal events, acute pancreatitis, > Grade 2 neurologic disorders or muscle weakness, and ≥ Grade 3 edema or hyperglycemia (refer to Appendix I).

6.5 Dose-Limiting Toxicity

DLTs for dose-escalation purposes will be determined during the first cycle (28 days) of study drug administration at the designated cohort dose. AEs occurring following Cycle 1 will also be evaluated by the investigator and the AbbVie TA MD and may be considered as dose limiting. Any of the following events that concur with the administration of venetoclax, pomalidomide, or dexamethasone, which cannot be attributed by the investigator to a clearly identifiable cause such as disease progression, concurrent illness, or concomitant medication, will be considered a DLT:

- Grade 4 neutropenia lasting more than 7 days
- Grade 3 or Grade 4 neutropenia with fever
- Grade 4 thrombocytopenia that has not recovered before the start of the next cycle of therapy

- Grade 2 or higher bleeding associated with Grade ≥ 3 thrombocytopenia
- Unexpected Grade 2 or higher toxicity which requires dose modification or delay of ≥ 1 week
- Clinical TLS
- Laboratory TLS if the metabolic abnormalities are deemed clinically significant by the investigator
- All other Grades 3, 4, or 5 AEs with the exception of the following:
    - Grades 3, 4 afebrile neutropenia
    - Grade 3 thrombocytopenia that does not result in bleeding
    - Grades 3, 4 lymphopenia
    - Grades 3, 4 leukopenia
    - Grade 3 or 4 hyperuricemia or hypocalcemia or Grade 3 hyperkalemia, if transient (i.e., lasting < 48 hours) and without manifestations of clinical TLS (i.e., creatinine ≥ 1.5 × ULN, cardiac arrhythmias, sudden death, or seizures)
    - Grade 3 fatigue
    - Grade 3 peripheral neuropathy
    - Grade 3 nausea, vomiting, and/or diarrhea that are responsive to treatment
    - Grade 3 hyperglycemia that is controllable with insulin or oral hyperglycemic agents within 24 hours
    - Grade 3 hypertension that is reversible within 24 hours
    - Grade 3 confusion that is reversible within 24 hours
    - Grade 3 or higher local reaction to subcutaneous injections that does not resolve within 24 hours
    - Grade 3 insomnia that is managed with a sedative or reversible within 24 hours
    - Grade 3 edema that is controlled with diuretics or reversible within 24 hours
    - Grade 3 dyspepsia that is managed with histamine 2 blockers/proton pump inhibitors or reversible within 24 hours

Any DLTs observed during the designated cohort dosing period will require a modification of the designated cohort dose as directed per the dose-escalation guidelines (Section 4.1).

Any DLT will require an interruption and possible discontinuation of venetoclax, pomalidomide, and/or dexamethasone. Venetoclax, pomalidomide, and/or dexamethasone may be reintroduced at a reduced dose if the toxicity grade returns to ≤ Grade 1 or to baseline if Grade 2 at study entry.

Drug interruption for up to 72 hours following transient (i.e., lasting < 48 hours) chemical changes and laboratory TLS may be allowed and may not be considered a DLT or require a dose reduction. If the TLS

has not resolved within 72 hours, then a dose reduction should be considered. The subject may be allowed to re-escalate to the final dose based on a risk assessment (including tumor burden status).

Any reduced dose level of venetoclax, pomalidomide, and/or dexamethasone will be defined by AbbVie after discussion between the investigator and the AbbVie TA MD. The dose of venetoclax, pomalidomide, and/or dexamethasone may be increased thereafter as defined by AbbVie after discussion between the investigator and the AbbVie TA MD. The venetoclax dose is not to exceed the highest tolerated dose level. All decisions regarding continued dosing for individual subjects will be medically managed by the investigator, in conjunction with the AbbVie TA MD, as appropriate. These decisions will be driven by the definition of DLTs as described above.

6.6 Product Complaints

A product complaint is any complaint related to the biologic or drug component of the product or to the medical device component(s).

For a product, this may include, but is not limited to, damaged/broken product or packaging, product appearance whose color/markings do not match the labeling, labeling discrepancies/inadequacies in the labeling/instructions (e.g., printing illegible), missing components/product, device not working properly, or packaging issues.

Product complaints concerning the investigational product and/or device must be reported to AbbVie within 24 hours of the study site's knowledge of the event. Product complaints occurring during the study will be followed up to a satisfactory conclusion.

7 STATISTICAL METHODS & DETERMINATION OF SAMPLE SIZE

7.1 Statistical and Analytical Plans

Complete and specific details of the statistical analysis will be described and fully documented in the SAP. All statistical analyses will be performed using SAS version 9.4 or newer (SAS Institute Inc., Cary, North Carolina, USA).

7.2 Determination of Sample Size

Approximately 60 subjects will be enrolled into this 2-part study.

Part 1, Dose Escalation

Part 1 will enroll approximately 3 to 6 subjects per cohort using a BOIN design, resulting in a total of 6 to 12 subjects.

Part 2, Dose Expansion

Part 2 will enroll approximately 50 subjects.

Arm A: t(11;14)-Positive

The historical ORR for pomalidomide + dexamethasone is 35%.[13,14] By adding venetoclax to this combination, an ORR of 70% is clinically meaningful for t(11;14)-positive subjects. The sample size for Arm A will be approximately 23 subjects. Allowing for a maximum 1-sided type 1 error rate of 0.025 and assuming an ORR of 35% from the historical data, 23 subjects will provide 90% power if the true ORR for t(11;14)-positive subjects treated with venetoclax + pomalidomide + dexamethasone is 70%.

Arm B: t(11;14)-Negative

The historical ORR for pomalidomide + dexamethasone is 35%. By adding venetoclax to this combination, an ORR of 60% is clinically meaningful for t(11;14)-negative subjects. The sample size for Arm B will be approximately 27 subjects. Allowing for a maximum 1-sided type 1 error rate of 0.1 and assuming an ORR of 35% from the historical data, 27 subjects will provide 90% power if the true ORR for t(11;14)-negative subjects treated with venetoclax + pomalidomide + dexamethasone is 60%.

7.3 Definition for Analysis Populations

The Full Analysis Set (FAS) includes all subjects who received at least 1 dose of study drug. The FAS will be used for all safety, PK, efficacy and baseline analyses.

7.4 Statistical Analyses for Efficacy

Exact tests for H_0: ORR ≤ 35% and H1: ORR > 35% with 1-sided significance levels 0.025 and 0.1 for Arms A and B, respectively, will be performed. Point estimates and exact 95% confidence intervals of ORR for each of the 2 arms (Arms A and B) will be calculated. Details of the analysis methods for all efficacy endpoints will be provided in the SAP.

7.5 Statistical Analyses for Safety

Details pertaining to the safety analyses can be found in the SAP.

7.6 Statistical Analyses for Pharmacokinetics

Details pertaining to the PK analyses can be found in the SAP.

7.7 Study Interim Analysis

Interim analyses may be conducted when adequate data from approximately 10 and 16 subjects are available from Arms A and B, respectively. Details pertaining to the safety analyses can be found in the SAP.

7.8 Safety Review Committee

A Safety Review Committee (SRC) will periodically review safety data across all studies with venetoclax in MM that do not have a study-specific independent monitoring committee. This review committee will be responsible for periodic, regular reviews to assess the safety of the interventions during the study. A separate charter will be prepared outside of the protocol outlining the SRC member responsibilities, frequency of data reviews, and relevant data to be assessed.

8 ETHICS

8.1 Independent Ethics Committee/Institutional Review Board

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IEC/IRB for review and approval. Approval of both the protocol and the informed consent form(s) must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IEC/IRB before the changes are implemented to the study. In addition, all changes to the consent form(s) will be IEC-/IRB-approved.

8.2 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, operations manual, International Council for Harmonisation (ICH) guidelines, applicable regulations and guidelines governing clinical study conduct, and the ethical principles that have their origin in the Declaration of Helsinki. Responsibilities of the investigator are specified in Appendix B.

8.3 Subject Confidentiality

To protect subjects' confidentiality, all subjects and their associated samples will be assigned numerical study identifiers or "codes." No identifiable information will be provided to AbbVie.

9 SOURCE DOCUMENTS AND CASE REPORT FORM COMPLETION

The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be attributable, legible, contemporaneous, original, accurate, and complete to ensure accurate interpretation of data. Clinical site monitoring is conducted to ensure that the rights and well-being of human subjects are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol, ICH Good Clinical Practice (GCP), and applicable local regulatory requirement(s).

10 DATA QUALITY ASSURANCE

AbbVie will ensure that the clinical trial is conducted and data are generated, documented, and reported in compliance with the protocol, ICH GCP, and applicable regulatory requirements.

11 COMPLETION OF THE STUDY

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

12 REFERENCES

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APPENDIX A. STUDY SPECIFIC ABBREVIATIONS AND TERMS

Abbreviation	Definition
AE	adverse event
ALT	alanine aminotransferase
AML	acute myeloid leukemia
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the plasma concentration versus time curve (AUC)
AUC_{0-24}	AUC from time 0 to 24 hours postdose
BCL	B-cell lymphoma
BCL-w	B-cell lymphoma-Walter and Eliza Hall Institute
BCL-X_L	B-cell lymphoma – extra large
BCRP	breast cancer resistance protein
BOIN	Bayesian optimal interval
CDK	cyclin-dependent kinase
CLL	chronic lymphocytic leukemia
C_{max}	maximum concentration
CR	complete remission
CrCL	creatinine clearance
CRF	Case Report Form
CRi	complete remission with incomplete blood count recovery
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
FAS	Full Analysis Set

FFPE	fixed formalin paraffin embedded
FISH	fluorescent in situ hybridization
FLC	free-light chain
GCP	Good Clinical Practice
G-CSF	granulocyte-colony stimulating factor
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HDAC	histone deacetylase
HR	hazard ratio
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
Ig	immunoglobulin
IHC	immunohistochemistry
IMiD	immunomodulatory drug
IMWG	International Myeloma Working Group
INR	international normalized ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
IV	intravenous
IVIG	intravenous immunoglobulin
K_i	inhibition rate constant
MCL	myeloid-cell leukemia
MM	multiple myeloma
M-protein	monoclonal-protein
MR	minimal response
MRD	minimal residual disease
MRI	magnetic resonance imaging
NCI	National Cancer Institute
NHL	non-Hodgkin's lymphoma
OATP	organic anion-transporting polypeptide
ORR	overall response rate
OS	overall survival
PD	progressive disease
PET	positron emission tomography

PFS	progression-free survival
P-gp	P-glycoprotein
PI	proteasome inhibitor
PK	pharmacokinetic(s)
PO	oral
POEMS	polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes
PR	partial response
PT	prothrombin time
QD	once daily
qPCR	quantitative polymerase chain reaction
qw	once weekly
REMS	risk evaluation and mitigation strategies
RNA	ribonucleic acid
R/R	relapsed or refractory
SAE	serious adverse event
SAP	Statistical Analysis Plan
sCR	stringent complete response
SD	stable disease
SLL	small lymphocytic lymphoma
SRC	Safety Review Committee
SUSAR	Suspected Unexpected Serious Adverse Reaction
TA MD	Therapeutic Area Medical Director
TLS	tumor lysis syndrome
T_{max}	time to maximum concentration
TTP	time-to-progression
ULN	upper limit of normal
VGPR	very good partial response

APPENDIX B. RESPONSIBILITIES OF THE INVESTIGATOR

Protocol M16-085: Venetoclax and Pomalidomide

Protocol Date: 24 June 2020

Clinical research studies sponsored by AbbVie are subject to the International Council for Harmonisation (ICH) Good Clinical Practices (GCP) and local regulations and guidelines governing the study at the site location. In signing the Investigator Agreement, the investigator is agreeing to the following:

1. Conducting the study in accordance with ICH GCP, the applicable regulatory requirements, current protocol and operations manual, and making changes to a protocol only after notifying AbbVie and the appropriate Institutional Review Board (IRB)/Independent Ethics Committee (IEC), except when necessary to protect the subject from immediate harm.
1. Personally conducting or supervising the described investigation(s).
2. Informing all subjects, or persons used as controls, that the drugs are being used for investigational purposes and complying with the requirements relating to informed consent and ethics committees (e.g., IEC or IRB) review and approval of the protocol and its amendments.
3. Reporting complaints that occur in the course of the investigation(s) to AbbVie.
4. Reading the information in the Investigator's Brochure/safety material provided, including the instructions for use and the potential risks and side effects of the investigational product(s).
5. Informing all associates, colleagues, and employees assisting in the conduct of the study about their obligations in meeting the above commitments.
6. Maintaining adequate and accurate records of the conduct of the study, making those records available for inspection by representatives of AbbVie and/or the appropriate regulatory agency, and retaining all study-related documents until notification from AbbVie.
7. Maintaining records demonstrating that an ethics committee reviewed and approved the initial clinical protocol and all of its amendments.
8. Reporting promptly, all changes in the research activity and all unanticipated problems involving risks to human subjects or others, to the appropriate individuals (e.g., coordinating investigator, institution director) and/or directly to the ethics committees and AbbVie.
9. Providing direct access to source data documents for study-related monitoring, audits, IEC/IRB review, and regulatory inspection(s).

Signature of Principal Investigator	Date

Name of Principal Investigator (printed or typed)

APPENDIX C. LIST OF PROTOCOL SIGNATORIES

Name	Title	Functional Area
[redacted]	[redacted]	Medical Writing
		Clinical Hematology Oncology
		Statistics
		Clinical Pharmacology and Pharmacometrics
		Clinical Program Development

APPENDIX D. ACTIVITY SCHEDULE

The following table shows the required activities for this study. The individual activities are described in detail in Appendix E.

Study Activities

Activity	Screening	Cycle 1				Cycles 2 to 3				Cycles 4+		Response Confirmation[a]	End-of-Treatment	Safety Follow-Up[b]
	Day –21 to Day –1	Day 1	Day 8	Day 15	Day 22	Day 1	Day 8	Day 15	Day 22	Day 1	Days 8, 15, 22			30-Day
INTERVIEWS & QUESTIONNAIRES														
Informed consent	✓													
Confirm eligibility	✓	✓												
Medical/oncology/surgical history	✓	✓												
History of/subsequent myeloma therapy	✓												✓	✓
Adverse event assessment	✓	✓	✓	✓	✓	✓		✓		✓			✓	✓
Prior/concomitant therapy	✓	✓	✓	✓	✓	✓		✓		✓			✓	✓
ECOG performance status	✓	✓				✓				✓			✓	
Clinic visit	✓	✓	✓	✓	✓	✓		✓		✓		✓	✓	✓
IMWG response assessment		✓				✓				✓		✓	✓	
LOCAL LABORATORY TESTS & EXAMINATIONS														
Complete physical examination	✓													
Symptom-directed physical examination		✓	✓			✓				✓			✓	✓
Height (screening only) and weight	✓	✓	✓	✓	✓	✓				✓			✓	✓
Vital signs	✓	✓	✓	✓	✓	✓		✓		✓			✓	✓
12-Lead electrocardiogram	✓					✓							✓	

Activity	Screening	Cycle 1				Cycles 2 to 3				Cycles 4+		Response Confirmation[a]	End-of-Treatment	Safety Follow-Up[b]
	Day –21 to Day –1	Day 1	Day 8	Day 15	Day 22	Day 1	Day 8	Day 15	Day 22	Day 1	Days 8, 15, 22			30-Day
Hematology	✓	✓	✓	✓	✓	✓		✓		✓			✓	✓
Clinical chemistry	✓	✓	✓	✓	✓	✓		✓		✓			✓	✓
TLS panel[c]		✓												
Serum pregnancy test	✓													
Urine pregnancy test[d]		✓	✓	✓	✓	✓		✓		✓	✓		✓	✓
Coagulation panel	✓	✓												
Amylase, lipase	✓													
Skeletal survey	✓	✓[e]				✓[e]				✓[e]		✓[e]	✓[e]	
Plasmacytoma evaluation	✓	✓[f]				✓[f]				✓[f]		✓[f]	✓[f]	
CENTRAL LABORATORY TESTS														
Serum β2 microglobulin	✓													
Viral serologies	✓													
Serum protein immunofixation	✓	✓				✓				✓		✓	✓	
Serum protein electrophoresis	✓	✓				✓				✓		✓	✓	
Serum quantitative immunoglobulins	✓	✓				✓				✓			✓	

Activity	Screening	Cycle 1				Cycles 2 to 3				Cycles 4+		Response Confirmation[a]	End-of-Treatment	Safety Follow-Up[b]
	Day –21 to Day –1	Day 1	Day 8	Day 15	Day 22	Day 1	Day 8	Day 15	Day 22	Day 1	Days 8, 15, 22			30-Day
Serum free light chain	✓	✓[g]				✓[g]				✓[g]		✓ CR/sCR	✓[g]	
Urine protein immunofixation	✓	✓				✓				✓		✓[h]	✓[h]	
Urine protein electrophoresis	✓	✓				✓				✓		✓[h]	✓[h]	
Bone marrow aspirate (including MRD)[i]	✓											✓ CR/sCR	✓ opt	
Bone marrow core biopsy	✓											✓ CR/sCR	✓ opt	
Venetoclax pharmacokinetic sample		✓		✓		✓ Cycle 2 only				✓ Cycles 4, 6, 8 only				
Pomalidomide pharmacokinetic sample		✓		✓										
Biomarker research blood sample		✓				✓				✓ Cycles 4, 5, 9 only			✓	
Optional biomarker research blood sample (expansion phase only)		✓				✓ Cycle 3 only							✓	
Rx TREATMENT														
Venetoclax		Days 1 through 28 of each cycle												
Pomalidomide		Days 1 through 21 of each cycle												

Activity	Screening	Cycle 1				Cycles 2 to 3				Cycles 4+		Response Confirmation[a]	End-of-Treatment	Safety Follow-Up[b]
	Day –21 to Day –1	Day 1	Day 8	Day 15	Day 22	Day 1	Day 8	Day 15	Day 22	Day 1	Days 8, 15, 22			30-Day
Dexamethasone		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓			
Subject diary		✓	✓	✓	✓	✓		✓		✓			✓	
Pomalidomide education and counseling guidance document and pomalidomide information sheet[j]		✓				✓				✓				

CR = complete response; ECOG = Eastern Cooperative Oncology Group; IMWG = International Myeloma Working Group; MRD = minimal residual disease; PFS = progression-free survival; sCR = stringent complete response; TLS = tumor lysis syndrome; VGPR = very good partial response

a. Required for every response of ≥ VGPR AND if subject is to be discontinued for progressive disease (i.e., progressive disease must be confirmed).

b. The safety follow-up visit will occur approximately 30 days after the last dose of study drug or before start of subsequent treatment, whichever occurs first.

c. For subjects with t(11;14) and > 50% bone marrow plasma cell infiltration or creatinine clearance < 50 mL/minute, TLS laboratory samples should be collected at approximately 6 hours after the first dose with venetoclax.

d. Females of childbearing potential with regular or no menstrual cycles must have pregnancy tests weekly for first month and then monthly. Females of childbearing potential with irregular menstrual cycles must have pregnancy tests weekly for the first month and then every 14 days while taking pomalidomide, at end-of-treatment, and 14 and 28 days following the last dose of pomalidomide.

e. If clinically indicated.

f. Performed during treatment only to confirm a minimal response or better, or to confirm progressive disease, or as clinically indicated.

g. Collect only for subjects without measurable M-protein in screening serum or urine.

h. Urine protein electrophoresis and urine immunofixation collection is mandatory for confirmation of VGPR, CR, and sCR, regardless of whether urine M-protein was measurable at baseline.

i. An MRD assessment will be required for every response of ≥ VGPR AND if subject is to be discontinued for progressive disease AND 6 and 12 months post-confirmation of CR/sCR for subjects who have maintained this response.

j. Pomalidomide education and counseling guidance document for each gender as well as pomalidomide information sheet must be completed and signed before starting pomalidomide and each time the subject receives a new supply of pomalidomide.

APPENDIX E. STUDY PROCEDURES

Subject Information and Informed Consent

The investigator or his/her representative will explain the nature of the study to the subject and answer all questions regarding the study. Prior to any study-related screening procedures being performed on the subject or any medications being discontinued by the subject in order to participate in this study, the informed consent statement will be reviewed, signed, and dated by the subject, the person who administered the informed consent, and any other signatories according to local requirements. Subjects may need to sign an assent document or other simplified version of the informed consent form where required by an Independent Ethics Committee (IEC)/Institutional Review Board (IRB) and/or local laws and regulations. A copy of the signed informed consent will be given to the subject and the original will be placed in the subject's medical record. An entry must also be made in the subject's dated source documents folder to confirm that informed consent was obtained before any study-related procedures were performed and that the subject received a signed copy.

Information regarding benefits for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the study can be found in the informed consent form.

Samples for optional pharmacogenetic analyses will only be collected if the subject has voluntarily signed and dated a separate written consent form for pharmacogenetic testing that has been approved by an IRB/IEC after the nature of the testing has been explained and the subject has had an opportunity to ask questions. The separate written consent may be part of the main consent form. If the subject does not consent to the pharmacogenetic testing, the subject will still be allowed to participate in the study.

Medical History

A complete medical history including history of tobacco, alcohol, and drug use will be taken at screening. The subject's medical history will be updated before the first dose of study drug (Cycle 1, Day 1). This updated medical history will serve as the baseline for clinical assessment. A detailed oncology history will also be collected including: histology, date of diagnosis of multiple myeloma (MM), any surgical procedures, and treatments administered (including dates and type of modality).

On Cycle 1, Day 1, any additional medical history observed after signing of the informed consent but before initial study drug administration and not considered related to study-required procedures will be recorded in the subject's medical history.

Eastern Cooperative Oncology Group Performance Status

For all subjects, the Eastern Cooperative Oncology Group (ECOG) performance status will be performed as outlined in Appendix D. Post-screening assessments may be done ≤ 3 days before the scheduled visit.

It is recommended, when possible, a subject's performance status will be assessed by the same person throughout the study. ECOG performance status will be assessed as follows:

Grade	Description
0	Fully active, able to carry on all predisease 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.
5	Dead

Adverse Event Assessment

Please refer to Appendix D.

Physical Examination

A complete physical examination will be performed at screening. The screening physical examination will serve as the baseline for the entire study. Any significant physical examination findings or clinically significant changes from baseline after the first dose will be recorded as adverse events (AEs). All findings, whether related to an AE or part of each subject's medical history, will be captured on the appropriate electronic case report form (eCRF) page.

Symptom-directed physical examinations will be performed as specified in Appendix D; however, at any visit, a symptom-directed physical examination may be performed as deemed necessary by the investigator. The Cycle 1, Day 1 examination is optional if the screening examination is conducted within ≤ 7 days. For other time points, the symptom-directed physical examinations may be done ≤ 3 days before a scheduled visit.

Height and Weight

Height will be measured at the screening visit only. Body weight will be measured at scheduled visits as specified in Appendix D. The subject should wear lightweight clothing and no shoes during weighing.

Vital Signs

Vital sign determinations of systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature will be obtained at visits as specified in Appendix D. In addition, vital signs will be measured as clinically indicated. Blood pressure and pulse rate should be measured after the subject has been sitting for at least 3 minutes and before study drug administration.

12-Lead Electrocardiogram

A 12-lead electrocardiogram (ECG) will be performed at the designated study visits as specified in Appendix D. The ECG should be performed before blood collection. The ECG may be performed up to 7 days before study drug administration on Day 1.

The ECGs will be evaluated by an appropriately trained physician at the site ("local reader"). The local reader from the site will sign and date all ECG tracings and will provide his/her global interpretation as a written comment on the tracing using the following categories:

- Normal ECG
- Abnormal ECG – not clinically significant
- Abnormal ECG – clinically significant

Only the local reader's evaluation of the ECG will be collected and documented in the subject's source folder. The automatic machine reading (i.e., machine-generated measurements and interpretation that are automatically printed on the ECG tracing) will not be collected. Clinically significant findings should be documented on the eCRF.

Clinical Laboratory Tests

Historical results may be used for screening laboratory tests if they are obtained within 21 days before the first dose.

All laboratory testing will be performed by the central or local laboratories. Required tests are listed in Table 3.

Local laboratories will be utilized to process and provide results for clinical laboratory tests allowing for immediate subject medical management. The principal investigator or subinvestigator will review, initial, and date all laboratory results after receipt from the local laboratory. Local laboratory values will be entered by the site directly onto the appropriate eCRF and laboratory normal ranges and certification for the laboratory that is used will be provided to the AbbVie clinical team if the result is clinically significant (i.e., necessitating an immediate treatment or treatment modification).

The blood samples for serum chemistry tests will be collected before study drug intake as specified in Appendix D. The Cycle 1, Day 1 tests are optional if the screening collection was within ≤ 7 days. For other time points, tests may be completed ≤ 7 days before the scheduled visit and must be reviewed before dosing. The baseline laboratory test results for clinical assessment for a particular test will be defined as the last measurement before the initial dose of study drug.

For chemistry laboratory tests performed for tumor lysis syndrome (TLS) prophylaxis and monitoring, refer to Table 3.

For subjects receiving intravenous (IV) hydration for TLS prophylaxis before the first dose, the baseline value will be the last laboratory value before the subject receives IV hydration for TLS prophylaxis. For subjects without IV hydration for TLS prophylaxis before the first dose, the baseline value will be the last laboratory value taken before the first dose of venetoclax.

For cycles with bone marrow assessments, hematology and chemistry laboratory tests should be performed on the same day as the bone marrow assessment whenever possible. If the assessment occurs outside of the hematology and chemistry visit window, then the laboratory tests should be repeated before dosing.

If a laboratory test value is outside the reference range and the investigator considers the laboratory result to be clinically significant, the investigator will:

- repeat the test to verify the out-of-range value;
- follow the out-of-range value to a satisfactory clinical resolution;
- reduce the dose or temporary interruption of study drug; or
- discontinue the subject from the study or require the subject to receive treatment; in this case, the laboratory result will be recorded as an AE.

Table 3. Clinical Laboratory Tests

Hematology	Clinical Chemistry	Other Tests
Hematocrit Hemoglobin White blood cell count Neutrophils Lymphocytes Monocytes Platelet count (estimate not acceptable)	Blood urea nitrogen Creatinine Total bilirubin Direct and indirect bilirubin Alanine aminotransferase (ALT) Aspartate aminotransferase (AST) Alkaline phosphatase Sodium Potassium Calcium Inorganic phosphorus Total protein Glucose Albumin Chloride Bicarbonate Creatinine clearance (Cockcroft-Gault calculation) Uric acid[b] Lactate dehydrogenase	Urine and serum[a] pregnancy human chorionic gonadotropin[c,d] Follicle-stimulating hormone[a,c,e] Viral serologies[a] hepatitis B surface antigen (HBsAg) hepatitis C virus (HCV) antibody (and RNA if HCV antibody is positive) Amylase[a,f] Lipase[a,f] Serum β2 microglobulin[a]
Coagulation		**TLS Chemistry Panel[g]**
Prothrombin time (PT) International normalized ratio (INR) Activated partial thromboplastin time (aPTT)		Creatinine Potassium Calcium Inorganic phosphorus Lactate dehydrogenase Uric acid[b]

RNA = ribonucleic acid; TLS = tumor lysis syndrome

a. Performed only at screening.

b. At room temperature, rasburicase causes enzymatic degradation of the uric acid in blood/plasma/serum samples potentially resulting in spuriously low plasma uric acid assay readings. The following special sample handling procedure must be followed to avoid ex vivo uric acid degradation. Uric acid must be analyzed in plasma. Blood must be collected into prechilled tubes containing heparin anticoagulant. Immediately immerse plasma samples for uric acid measurement in an ice water bath. Plasma samples must be prepared by centrifugation in a precooled centrifuge (4°C). Finally, the plasma must be maintained in an ice water bath and analyzed for uric acid within 4 hours of collection.

c. Females only.

d. Pregnancy testing is not required for females of nonchildbearing potential.

e. If needed to determine postmenopausal status.

f. Repeat if clinically indicated.

g. For subjects with t(11;14) and > 50% bone marrow plasma cell infiltration or creatinine clearance < 50 mL/minute, TLS laboratory samples should be collected at approximately 6 hours after the first dose with venetoclax.

Serum Pregnancy Test

Women of childbearing potential must have 2 negative pregnancy tests before initiating therapy. The first serum pregnancy test should be completed 10 to 14 days before the first dose of study drug and confirmed within 24 hours before the first dose. The subject may not receive study drug until the results have been verified as negative. If the first serum pregnancy test is positive, the subject is considered a screen failure. If the first serum pregnancy test is negative, the subject should complete a urine pregnancy test to determine eligibility.

If the repeat serum pregnancy test is:

- positive, the subject is considered a screen failure;
- negative, the subject can be enrolled into the trial; or
- borderline, the AbbVie Therapeutic Area Medical Director (TA MD) will be consulted.

If the first serum pregnancy test is borderline, the subject should repeat the test to determine eligibility.

If the repeat serum pregnancy test is:

- positive, the subject is considered a screen failure;
- negative, the subject can repeat the serum pregnancy test; or
- borderline, the AbbVie TA MD will be consulted.

Pregnancy testing is not required for females of nonchildbearing potential. Determination of postmenopausal status will be made during the screening period based on the subject's history.

A pregnant or breastfeeding female will not be eligible for participation or continuation in this study.

Urine Pregnancy Test

Urine pregnancy tests for all women of childbearing potential will be performed at visits indicated in Appendix D per recommendations in the pomalidomide package insert[10] and venetoclax IB.[9] Once on treatment, subjects receiving pomalidomide will have subsequent pregnancy tests weekly during the first month then monthly thereafter in females with regular menstrual cycles. For females with irregular menstrual cycles, weekly urine pregnancy testing is required for the first month and then every 14 days while on pomalidomide, at end-of-treatment, and 14 and 28 days following the last dose of pomalidomide. Additional urine pregnancy tests can be done at any visit, as needed.

If the urine pregnancy test (which is performed at the site) is negative, begin or continue dosing. If urine pregnancy test is positive or indeterminate, withhold dosing and perform a serum pregnancy test. Pregnant subjects must discontinue from the study.

Sensitivity of urine test must be ≥ 25 IU/L. Additional measures may be required per local prescribing information.

Coagulation

Prothrombin time (PT) and activated partial thromboplastin time (aPTT)/international normalized ratio (INR) samples will be collected as specified in Appendix D. The coagulation panel should be repeated on Day 1 of each cycle only for subjects taking Vitamin K antagonists or if otherwise clinically indicated.

Viral Serology

Samples will be collected to identify hepatitis B virus (hepatitis B surface antigen [HBsAg]), and hepatitis C virus (HCV) (HCV antibody and ribonucleic acid [RNA] if HCV antibody is positive) as listed in Table 3.

Viral serology samples are to be collected and sent to the central laboratory for testing.

Disease Assessment

For all subjects, disease assessments will be performed as outlined in Appendix D. Disease assessments may be performed approximately 7 days before the scheduled visit.

Analysis of serum protein immunofixation, serum protein electrophoresis, serum quantitative immunoglobulins, serum free-light chains (FLCs), urine protein immunofixation, urine protein electrophoresis, plasmacytoma evaluation (if applicable), skeletal survey, and bone marrow aspirate and biopsy will be utilized for disease assessment. Subjects will be evaluated using the International Myeloma Working Group (IMWG) 2016 criteria for disease response and progression.[15] All local laboratory results must be entered into the eCRF.

Laboratory Tests for Multiple Myeloma

All serum and urine laboratory tests for IMWG assessments must be sent to a certified central laboratory and may also be collected and sent to the local laboratory per the investigator's discretion. IMWG assessments per protocol should not be made using local laboratory values (except for bone marrow and imaging).

Serum protein immunofixation, serum protein electrophoresis, serum quantitative immunoglobulins, serum FLCs, urine protein immunofixation, and urine protein electrophoresis may be performed approximately 7 days before the scheduled visit day.

Serum Protein Electrophoresis, Serum Protein Immunofixation, Serum Quantitative Immunoglobulins

Blood samples for serum protein electrophoresis, serum protein immunofixation, and serum quantitative immunoglobulin testing will be collected as outlined in Table 4. Serum protein electrophoresis and serum immunofixation will be collected for all subjects at baseline and throughout the study until progressive disease (PD) or withdrawal of consent, regardless of serum protein electrophoresis being measurable or monoclonal-protein (M-protein) presence at baseline.

Importantly, the assessment of serum protein electrophoresis M-protein and serum immunofixation at the time of possible VGPR or complete response (CR)/stringent complete response (sCR) is mandatory, even in subjects without measurable values at baseline.

Serum Free Light Chains

Blood samples for serum FLC testing will be collected for all subjects as outlined in Table 4.

Subjects with measurable disease in either serum protein electrophoresis and/or urine protein electrophoresis will be assessed for response only based on these 2 tests and not by the FLC assay. FLC response criteria are only applicable to subjects without measurable disease in the serum or urine protein electrophoresis and to fulfill the requirements of sCR or CR per IMWG criteria.[15]

Urine Protein Immunofixation and Urine Protein Electrophoresis, 24-Hour Urine

Urine samples (24-hour) for urine protein immunofixation and urine protein electrophoresis for M-protein testing will be collected for all subjects as outlined in Table 4. Urine protein electrophoresis and urine immunofixation will be collected for all subjects at baseline and throughout the study until PD or withdrawal of consent, regardless of urine protein electrophoresis being measurable or M-protein presence at baseline.

Importantly, assessment of urine protein electrophoresis M-protein and urine immunofixation at the time of possible very good partial response (VGPR) or CR/sCR is mandatory, even in subjects without measurable values at baseline.

Subjects with measurable disease at baseline by serum protein electrophoresis and urine protein electrophoresis must be followed by both serum protein electrophoresis and urine protein electrophoresis assessment of M-protein for response assessment.

Skeletal Survey

Skeletal survey using conventional radiography will be done at screening. Historical skeletal survey results obtained within 30 days before the first dose may be used for screening. A skeletal survey will be comprised of the following:

- lateral radiograph of skull
- antero-posterior and lateral views of the spine
- antero-posterior views of pelvis, ribs, femora, tibiae, fibulae, humeri, ulnae, and radii

Skeletal surveys should be completed as outlined in Table 4. The same radiological method should be used throughout the study (x-ray, conventional or low dose computed tomography [CT] scan, positron emission tomography [PET]-CT [CT component only], or magnetic resonance imaging [MRI]). After the screening procedure, the skeletal survey should be done while on study only if clinically indicated. The number and location of skeletal and lytic lesions should be recorded on the eCRF. While the subject is on treatment, survey (if done) should record any changes to the number or size of lytic lesions as well as the number and location of any new skeletal or lytic lesions. Changes in measurable lesions over the course of therapy will be assessed using IMWG criteria (Appendix F).[15]

Plasmacytoma Evaluation

Plasmacytoma evaluation via physical examination or imaging (if clinically indicated) should be completed as outlined in Table 4.

CT, PET-CT (CT component only), or MRI (same radiological method should be used throughout study if possible) should be performed in all subjects if clinically indicated at baseline to assess for the presence of extramedullary plasmacytoma. To minimize unnecessary radiation in myeloma subjects where progression is primarily based on serum and urine M-protein, on-study assessments should only be performed if clinically indicated (e.g., pain, concern for disease progression), whether or not present at baseline, to confirm minimal response (MR) or better if plasmacytoma present at baseline, and at the time of CR/sCR assessment.

A sum of the products of the longest diameters and longest perpendicular diameter for all measurable lesions will be calculated at baseline. This sum will be used as the reference for on-study assessments by which to characterize the objective tumor response.

All documented measurable lesions are to be followed throughout the trial. All assessments to be used for tumor response evaluation, including the baseline assessment, must be performed using the same method for repeat assessment. CT and MRI scanning are the preferable methods of assessment. Conventional CT and MRI should be performed with contiguous cuts of 10 mm or less or with cuts of 5 (or 10) mm if spiral CT scanning is used. Imaging-based evaluation is preferred to evaluation by clinical examination. Evaluation by chest x-ray is less preferable than CT or MRI, and should only be used for well-defined lesions surrounded by aerated lung. Clinical examination is only acceptable when lesions are superficial such as a skin nodule or palpable lymph node and the measurements must be properly documented. Ultrasound is not acceptable for documentation of measurable disease.

Duplicate copies of all imaging studies used for tumor response evaluation will be made available for review by AbbVie or designee upon request.

Measurable disease are lesions that can be accurately measured in 2 dimensions and both diameters must be ≥ 20 mm when evaluated by standard CT scanning or ≥ 10 mm when evaluated by spiral CT scanning. Nonmeasurable disease are all other lesions (or sites of disease), including those that are too small (i.e., do not meet above criteria), occur within a previously irradiated area (unless they are documented as new lesions since the completion of radiation therapy), bone lesions, leptomeningeal disease, ascites, pleural or pericardial effusion (exception for effusions documented by cytology as not malignant or present at baseline without progression), lymphangitis cutis/pulmonis, abdominal masses that are not pathologically/cytologically confirmed and followed by imaging techniques, and cystic lesions.

Bone Marrow Aspirate and Biopsy

Bone marrow aspirate and biopsy should be completed as outlined in Table 4. Bone marrow aspirates and biopsies performed as standard of care throughout the study should also be captured on an eCRF.

A sufficient bone marrow aspirate or biopsy must be collected for clinical assessment (pathology) performed by central laboratory as well as for shipment of a portion to AbbVie (or designee) for the biomarker analyses. Samples should be assessed for IWMG first, then split for biomarker analysis.

Assessment of bone marrow for percentage plasma cells is required within 21 days before the first dose for baseline assessment (screening visit) and while on study to confirm CR (i.e., subjects who become immunofixation negative) or at time of suspected disease progression, if clinically indicated.

Bone marrow plasma cell clonality must also be evaluated at the time of CR (< 5% plasma cells) to assess for sCR, if applicable. Flow cytometry is preferred over immunohistochemistry (IHC) for assessment of clonality by κ and λ staining. Flow cytometry will be performed only to assess for sCR locally per institution standard practice. If local flow cytometry to assess clonality is not available at the time of CR, a core biopsy and/or clot section should be evaluated by IHC staining for κ or λ or light chain restriction. To confirm a CR, a second confirmation bone marrow analysis for CR is not needed.

A bone marrow aspirate collection is mandatory at screening and to confirm sCR/CR. At screening, fresh samples should be obtained within 21 days before first dose of study drug and, when possible, should be obtained after all other eligibility criteria have been met. A bone marrow aspirate is optional at time of treatment completion or disease progression.

Bone marrow core biopsy (fixed formalin paraffin embedded [FFPE] core) should be also collected, unless not recommended per institutional guidelines. However, a bone marrow biopsy is mandatory in the circumstance that an aspirate sample is not available (e.g., due to a dry tap). Fresh biopsies are preferred but archived tissue is acceptable if representative of current disease and if collected within the previous 12 weeks without intervening treatment. Core block or tissue slides are acceptable. Bone marrow core biopsies are optional to confirm sCR, CR, or at the time of treatment completion or disease progression.

Table 4. Assessments for IMWG Response Criteria

	Screening	Cycle 1, Day 1[a]	Day 1 of each Subsequent Cycle	Response Confirmation (sCR, CR, or VGPR)	End-of-Treatment
Serum protein electrophoresis	X	X	X	X	X
Serum protein immunofixation	X	X	X	X	X
Serum quantitative immunoglobulins	X	X	X		X
Serum free light chain	X	X[b]	X[b]	X (CR/sCR only)	X[b]
Urine protein immunofixation	X	X	X	X[c]	X[c]
Urine protein electrophoresis	X	X	X	X[c]	X[c]
Skeletal survey	X	If clinically indicated.			
Plasmacytoma evaluation	If clinically indicated.	Performed during treatment only to confirm a minimal response or better, or to confirm progressive disease, or as clinically indicated.			
Bone marrow aspirate and biopsy	X			X (sCR or CR only)	X[d]

CR = complete response; sCR = stringent complete response; IMWG = International Myeloma Working Group; M-protein = monoclonal-protein; VGPR = very good partial response

a. For Cycle 1, Day 1, screening results or assessments may be used if done within 7 days of Cycle 1, Day 1.

b. Collect only for subjects without measurable M-protein in screening serum or urine.

c. Urine protein electrophoresis and urine immunofixation collection is mandatory for confirmation of VGPR, CR, and sCR, regardless of whether urine M-protein was measurable at baseline.

d. Collection of bone marrow sample at progressive disease or end of treatment visit is optional.

Note: Samples will be collected on the days indicated with a window of approximately 7 days before the scheduled visit.

Source: Kumar 2016.[15]

IMWG Criteria for Response and Progression

Subjects will be assessed for response using the 2016 IMWG response criteria (Appendix F).[15] Disease status categories include sCR, CR, VGPR, partial response (PR), MR, stable disease (SD), and PD.

All response categories (i.e., sCR, CR, VGPR, PR, MR, and PD) require 2 consecutive assessments for confirmation and can be made at any time before the institution of any new therapy (no minimum interval is required and assessments can be done the same day). However, to confirm response or PD, 2 discrete samples are required and testing cannot be based on the splitting of a single sample. Only 1 bone marrow assessment is required. All response categories sCR, CR, VGPR, PR, MR, and SD also require no known evidence of progressive or new bone lesions if radiographic studies were performed. Radiographic studies are not required to satisfy these response requirements, unless plasmacytoma is

present at baseline. Any soft tissue plasmacytoma documented at baseline must undergo serial monitoring as per Table 4.

Subjects with measurable disease in both serum and urine at study entry are required to meet response criteria in both serum and urine to qualify for an MR or better. The overall assigned level of response is determined by the lowest level of response. However, criteria for PD only need to be met and confirmed in 1 parameter (serum or urine).

Additional Notes on Specific Response Categories

Stringent Complete Response: Serum and urine M-protein testing is required to fulfill requirements of sCR regardless of whether disease at baseline was measurable on serum, urine, both, or neither.

Complete Response: Serum and urine M-protein testing is required to fulfill requirements of CR regardless of whether disease at baseline was measurable on serum, urine, both, or neither.

It is not essential to perform a bone marrow core biopsy, but if a core biopsy is performed this must also contain < 5% plasma cells.

Very Good Partial Response: Serum and urine M-protein testing is required to fulfill requirements of VGPR regardless of whether disease at baseline was measurable on serum, urine, both, or neither.

Minimal Response: The MR category does not apply for subjects whose disease is only measurable by FLC.

Stable Disease: Subjects should be categorized as SD until they meet the criteria for any response category (sCR, CR, VGPR, and PR) or have PD.

Progressive Disease: Two consecutive assessments for confirmation of PD made at any time before the start of new therapy are required per IMWG criteria (Appendix F). The second assessment may be taken immediately if PD is suspected. If PD is suspected by rising serum or urine M-protein (or FLC in subjects without measurable disease), 2 consecutive assessments from central laboratory readings should be obtained.

If PD is suspected by clinical symptoms, a plasmacytoma evaluation and/or skeletal survey should be obtained, as clinically indicated, and compared with baseline assessments to determine whether a new bone lesion or plasmacytoma has developed or an existing lesion or plasmacytoma has worsened. Serum and urine protein electrophoresis are also required.

The following assessments are not sufficient to determine PD:

- Rising serum FLC if disease is measurable in the serum, urine, or both.
    - Serum FLC can be used to determine PD according to the IMWG criteria only for subjects without measurable serum and urine M-protein.
- Clinical relapse based on indicators that are not part of the IMWG criteria for PD (e.g., decrease in hemoglobin, hypercalcemia, increase in serum creatinine, hyperviscosity), and relapse from clinical relapse categories should not be considered PD.

- General worsening of the subject's condition. If a subject's condition has deteriorated to a point that remaining on protocol therapy is not an option, every effort should be made to document PD by at least one of the following assessments prior to the initiation of new therapy: serum protein electrophoresis, urine protein electrophoresis, bone marrow biopsy, plasmacytoma evaluation, or skeletal survey.

Investigators are requested not to discontinue subjects from treatment for presumed lack of response after only 1 cycle of study treatment.

Clinical Relapse: Clinical relapse is defined per IMWG criteria (Appendix F) and cannot be used to determine PD.

Evaluation of Disease

IMWG assessments will be reviewed by the investigator per the IMWG criteria (Appendix F). If the investigator confirms that the subject meets the criteria for PD by 2 consecutive assessments, the subject will be deemed as having met an event of disease progression. For the purposes of this study, the date of progression will be the date on which the IMWG assessments were obtained.

Biomarker Sampling

Biospecimens (blood, plasma, serum, bone marrow aspirates, and bone marrow core biopsies) will be collected to support the biomarker research objectives of the study. Refer to Table 5 for the schedule of mandatory and optional biomarker research sample collections. Assessments may include, but are not limited to, biomarkers related to the pathway(s) targeted by the study drug or those believed to be related to the disease(s) being studied. The information learned from analyzing these samples may be used to investigate factors influencing response to treatment, scientific questions related to MM, and/or in the development of new therapies and diagnostic tests.

Evaluations may include B-cell lymphoma (BCL)-2 family member expression, immune cell phenotyping and quantification, T-cell clonality, chromosomal abnormalities (immunoglobulin [Ig]H translocations, amplifications, or deletions), and/or minimal residual disease (MRD) negativity. Plasma and serum samples may be analyzed for mutational status of circulating tumor deoxyribonucleic acid (DNA) and measurement of relevant cytokine, chemokine, matrix metalloproteinases, and markers of bone turnover (formation/resorption). The analyses of tumor tissue/cells may include but are not limited to IHC- and quantitative polymerase chain reaction (qPCR)-based assays for BCL-2 family members or other nucleic acids or proteins that may regulate the expression of these molecules. Gene sequencing- and hybridization-based techniques may also be used on any of the above specimens for exploratory research. MRD negativity in bone marrow aspirates will be defined at 10^{-5} threshold as assessed by next-generation sequencing in subjects at the time of suspected CR/sCR, and at 6 and 12 months post-confirmation of CR/sCR for subjects who maintained this response. Additionally, exploratory analysis of MRD negativity at the 10^{-4} and 10^{-6} thresholds may be performed. The samples may be analyzed as part of a multistudy assessment of factors influencing the subjects' response to the study drugs (or drugs of the same or similar class) and/or progression of the subjects' disease-related conditions. The information obtained from analyzing these samples may be used to investigate factors influencing response to treatment, scientific questions related to MM, and/or the development of new therapies

and diagnostic tests, or technologies. The results from these analyses may not be included with the clinical study report.

Blood samples may also be sequenced and data analyzed for genetic factors contributing to the disease or to the subject's response to venetoclax, pomalidomide, or other study treatment in terms of pharmacokinetics (PK), efficacy, tolerability, and safety. Such genetic factors may include genes for drug metabolizing enzymes, drug transport proteins, genes within the target pathway, genes believed to be related to the disease or to drug response. Some genes currently insufficiently characterized or unknown may be understood to be important at the time of analysis. The results are exploratory in nature and may not be included with the clinical study report.

All biomarker samples should be labeled and shipped as outlined in the study-specific laboratory manual. AbbVie (companies working with AbbVie) will store these samples in a secure storage space with adequate measures to protect confidentiality. The samples may be retained while research on venetoclax/pomalidomide, or drugs in these classes, or MM and related conditions continues, but for no longer than 20 years after study completion, or per local requirement.

Bone Marrow Aspirate Collection

A sufficient bone marrow aspirate must be collected for clinical assessment as well as for biomarker analyses. Priority of the aspirate sample split is as follows:

- assessment of disease response by IMWG criteria (except at screening)
- fluorescent in situ hybridization (FISH)
- gene expression analysis
- MRD assessment

For all subjects in the study who consent to optional biomarker research, optional bone marrow aspirate samples may be collected at end-of-treatment if deemed feasible by the investigator.

Priority of the bone marrow aspirate sample split is as follows:

- gene expression analysis
- FISH

Bone Marrow Core Biopsy Tissue Collection

One of the following forms of pretherapy tumor tissue (newly collected tissue or archived tissue) will be collected at screening to enable biomarker assessments as outlined in the study objectives:

- **Fresh tumor tissue:** Fresh bone marrow core biopsies performed during screening are preferred unless not recommended per institution guidelines. Tissue should be fixed, decalcified, and embedded in paraffin according to institutional procedures. While sending FFPE blocks is preferred, slides prepared by the local pathology laboratory are acceptable and should be prepared as described in the study-specific laboratory manual. In addition, a pathology report

with the subject identifying information redacted should be submitted along with the tissue sample.

- **Archived bone marrow core biopsy tissue:** The most recent archived diagnostic specimen is acceptable provided the sample is representative of the subject's current disease state at the time of study entry and within 12 weeks before the first dose of study drug. While sending FFPE blocks is preferred, slides prepared by the local pathology laboratory are acceptable and should be prepared and stored as described in the study-specific laboratory manual. In addition, a pathology report with the subject identifying information redacted should be submitted along with the tissue sample.

For all subjects in the study who consent to optional biomarker research, optional bone marrow core biopsy samples may be collected at end-of-treatment (prior to the initiation of a new antimyeloma treatment) if deemed feasible by the investigator. While sending FFPE blocks is preferred, slides prepared by the local pathology laboratory are acceptable and should be prepared and stored as described in the study-specific laboratory manual. In addition, a pathology report with the subject identifying information redacted should be submitted along with the tissue samples.

Optional Biomarker Research Sample

Optional whole blood samples for pharmacogenetics (DNA and RNA) will be collected on Cycle 1 (Day 1), Cycle 3 (Day 1), and end-of-treatment from each subject who consents to optional biomarker analysis.

Table 5. Schedule of Biomarker Research Sample Collections

Samples	Biomarker	Screen	Cycle 1, Day 1	Cycles 2 – 5 and 9, Day 1	Response Confirm of sCR/CR	6 Months Post Confirm of sCR/CR	12 Months Post Confirm of sCR/CR	End-of-Treatment
		Mandatory Peripheral Blood Collections						
Peripheral Blood	Immuno-phenotyping (4 mL)		Predose	Predose				X
Peripheral Blood	Immuno-sequencing (4 mL)		Predose	Predose				X
Peripheral Blood	Serum markers (3.5 mL)		Predose	Predose				X
Peripheral Blood	Plasma markers (3 mL)		Predose	Predose				X
		Mandatory and Optional Bone Marrow Collections						
Bone marrow aspirate	Gene expression (12 mL)	X						X (optional)
Bone marrow aspirate	MRD assessment (3 mL)	X			X[a]	X[b]	X[b]	
Bone marrow aspirate	FISH (3 mL)	X						X (optional)
Bone marrow core biopsy[c]	IHC (FFPE blocks or slides)	X			X			X (optional)
		Optional Peripheral Blood Collections (Expansion Phase only)						
Peripheral blood	PGx DNA/RNA (6.5 mL)		X	X (Cycle 3 only)				X

CR = complete response; DNA = deoxyribonucleic acid; FFPE = formalin fixed parafin embedded; FISH = fluorescent in situ hybridization; IHC = immunohistochemistry; MRD = minimal residual disease; PGx = pharmacogenetics; RNA = ribonucleic acid; sCR = stringent complete response

a. Only for subjects who are suspected to have a CR/sCR.

b. For subjects who achieve a CR/sCR and continue to have this response, a bone marrow aspirate will be collected at 6 months and 12 months post-confirmed CR/sCR.

c. Unless not recommended per institutional guidelines. A bone marrow biopsy is mandatory in the circumstance that an aspirate sample is not available (e.g., due to a dry tap).

Dispense Study Drug

Study drug will be dispensed to subjects beginning at baseline (Day 1) and as specified in Appendix D. The first dose of study drug will be administered after all other baseline (Day 1) procedures are completed. The pomalidomide education and counseling guidance document must be completed and signed by a trained counselor at the participating clinical site before each dispensing of pomalidomide. A copy of the document must be maintained in the subject's records for each dispense. The pomalidomide information will be given to the subject receiving pomalidomide. The subject must read the information sheet before starting pomalidomide and each time the subject receives a new supply of pomalidomide. At the visits specified in Appendix D, the site personnel will review and retain a copy of the dosing diary, review returned study drug kits, and empty study drug packaging to verify compliance.

Pharmacokinetic Sampling

Blood samples (3 mL each) will be collected for analysis of venetoclax and pomalidomide plasma concentrations. Blood samples will be collected at the time points presented in Table 6.

Table 6. Pharmacokinetic Sampling Times

Blood Samples[a,b]	
Cycle 1	**Cycles 2, 4, 6, 8**
Days 1 and 15	**Day 1**
Part 1: Venetoclax Samples	
0 (predose), 2, 4, 6, 8, and 24 hours postdose	0 (predose)
Part 1: Pomalidomide Samples	
0 (predose), 1, 2, 4, 6, and 24 hours postdose	--
Part 2: Venetoclax Samples	
0 (predose), 2 and 4 hours postdose	0 (predose)
Part 2: Pomalidomide Samples	
0 (predose), 2 and 4 hours postdose	--

a. All samples will be shipped to central laboratory for processing.

b. All PK samples need to be collected within the ± 10% window from the nominal sampling times.

All 0-hour (predose) samples are relative to the respective study drug administrations. The timing of blood collections will take priority over all other scheduled study activities except for dose administration. The date and time (to the nearest minute) of each blood sample collection will be recorded.

Additionally, the date and time (to the nearest minute) of each venetoclax and pomalidomide dose and whether or not the venetoclax dose was taken within 30 minutes after the completion of meal will be recorded for each scheduled PK sampling day and for the 2 doses before each scheduled PK day (if applicable). Sites will ensure all information is captured through source documents (site or subject calendar/diary provided by AbbVie).

Venetoclax Samples

Disposition of Samples

Whole blood will be collected into appropriately labeled tubes and processed as outlined in the most current version of Study M16-085 laboratory manual. An inventory of the samples included will accompany the package. Arrangements will be made with AbbVie for the transfer of samples to:

Attn: AbbVie Sample Receiving
[redacted]
c/o: Delivery Services
1150 S Northpoint Blvd
Waukegan, IL 60085

Phone: [redacted]
Fax:
Email:

Measurement Method

Plasma concentrations of venetoclax will be determined by the bioanalysis department at AbbVie using a validated method. Plasma concentration of possible venetoclax metabolite(s) may be determined with validated or nonvalidated methods.

Pomalidomide Samples

Disposition of Samples

Whole blood will be collected into appropriately labeled tubes and processed as outlined in the most current version of Study M16-085 laboratory manual. An inventory of the samples included will accompany the package. Arrangements will be made with inVentiv Health Clinique, Inc. for the transfer of samples to:

Attn: Sample Receiving
inVentiv Health Clinique, Inc.
2500 Rue Einstein
Québec (Québec), Canada G1P 0A2

Phone: (418) 527-4000
Fax: [redacted]
Email: [redacted]

Measurement Method

Plasma concentrations of pomalidomide will be determined using a validated method under the supervision of bioanalysis department at AbbVie.

APPENDIX F. IMWG RESPONSE CRITERIA FOR MULTIPLE MYELOMA (2016)

Response Subcategory	Response Criteria[a]
Stringent complete response*	• Negative immunofixation on the serum and urine (regardless of whether disease at baseline was measurable in serum, urine, both, or neither) and • Disappearance of any soft tissue plasmacytomas and • < 5% plasma cells in bone marrow[b] and • Normal FLC ratio** and • Absence of clonal cells in bone marrow[b] by immunohistochemistry (κ/λ ratio ≤ 4:1 or ≥ 1:2 for κ and λ patients, respectively, after counting ≥ 100 plasma cells)[c]
Complete response*,[c]	• Negative immunofixation on the serum and urine (regardless of whether disease at baseline was measurable on serum, urine, both, or neither) and • Disappearance of any soft tissue plasmacytomas and • < 5% plasma cells in bone marrow[b] and • For subjects in whom the only measurable disease is by serum FLC levels, a normal FLC ratio** is also required
Very good partial response*	• Serum and urine M-protein detectable by immunofixation but not on electrophoresis or • ≥ 90% reduction in serum M-protein plus urine M-protein < 100 mg per 24 hours • For subjects in whom the only measurable disease is by serum FLC levels, VGPR is defined as: • ≥ 90% decrease in the difference between involved and uninvolved FLC levels

Partial response	• ≥ 50% reduction of serum M-protein and
	• Reduction in 24-hour urinary M-protein by ≥ 90% or to < 200 mg per 24 hours
	  • If the serum and urine M-protein are unmeasurable,[d] a ≥ 50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria
	  • If the serum and urine M-protein are unmeasurable,[d] and serum-free light assay is also unmeasurable, a ≥ 50% reduction in plasma cells is required in place of M-protein provided baseline bone marrow plasma-cell percentage was ≥ 30%
	• ≥ 50% reduction in the size of soft tissue plasmacytomas is also required, if present at baseline

Minimal response	• 25% – 49% reduction of serum M-protein and • 50% – 89% reduction in 24-hour urinary M-protein and • ≥ 50% reduction in the size (SPD)[f] of soft tissue plasmacytomas if present at baseline

Response Subcategory	Response Criteria[a]
Stable disease[e]	• Not meeting criteria for CR, VGPR, PR, MR or progressive disease

Progressive disease	• Any one or more of the following criteria:
	  • Increase of 25% from lowest confirmed response value in one or more of the following criteria:
	  • Serum M-protein (absolute increase must be ≥ 0·5 g/dL);
	  • Serum M-protein increase ≥ 1 g/dL, if the lowest M-component was ≥ 5 g/dL;
	  • Urine M-protein (absolute increase must be ≥ 200 mg/24 hr);
	  • In patients without measurable serum and urine M-protein levels, the difference between involved and uninvolved FLC levels (absolute increase must be > 10 mg/dL);
	  • In patients without measurable serum and urine M-protein levels and without measurable involved FLC levels, bone marrow plasma-cell percentage irrespective of baseline status (absolute increase must be ≥ 10%);
	  • Appearance of a new lesion(s), ≥ 50% increase from nadir in SPD[f] of > 1 lesion, or ≥ 50% increase in the longest diameter of a previous lesion > 1 cm in short axis;
	• ≥ 50% increase in circulating plasma cells (minimum of 200 cells/μL) if this is the only measure of disease

Clinical relapse	• Clinical relapse requires one or more of the following criteria:
	  • Direct indicators of increasing disease and/or end organ dysfunction (CRAB features) related to the underlying clonal plasma-cell proliferative disorder. It is not used in calculation of time-to-progression or progression-free survival but is listed as something that can be reported optionally or for use in clinical practice;
	  • Development of new soft tissue plasmacytomas or bone lesions (osteoporotic fractures do not constitute progression);
	  • Definite increase in the size of existing plasmacytomas or bone lesions. A definite increase is defined as a 50% (and ≥ 1 cm) increase as measured serially by the SPD[f] of the measurable lesion;
	  • Hypercalcemia (> 11 mg/dL);
	  • Decrease in hemoglobin of ≥ 2 g/dL not related to therapy or other non-myeloma-related conditions;
	  • Rise in serum creatinine by 2 mg/dL or more from the start of the therapy and attributable to myeloma;
	• Hyperviscosity related to serum paraprotein

CR = complete response; CRAB = calcium elevation, renal failure, anemia, lytic bone lesions; CT = computed tomography; FLC = free-light chain; IMWG = International Myeloma Working Group; M-protein = monoclonal-protein; MR = minimal response; MRI = magnetic resonance imaging; PET = positron emission tomography; PR = partial response; SPD = sum of the products of the maximal perpendicular diameters of measured lesions; VGPR = very good partial response

a. All response categories require 2 consecutive assessments made at any time before the institution of any new therapy; all categories also require no known evidence of progressive or new bone lesions or extramedullary plasmacytomas if radiographic studies were performed. Radiographic studies are not required to satisfy these response requirements.

b. Confirmation with repeat bone marrow biopsy not needed.

c. Presence/absence of clonal cells on immunohistochemistry is based upon the k/λ ratio. An abnormal k/λ ratio by immunohistochemistry requires a minimum of 100 plasma cells for analysis. An abnormal ratio reflecting presence of an abnormal clone is k/λ of > 4:1 or < 1:2.

d. Measurable disease is defined as meeting at least one of the following 3 measurements: serum M-protein ≥ 1 g/dL (≥ 10 g/L) or urine M-protein ≥ 200 mg/24 hours or serum FLC assay with an involved FLC level ≥ 10 mg/dL (≥ 100 mg/L) provided serum FLC ration is abnormal.

e. Not recommended for use as an indicator of response; stability of disease is best described by providing the time to progression estimates.

f. Plasmacytoma measurements should be taken from the CT portion of the PET/CT, or MRI scans, or dedicated CT scans where applicable. For patients with only skin involvement, skin lesions should be measured with a ruler. Measurement of tumor size will be determined by the SPD.

Notes:

* Clarification to IMWG criteria for coding CR and VGPR in subjects whom the only measurable disease is by serum FLC levels. In these subjects, CR is defined as a normal FLC ratio of 0.26 to 1.65 in addition to CR criteria listed above, and VGPR is defined as a ≥ 90% decrease in the difference between involved and uninvolved FLC levels.

** Serum and urine M-protein testing is required to fulfill requirements of VGPR and CR categories regardless of whether disease at baseline was measurable in serum, urine, both, or neither.

APPENDIX G. TUMOR LYSIS SYNDROME CLASSIFICATION

Metabolic Abnormality	Criteria for Classification of Laboratory Tumor Lysis Syndrome*	Criteria for Classification of Clinical Tumor Lysis Syndrome**
Hyperuricemia	Uric acid > 8.0 mg/dL (475.8 µmol/L)	Not applicable
Hyperphosphatemia	Phosphorus > 4.5 mg/dL (1.5 mmol/L)	Not applicable
Hyperkalemia	Potassium > 6.0 mmol/L	Cardiac dysrhythmia or sudden death probably or definitely caused by hyperkalemia
Hypocalcemia	Corrected calcium < 7.0 mg/dL (1.75 mmol/L) or ionized calcium < 1.12 mg/dL (0.3 mmol/L)#	Cardiac dysrhythmia, sudden death, seizure, neuromuscular irritability (tetany, paresthesias, muscle twitching, carpopedal spasm, Trousseau's sign, Chvostek's sign, laryngospasm, or bronchospasm), hypotension, or heart failure probably or definitely caused by hypocalcemia
Acute kidney injury!	Not applicable	Increase in the serum creatinine level of 0.3 mg/dL (26.5 µmol/L) or the presence of oliguria (average urine output < 0.5 mL/kg/hr for a 6-hour period)

* Laboratory TLS requires 2 or more metabolic abnormalities must be present during the same 24-hour period within 3 days before the start of therapy or up to 7 days afterward.

** Clinical TLS requires the presence of laboratory TLS plus one or more findings from the clinical TLS list.

Corrected calcium = measured calcium level in mg/dL + 0.8 × (4 – albumin in g/dL).

! Acute kidney injury, unless attributable to another cause, represents clinical TLS even if criteria for laboratory TLS are not satisfied.

* Not directly or probably attributable to the therapeutic agent.

Source: Howard SC, Jones DP, Pui CH. The tumor lysis syndrome. N Engl J Med. 2011;364(19):1844-54.

APPENDIX H. RECOMMENDATIONS FOR INITIAL MANAGEMENT OF ELECTROLYTE IMBALANCES AND PREVENTION OF TUMOR LYSIS SYNDROME IN MULTIPLE MYELOMA SUBJECTS

If a subject reports taking any over-the-counter or prescription medications, vitamins and/or herbal supplements or if administration of any medication becomes necessary from 30 days before the screening visit through 30 days after last dose of study drug, the name of the medication, dosage information including dose, route, and frequency, date(s) of administration including start and end dates, and reason for use must be recorded on the appropriate electronic Case Report Form (eCRF).

Abnormality	Management Recommendations
Hyperkalemia (Including Rapidly Rising Potassium)	
Potassium ≥ 0.5 mmol/L increase from prior value (even if potassium within normal limits [WNL])	• Recheck potassium, phosphorus, uric acid, calcium, and creatinine in 1 hour immediately. If further ≥ 0.2 mmol/L increase in potassium, but still < upper limit of normal (ULN), manage as per potassium ≥ ULN. Otherwise recheck in 1 hour. • Resume per protocol testing if change in potassium is < 0.2 mmol/L, potassium < ULN, and no other evidence of tumor lysis. • At discretion of investigator, may recheck prior to hospitalization. If stable or decreased and still WNL, hospitalization is at the discretion of the investigator. Potassium, phosphorus, uric acid, calcium, and creatinine must be rechecked within 24 hours.
Potassium > ULN	• Perform immediate ECG and commence telemetry. • Nephrology (or acute dialysis service or other) notification with consideration of initiating dialysis. • Administer kayexalate 60 g (or Resonium A 60 g). • Administer furosemide 20 mg IV × 1. • Administer calcium gluconate 100 to 200 mg/kg IV slowly if there is ECG/telemetry evidence of life threatening arrhythmias. • Recheck potassium, phosphorus, uric acid, calcium, and creatinine in 1 hour immediately. • If potassium < ULN 1 hour later, repeat potassium, phosphorus, uric acid, calcium, and creatinine 1, 2, and 4 hrs, if no other evidence of tumor lysis.

Abnormality	Management Recommendations
Hyperkalemia (Including Rapidly Rising Potassium) (continued)	
Potassium ≥ 6.0 mmol/L (6.0 mEq/L) and/or symptomatic (e.g., muscle cramps, weakness, paresthesias, nausea, vomiting, diarrhea)	• Perform immediate ECG and commence telemetry. • Nephrology (or acute dialysis service or other) assessment with consideration of initiating dialysis. • Administer kayexalate 60 g (or Resonium A 60 g). • Administer furosemide 20 mg IV × 1. • Administer insulin 0.1 U/kg IV + D25 2 mL/kg IV. • Administer sodium bicarbonate 1 to 2 mEq/kg IV push. • If sodium bicarbonate is used, rasburicase should not be used as this may exacerbate calcium phosphate precipitation. • Administer calcium gluconate 100 to 200 mg/kg IV slowly if there is ECG/telemetry evidence of life threatening arrhythmias. Do not administer in same IV line as sodium bicarbonate. • Recheck potassium, phosphorus, uric acid, calcium, and creatinine every hour immediately.
Hyperuricemia	
Uric acid ≥ 8.0 mg/dL (476 µmol/L)	• Consider rasburicase (dose per institutional guidelines). • If rasburicase is used, sodium bicarbonate should not be used as this may exacerbate calcium phosphate precipitation. • Recheck potassium, phosphorus, uric acid, calcium, and creatinine in 1 hr immediately.

Uric acid ≥ 10 mg/dL (595 µmol/L)
OR
Uric acid ≥ 8.0 mg/dL (476 µmol/L) with 25% increase and creatinine increase ≥ 0.3 mg/dL (≥ 0.027 mmol/L) from predose level
	• Administer rasburicase (dose per institutional guidelines).
	  • If rasburicase is used, sodium bicarbonate should not be used as this may exacerbate calcium phosphate precipitation.
	• Consult nephrology or acute dialysis service (or other).
	• Recheck potassium, phosphorus, uric acid, calcium, and creatinine in 1 hr immediately.
	  • If uric acid < 8.0 mg/dL 1 hour later, repeat potassium, phosphorus, uric acid, calcium, and creatinine 2 and 4 hrs later, if no other evidence of tumor lysis.

Abnormality	Management Recommendations
Hypocalcemia	
Calcium ≤ 7.0 mg/dL (1.75 mmol/L) AND Patient symptomatic (e.g., muscle cramps, hypotension, tetany, cardiac arrhythmias)	• Administer calcium gluconate 50 to 100 mg/kg IV slowly with ECG monitoring. • Telemetry. • Recheck potassium, phosphorus, uric acid, calcium, and creatinine in 1 hr immediately. • If calcium normalized 1 hr later, repeat potassium, phosphorus, uric acid, calcium, and creatinine 2 and 4 hrs later, if no other evidence of tumor lysis. • Calculate corrected calcium and check ionized calcium if albumin low.
Hyperphosphatemia	
Phosphorus ≥ 5.0 mg/dL (1.615 mmol/L) with ≥ 0.5 mg/dL (0.16 mmol/L) increase	• Administer a phosphate binder (e.g., aluminum hydroxide, calcium carbonate, sevelamer hydroxide, or lanthanum carbonate). • Nephrology (or acute dialysis service or other) notification (dialysis required for phosphorus ≥ 10 mg/dL). • Recheck potassium, phosphorus, uric acid, calcium, and creatinine in 1 hr immediately. • If phosphorus < 5.0 mg/dL 1 hour later, repeat potassium, phosphorus, uric acid, calcium, and creatinine 2 and 4 hrs later, if no other evidence of tumor lysis.
Creatinine	
Increase ≥ 25% from baseline	• Start or increase rate of IV fluids. • Recheck potassium, phosphorus, uric acid, calcium, and creatinine in 1 to 2 hrs immediately.

ECG = electrocardiogram; IV = intravenous

APPENDIX I. RECOMMENDED DOSE REDUCTIONS RELATED TO DRUG TOXICITIES AND USE WITH CONCOMITANT MEDICATIONS

If a subject reports taking any over-the-counter or prescription medications, vitamins and/or herbal supplements or if administration of any medication becomes necessary from 30 days before the screening visit through 30 days after last dose of study drug, the name of the medication, dosage information including dose, route, and frequency, date(s) of administration including start and end dates, and reason for use must be recorded on the appropriate electronic Case Report Form (eCRF).

Subjects should receive full supportive care during study participation, including transfusion of blood products, fluid and electrolyte replacement, and antibiotics when appropriate. Subjects who use oral contraceptives, hormone-replacement therapy, or other maintenance therapy should continue their use. For guidance regarding medications for management of tumor lysis syndrome (TLS) and neutropenia, refer to Section 6.4.

General guidelines regarding prohibited, cautionary, and allowed medications are summarized in Section 5.3 and Section 5.4. A sample list of prohibited and cautionary medications that that may interact with study drugs is provided in Appendix J. It is not possible to produce a complete list of medications that fall into these categories; if in question, please refer to the appropriate product label.

Concomitant administration of moderate or strong cytochrome P450 (CYP)3A and strong CYP1A2 inhibitors is prohibited during Part 1 (dose escalation), Cycle 1. Use of strong or moderate CYP3A inhibitors and strong CYP1A2 inhibitors is allowed (with appropriate venetoclax and pomalidomide dose reductions, respectively) after Part 1 (dose escalation), Cycle 1 and throughout the study for subjects enrolled in Part 2 (dose expansion) if no appropriate therapeutic alternative exists. Venetoclax dose reductions for concomitant administration with moderate or strong CYP3A inhibitors are presented in Table 7. Subjects should be monitored more closely for signs of toxicities and the venetoclax dose may need to be further reduced. Pomalidomide dose reductions for concomitant use with strong CYP1A2 inhibitors are presented in Table 8. Subjects should be monitored more closely for signs of toxicities and the venetoclax dose may need to be further reduced. After discontinuation of the CYP3A inhibitor, wait for 3 days before venetoclax dose is increased back to the target dose.

Concomitant administration of moderate or strong CYP3A inducers is prohibited during Cycle 1 (dose escalation), Part 1. After completion of Cycle 1 (dose escalation), Part 1, and throughout the study for subjects enrolled in Part 2 (dose expansion), concomitant use of moderate or strong CYP3A inducers should still be avoided. Alternative treatments with less CYP3A induction should be considered.

Study drug dose levels are presented in Table 9. Toxicities related to venetoclax, pomalidomide, and dexamethasone are presented in Table 10, Table 11, and Table 12, respectively.

Table 7. Dose Modifications for Venetoclax with Concomitant Moderate and Strong CYP3A Inhibitor Use

Venetoclax Dose with No Moderate or Strong CYP3A Inhibitor	Venetoclax Dose if Co-Administered with a Moderate CYP3A Inhibitor	Venetoclax Dose if Co-Administered with a Strong CYP3A Inhibitor
400 mg	200 mg	100 mg
600 mg	300 mg	100 mg
800 mg	400 mg	200 mg

CYP = cytochrome P450

Table 8. Dose Modifications for Pomalidomide with Concomitant Strong CYP1A2 Inhibitor Use

Assigned Pomalidomide Dose	Pomalidomide Dose if Co-Administered with a Strong CYP1A2 Inhibitor
4 mg	2 mg

CYP = cytochrome P450

The AbbVie Therapeutic Area Medical Director (TA MD) identified in Appendix L should be contacted if there are any questions regarding concomitant or prior therapy(ies) and venetoclax or pomalidomide dose reductions.

Table 9. Study Drug Dose Levels

Dose	Venetoclax	Pomalidomide	Dexamethasone (< 75 years of age)	Dexamethasone (≥ 75 years of age)
Starting dose	800 mg	4 mg	40 mg	20 mg
Dose level –1	600 mg	3 mg	20 mg	12 mg
Dose level –2	400 mg	2 mg	12 mg	8 mg
Dose level –3	200 mg	1 mg	8 mg	4 mg

Table 10. Toxicities Related to Venetoclax

Toxicities	Recommended Action
Grade 3 or Grade 4 neutropenia with infection or fever; or Grade 4 hematologic toxicities (except for lymphopenia)	• G-CSF or growth factors for neutropenia should be administered with venetoclax if clinically indicated. • For Grade 4 neutropenia (ANC < 500 cells/µL) without infection, anti-infective prophylaxis (e.g., amoxicillin/clavulanic acid or levofloxacin or equivalent per institutional guidelines) is recommended until the neutropenia improves to Grade 3 or better (ANC > 500 cells/µL). • First episode: Interrupt venetoclax and once the toxicity has resolved to Grade 1 or baseline level, venetoclax may be resumed at the same dose. • For subsequent episodes: Interrupt venetoclax. Consider using G-CSF as clinically indicated. Follow dose reduction guidelines when resuming treatment with venetoclax after resolution. A larger dose reduction may occur at the discretion of the investigator and according to the dose reduction guidelines.
Grade ≥ 3 or serious infections	• Interrupt venetoclax and upon resolution, treatment can either be resumed at a reduced dose (see Table 9) or discontinued, at the discretion of the investigator.
Grade 3 or 4 non-hematologic events	• First episode: Interrupt venetoclax. Once toxicity has resolved to Grade ≤ 1 or baseline, venetoclax may be resumed at the same dose. No dose modification is required. • For subsequent episodes: Interrupt venetoclax. Follow dose reduction guidelines when resuming treatment with venetoclax after resolution. A larger dose reduction may occur at the discretion of the investigator and according to the dose reduction guidelines.
Blood chemistry changes or symptoms suggestive of TLS	• Withhold the next day's dose. If resolved within 24 – 48 hours of last dose, resume at the same dose. • For any blood chemistry changes requiring more than 48 hours to resolve, resume at a reduced dose. • For any events of clinical TLS, resume at a reduced dose following resolution.

ANC = absolute neutrophil count; G-CSF = granulocyte-colony stimulating factor; TLS = tumor lysis syndrome

Table 11. Toxicities Related to Pomalidomide

Toxicity	Recommended Action
Neutropenia: ANC < 0.5×10^9/L, or febrile neutropenia (fever ≥ 38.5°C and ANC < 1×10^9/L)	• Interrupt pomalidomide treatment, follow complete blood counts weekly. Add G-CSF (at discretion of the treating physician). • ANC returns to ≥ 0.5×10^9/L (or per local guidelines), resume pomalidomide treatment at 3 mg/day. • For each subsequent drop to < 0.5×10^9/L, interrupt pomalidomide treatment. • ANC returns to ≥ 1×10^9/L, resume pomalidomide treatment at 1 mg less than the previous dose.[a]
Thrombocytopenia: Platelet count < 25×10^9/L	• Interrupt pomalidomide treatment for remainder of cycle. • Platelet count returns to ≥ 50×10^9/L, resume pomalidomide treatment at 1 dose level lower.
Angioedema: Grade 4 rash, exfoliative or bullous rash	• Permanently discontinue pomalidomide.
Other Grade 3/4 toxicities judged to be related to pomalidomide	• Interrupt pomalidomide treatment. • Restart treatment at 1 dose level lower than the previous dose when toxicity has resolved to ≤ Grade 2 at the physician's discretion.

ANC = absolute neutrophil count; G-CSF = granulocyte-colony stimulating factor

a. If adverse reactions occur after dose reductions to 1 mg, then study drug should be discontinued.

Table 12. Toxicities Related to Dexamethasone

Toxicity	Recommended Action
Dyspepsia = Grades 1 – 2	Maintain dose and treat with histamine (H2) blockers or equivalent. Decrease by 1 dose level if symptoms persist.
Dyspepsia ≥ Grade 3	Interrupt dose until symptoms are controlled. Add H2 blocker or equivalent and decrease 1 dose level when dose restarted.
Edema ≥ Grade 3	Use diuretics as needed and decrease dose by 1 dose level.
Confusion or mood alteration ≥ Grade 2	Interrupt dose until symptoms resolve. When dose restarted, decrease dose by 1 dose level.
Muscle weakness ≥ Grade 2	Interrupt dose until muscle weakness ≤ Grade 1. Restart with dose decreased by 1 level.
Hyperglycemia ≥ Grade 3	Decrease dose by 1 dose level. Treat with insulin or oral hypoglycemic agents as needed.
Acute pancreatitis	Discontinue dexamethasone treatment regimen.
Other ≥ Grade 3 dexamethasone-related adverse events	Stop dexamethasone dosing until adverse event resolves to ≤ Grade 2. Resume with dose reduced by 1 dose level.

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APPENDIX J. SAMPLE LIST OF PROHIBITED AND CAUTIONARY MEDICATIONS THAT MAY INTERACT WITH STUDY DRUGS

Prohibited During Part 1, Cycle 1 and Cautionary in Part 1, ≥ Cycle 2 and in Part 2, All Cycles
Strong CYP1A2 inhibitors[††] – ciprofloxacin, enoxacin, fluvoxamine, zafirlukast
Strong CYP3A inhibitors[†] – boceprevir, clarithromycin, cobicistat, conivaptan, danoprevir/ritonavir, elvitegravir/ritonavir, idelalisib,* indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, paritaprevir/ritonavir combinations, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, tipranavir/ritonavir, troleandomycin, voriconazole
Moderate CYP3A inhibitors[‡] – amprenavir, aprepitant, atazanavir, cimetidine, ciprofloxacin, clotrimazole, crizotinib,* cyclosporine,* darunavir/ritonavir, diltiazem,[a] erythromycin, fluconazole, fosamprenavir, imatinib,* isavuconazole, tofisopam, verapamil
Strong CYP3A inducers – avasimibe, carbamazepine, enzalutamine, mitotane, phenytoin, rifampin, St John's wort
Moderate CYP3A inducers – bosentan, efavirenz, etravirine, modafinil, nafcillin
Cautionary
Warfarin**
P-gp substrates – aliskiren, ambrisentan, colchicine, dabigatran etexilate, digoxin, everolimus,* fexofenadine, lapatinib,* loperamide, maraviroc, nilotinib,* ranolazine, saxagliptin, sirolimus,* sitagliptin, talinolol, tolvaptan, topotecan*
BCRP substrates – methotrexate,* mitoxantrone,* irinotecan,* lapatinib,* rosuvastatin, sulfasalazine, topotecan*
OATP1B1/1B3 substrates – atrasentan, atorvastatin, ezetimibe, fluvastatin, glyburide, rosuvastatin, pitavastatin, pravastatin, repaglinide, simvastatin acid, telmisartan, valsartan, olmesartan
P-gp inhibitors – amiodarone, azithromycin, captopril, carvedilol, dronedarone, felodipine, quercetin, quinidine, ronalzine, ticagrelor
BCRP inhibitors – gefitinib*
Corticosteroids – cortisone, hydrocortisone, methylprednisolone, prednisolone, prednisone, triamcinolone, betamethasone, dexamethasone

BCRP = breast cancer resistance protein; CYP = cytochrome P450; FDA = Food and Drug Administration; OATP = organic anion-transporting polypeptide; P-gp = P-glycoprotein; USPI = United States package insert

a. Moderate CYP3A inhibitor per venetoclax FDA USPI.

* These are anticancer agents; contact the AbbVie Therapeutic Area Medical Director before use.

** Closely monitor the international normalized ratio.

† If a subject requires use of these medications, use with caution and reduce the venetoclax dose by 75%. After discontinuation of the CYP3A inhibitor, wait for 3 days before venetoclax dose is increased back to the target dose.

‡ If subject requires use of these medications, use with caution and reduce the venetoclax dose by 50%. After discontinuation of CYP3A inhibitor, wait for 3 days before venetoclax dose is increased back to the target dose.

†† If a subject requires use of these medications, use with caution and reduce the pomalidomide dose by 50%.

Note: this is not an exhaustive list. For an updated list, see the following link:

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm

In addition to the medications listed in this table, subjects receiving venetoclax should not consume grapefruit, grapefruit products, Seville oranges (including marmalade containing Seville oranges), or Star fruits. Herbal and natural remedies are to be avoided.

APPENDIX K. CORTICOSTEROID CONVERSION TABLE

Corticosteroid Conversion Table	
Glucocorticoid	**Approximate Equivalent Dose (mg)**
Short-Acting	
Cortisone	25
Hydrocortisone	20
Intermediate-Acting	
Methylprednisolone	4
Prednisolone	5
Prednisone	5
Triamcinolone	4
Long-Acting	
Betamethasone	0.6 - 0.75
Dexamethasone	0.75

References:

Dixon JS. Second-line Agents in the Treatment of Rheumatic Diseases. Informa Health Care. 1991;456.

Meikle AW, Tyler FH. Potency and duration of action of glucocorticoids. Am J of Med. 1977;63(2):200-7.

Webb R, Singer M. Oxford Handbook of Critical Care. Oxford; New York: Oxford University Press, 2005.

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APPENDIX L. SAFETY REPORTING CONTACT INFORMATION

Email: [redacted]

FAX to: [redacted]

For safety concerns, contact the oncology safety team at:

Oncology Safety Team
AbbVie Inc.
[redacted]
1 North Waukegan Road
North Chicago, Illinois 60064
Office: [redacted]
Email: [redacted]

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

Primary Therapeutic Area Medical Director
EMERGENCY MEDICAL CONTACT:
[redacted]
AbbVie Inc.
1 North Waukegan Road
North Chicago, IL 60064

Contact Information:

Office: [redacted]
Mobile:
Email:

In emergency situations involving study subjects when the primary Therapeutic Area Medical Director (TA MD) is not available by phone, please contact the 24-hour AbbVie Medical Escalation Hotline where your call will be redirected to a designated backup AbbVie TA MD:

HOTLINE: [redacted]

AbbVie will be responsible for Suspected Unexpected Serious Adverse Reactions (SUSAR) reporting for the Investigational Medicinal Product (IMP) in accordance with global and local guidelines and Appendix A of the Investigator's Brochure will serve as the Reference Safety Information (RSI). The RSI in effect at the start of a DSUR reporting period serves as the RSI during the reporting period. For follow-up reports, the RSI in place at the time of occurrence of the 'suspected' Serious Adverse Reaction will be used to assess expectedness.[9]

APPENDIX M. PROTOCOL AMENDMENT SUMMARY OF CHANGES

Previous Protocol Versions

Protocol	Date
Version 1.0	02 February 2018
Version 2.0	11 June 2018
Version 3.0	15 March 2019
Version 4.0	02 October 2019

The purpose of this amendment is to correct minor clerical errors for consistency and other administrative changes throughout the protocol in addition to the following:

- **Rationale:** To update pneumococcal and influenza vaccination requirements in Section 5.4.
  - Updated pneumococcal influenza vaccination requirements to remove requirement for re-vaccination if subjects were already vaccinated.
- **Rationale:** To update the list of signatories in Appendix C per current standard operating procedure.
  - Replaced [redacted] and [redacted] with [redacted].
  - Removed [redacted] as a signatory.
- **Rationale:** To delete the progression-free survival follow-up visits.
  - Removed progression-free survival follow-up visits to the Schedule of Activities, Appendix D.
  - Removed the subject criteria for progression-free survival follow-up and the frequency of the visits in Appendix E.
- **Rationale:** To delete the survival follow-up assessments.
  - Removed survival follow-up visits to the Schedule of Activities, Appendix D.
  - Removed the survival status activity row to the Schedule of Activities, Appendix D.
  - Removed the summary of the data collected and the frequency for the survival follow-up visits in Appendix E.