1.0 Title Page

Clinical Study Protocol M14-031

A Phase 3, Multicenter, Randomized, Double Blind Study of Bortezomib and Dexamethasone in Combination with Either Venetoclax or Placebo in Subjects with Relapsed or Refractory Multiple Myeloma Who are Sensitive or Naïve to Proteasome Inhibitors

Incorporating Administrative Change 1 and Amendment 0.01 (France Only), Japan Local Amendment 1, Global Amendments 1, 2, 3, 4, 5, 6, 7, and 8

AbbVie Investigational Product:	Venetoclax (ABT-199)
Date:	16 December 2020
Development Phase:	3
Study Design:	This is a Phase 3, multicenter, randomized, double blind, placebo-controlled study evaluating the efficacy and safety of venetoclax plus bortezomib and dexamethasone in subjects with relapsed or refractory multiple myeloma who are considered sensitive or naïve to proteasome inhibitors and received 1 to 3 prior lines of therapy for multiple myeloma.
EudraCT Number:	2015-004411-20
Investigators:	Multicenter Study: Site Investigator information is on file at AbbVie.
Sponsor:	AbbVie* Collaborative Partners: Genentech/Roche.

Sponsor/Emergency Contact:	[redacted] Medical Director Pharmacyclics Switzerland GmbH (An AbbVie Company) Mühlentalstrasse 36 CH-8200 Schaffhausen	Phone: [redacted] Cell: Fax: Emergency 24 hour Number: +1 973-784-6402

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

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

1.1 Protocol Amendment: Summary of Changes

Previous Protocol Versions

Protocol	Date
Original	05 February 2016
Amendment 0.01 (France Only)	24 June 2016
Japan Local Amendment 1	27 May 2016
Global Amendment 1	16 June 2017
Global Amendment 2	15 December 2017
Global Amendment 3	09 March 2018
Global Amendment 4	09 January 2019
Protocol Administrative Change 1	23 January 2019
Global Amendment 5	15 March 2019
Global Amendment 6	24 September 2019
Global Amendment 7	20 April 2020

The purpose of this amendment is to incorporate necessary protocol modifications due to the COVID-19 pandemic, as well as the following:

- Update Section 1.2, Synopsis; Section 2.0, Table of Contents:

  Rationale: *to ensure consistency with information throughout the protocol.*
- Update Section 1.3, List of Abbreviations and Definition of Terms:

  Rationale: *to add COVID-19, DSUR, DTP, and SARS-CoV-2 abbreviations.*
- Update Section 3.5, Benefits and Risks:

  Rationale: *to include information on the re-evaluation of the benefit and risk to subjects participating in the study related to COVID-19 infection. Based on the population and disease being studied and the anticipation that COVID-19 related risks are not expected to differ substantially between study subjects and the broader population of subjects receiving treatment for multiple myeloma, no change to the benefit/risk balance for subjects in this study is expected.*
- Update Section 5.1, Overall Study Design and Plan; Section 5.2.4.1, Pretreatment Requirements; Section 5.3.1, Efficacy and Safety Measurements

Assessed; Section 5.3.1.1, Study Procedures; Section 5.3.1.1.1, Screening and Treatment Assessments; Section 5.3.1.1.1, Screening and Treatment Assessments – Table 3. Clinical Laboratory Tests; Section 5.3.1.1.2, Follow-up; Section 5.3.1.3, Collection and Handling of Biomarker and Exploratory Research Samples; Section 5.3.7.1, Disease Assessments; Section 5.3.7.3, Evaluation of Disease; Section 5.4.1, Discontinuation of Individual Subjects from Treatment; Section 5.4.2, Withdrawal from Study Visits; Section 5.5.1, Treatments Administered; Section 6.1.5, Adverse Event Reporting; Section 6.2, Guidelines for Dose Modifications and Treatment; Section 7.0, Protocol Deviations; Section 9.2, Ethical Conduct of the Study; Section 10.1, Source Documents; Section 11.0, Data Quality Assurance:

Rationale: *to provide COVID-19 pandemic-related acceptable protocol modifications.*

- Update Section 5.1, Overall Study Design and Plan: Description; Section 5.3.1.1.1, Screening and Treatment Assessments; Section 5.3.1.1.2, Follow-up; Section 5.3.7.1, Disease Assessments; Section 5.3.7.1, Disease Assessments, Table 4. Assessments for IMWG Response Criteria; Section 5.4.1, Discontinuation of Individual Subjects from Treatment; Section 5.4.3, Withdrawal from Follow-Up:

  Rationale: *the final OS analysis is planned for when approximately 116 OS events occur. All objectives specified in the protocol will be completed with the final OS analysis and therefore from a statistics/scientific perspective: 1) maintaining the study blind is not required 2) all data considered for analysis per protocol can be considered mature.*

- Update Section 5.1, Overall Study Design and Plan: Description; Section 5.4.1, Discontinuation of Individual Subjects from Treatment; Section 5.5.1, Treatments Administered:

  Rationale: *to provide treatment flexibility with bortezomib and dexamethasone dosing per investigator decision once subjects are unblinded.*

- Update Section 5.1, Overall Study Design and Plan: Description; Section 5.3.1.1.1, Screening and Treatment Assessments; Section 5.5.1, Treatments Administered; Section 6.1.7.1, Management of Cytopenias and Infection; Section 6.2.1, Dose Modifications or Delays for Venetoclax/Placebo

Toxicities; Section 6.2.2, Dose Modifications for Moderate or Strong CYP3A Inhibitors Used with Venetoclax/Placebo:

Rationale: *to provide flexibility and simplify study-related procedures for subjects in Arm 2 (Placebo + Bd) at the time of unblinding, as these measures may no longer be applicable to them.*

- Update Section 5.1, Overall Study Design and Plan: Description; Section 5.5.5.2, Blinding of Data for Independent Data Monitoring Committee (IDMC):

  Rationale: *once subjects are unblinded and the final OS analysis is complete, the IDMC supervision will be complete. AbbVie will continue to monitor subjects' safety.*

- Update Section 5.1, Overall Study Design and Plan; Section 5.3.1.1.2, Follow-up; Section 5.4.1, Discontinuation of Individual Subjects from Treatment; Section 5.4.2, Withdrawal from Study Visits:

  Rationale: *to provide an updated end of study guidance once the number of events required for the final OS analysis is reached, as all protocol specified objectives will be complete after the final OS analysis.*

- Update Section 5.1, Overall Study Design and Plan: Description, Figure 1. Study Schema:

  Rationale: *to align with the updated end of study guidance.*

- Update Section 5.3.1.1.1, Screening and Treatment Assessments; Appendix E, Schedule of Assessments – Treatment: Cycles 1 – 8:

  Rationale: *administrative changes.*

- Update Section 5.3.7.1, Disease Assessments; Section 5.3.7.2, IMWG Criteria for Response and Progression; Section 5.4.1, Discontinuation of Individual Subjects from Treatment:

  Rationale: *after the unblinding, study subjects who are benefiting from study treatment will be able to continue in the study as, due to the partial clinical hold, they are not able to be rolled over into an extension study.*

- Update Section 5.3.7.1, Disease Assessments:

  Rationale: *to inform that imaging scans are no longer required to be sent to an independent central imaging vendor because 1) the planned primary*

progression free survival analysis was completed at the first interim analysis; 2) the primary progression free survival/response data is considered mature with no further changes expected.

- Update Section 5.5.5.3, Unblinding Process:

  Rationale: *since objectives specified in the protocol will be completed with the final OS analysis and, from a statistics/scientific perspective, keeping the study blinded following the final OS analysis is not needed, the study can be unblinded once final OS analysis is complete.*

- Update Section 6.1.5, Adverse Event Reporting; Section 10.1, Source Documents; Section 11.0, Data Quality Assurance; Appendix N, Protocol Amendment: List of Changes:

  Rationale: *to align with the current templated standard language.*

- Update Section 13.0, Completion of the Study:

  Rationale: *to define Last Subject Last Visit at the time the number of OS events required for the final OS analysis is reached.*

- Update Appendix B, List of Protocol Signatories:

  Rationale: *to reflect current list of protocol signatories.*

- Update Appendix E, Schedule of Assessments – Treatment: Cycles 1 – 8; Appendix F, Schedule of Assessments – Treatment: Cycles 9 and Beyond Through Treatment Completion Visit; Appendix G, Schedule of Assessments – Follow-up; Appendix I, Sample List of Excluded and Cautionary Medication:

  Rationale: *to align with protocol changes and intended study visits.*

1.2 Synopsis

AbbVie Inc.	**Protocol Number:** M14-031
Name of Study Drug: Venetoclax (ABT-199)	**Phase of Development:** 3
Name of Active Ingredient: Not available	**Date of Protocol Synopsis:** 16 December 2020
Protocol Title: A Phase 3, Multicenter, Randomized, Double Blind, Study of Bortezomib and Dexamethasone in Combination with Either Venetoclax or Placebo in Subjects with Relapsed or Refractory Multiple Myeloma Who are Sensitive or Naïve to Proteasome Inhibitors	
Objectives: The primary objective of the study is to compare the progression-free survival (PFS) between treatment arms in subjects with relapsed or refractory multiple myeloma who are considered sensitive or naïve to proteasome inhibitors and received 1 to 3 prior lines of therapy for multiple myeloma. The secondary objectives are to compare, between treatment arms, the following: Very Good Partial Response (VGPR) or better response rate; PFS in subjects with high BCL-2 expression; duration of response (DOR); Patient Reported Outcomes (PRO) including Worst Pain (Brief Pain Inventory – Short Form [BPI-SF]), Physical Functioning and Global Health Status/Quality of Life (GHS/QoL) (European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core [EORTC QLQ-C30]), and Fatigue (Patient Reported Outcomes Measurement Information System [PROMIS] Cancer Fatigue Short Form [SF]); overall survival (OS); time to disease progression (TTP); objective response rate (ORR); minimal residual disease (MRD) negativity rate; and safety.	
Investigators: Multicenter	
Study Sites: Approximately 120 sites	
Study Population: Adult male and female subjects with relapsed or refractory multiple myeloma who are considered sensitive or naïve to proteasome inhibitors, have received 1 to 3 prior lines of therapy for multiple myeloma, and have measurable disease per International Myeloma Working Group (IMWG) criteria.	
Number of Subjects to be Enrolled: Approximately 280	
Methodology: This is a Phase 3, multicenter, randomized, double blind, placebo-controlled, parallel group study. This study is designed to evaluate the efficacy and safety of venetoclax plus bortezomib and dexamethasone (Bd) in subjects with relapsed or refractory multiple myeloma who are considered sensitive or naïve to proteasome inhibitors and have received 1 to 3 prior lines of therapy for multiple myeloma. The study will consist of three phases: Screening, Treatment, and Follow-Up. Serum, plasma, bone marrow aspirate and bone marrow core biopsy tissue will be collected for biomarker analysis and exploratory research at designated time points throughout the study. **Screening** Unless otherwise specified, screening procedures must be performed within 21 days prior to randomization, including disease assessments per the IMWG criteria. Procedures that are completed as standard of care within 7 days prior to consent may be considered for screening. Laboratory tests not meeting eligibility criteria can be repeated during the screening period to confirm eligibility.	

Methodology (Continued):

Screening (Continued)

Subjects who do not randomize within 21 days of screening will be screen-failed.

Subjects who are screen-failed may be re-screened one additional time. Subjects who are re-screened will be re-consented. Re-screened subjects will keep their original screening number and will begin the screening period once again.

Once screening procedures are complete and eligibility is confirmed, subjects will be randomized 2:1 to one of the following two arms:

- Arm 1: Venetoclax plus Bd
- Arm 2: Placebo plus Bd

Subjects will be stratified based on prior exposure to bortezomib or other proteasome inhibitors (proteasome inhibitor-naïve versus proteasome inhibitor-sensitive) and the number of prior lines of therapy (1 versus 2 or 3).

Treatment

During Treatment, all subjects will receive venetoclax/placebo orally (PO) once daily (QD) plus Bd as follows beginning on Cycle 1 Day 1. Venetoclax/Placebo and dexamethasone should be taken at the site on days when bortezomib is administered (Days 1, 4, 8 and 11 of Cycles 1 – 8, and Days 1, 8, 15 and 22 of Cycles 9 and beyond). On all other days, subjects can self-administer venetoclax/placebo QD. Dexamethasone can be self-administered on Days 2, 5, 9 and 12 of Cycles 1 – 8 and Days 2, 9, 16 and 23 of Cycles 9 and beyond. Delays of up to 7 days in the initiation of a cycle due to toxicity or scheduling issues will be allowed. Unless otherwise noted, cycle visits may be completed within a window of ± 1 day provided the 72-hour bortezomib requirement is kept.

Cycles 1 – 8, 21-Day Cycle Length

- Venetoclax 800 milligram (mg)/Placebo QD on Days 1 – 21
- Bortezomib 1.3 mg/meter $(m)^2$ on Days 1, 4, 8 and 11
- Dexamethasone 20 mg on Days 1, 2, 4, 5, 8, 9, 11 and 12

Cycles 9 and Beyond, 35-Day Cycle Length

- Venetoclax 800 mg/Placebo QD on Days 1 – 35*
- Bortezomib 1.3 mg/m^2 on Days 1, 8, 15 and 22**
- Dexamethasone 20 mg on Days 1, 2, 8, 9, 15, 16, 22 and 23***

* Placebo tablet administration will be discontinued for subjects in Arm 2 (Placebo + Bd) once subjects are unblinded.

** Bortezomib dosing frequency may be reduced or discontinued per investigator's decision and institutional guidelines once subjects are unblinded.

*** Dexamethasone dosing (frequency and/or dose) may be reduced or discontinued per investigator's decision and institutional guidelines once subjects are unblinded.

When unblinding occurs, if subjects from Arm 1 (Venetoclax + Bd) and Arm 2 (Placebo + Bd) are on dexamethasone monotherapy, they must be discontinued from the study treatment and from the study once the Safety Follow-Up Visit is completed.

Study visits will occur on Days 1, 4, 8, and 11 of Cycles 1 – 8. Study visits during Cycle 9 and beyond will occur on Days 1, 8, 15 and 22.

Methodology (Continued):

Treatment (Continued)

Subjects will continue their treatment assignment until documented disease progression per Investigator assessment, unacceptable toxicity, withdrawal of consent, or the subject meets other protocol criteria for discontinuation (whichever occurs first). All subjects will have a Treatment Completion Visit (TCV) performed when treatment is discontinued unless subject has withdrawn consent to participate in the study.

Baseline IMWG assessments will be obtained at Cycle 1 Day 1 prior to first dose of study treatment, unless the Screening IMWG assessments were completed within 7 days of Cycle 1 Day 1. Post-baseline IMWG assessments will be performed throughout the study on Day 1 (± 1 week) of every cycle starting on Cycle 2 Day 1 and continuing until disease progression per the IMWG criteria, or the subject withdraws consent.

In addition to being reviewed by the Investigator and/or qualified site staff, all disease assessment information will be sent to an Independent Review Committee (IRC). Interpretations from the IRC will not be sent to the site.

With the completion of the PFS analysis, post-baseline IMWG assessments are no longer required to be sent to the IRC and will be reviewed only by the Investigator and/or qualified medical site staff.

Follow-Up

All subjects should have one Safety Follow-Up Visit approximately 30 days after the last dose of study treatment.

Subjects who discontinue study treatment for reasons other than progressive disease (e.g., toxicity, non-compliance, etc.) or subjects who receive an off protocol new anti-multiple myeloma therapy will remain on study and continue to be followed for disease progression per the IMWG criteria every 4 weeks (± 1 week) following last dose of treatment for the first year, and then every 12 weeks (± 1 week) thereafter, until progressive disease (PD) or until the number of Overall Survival (OS) events required for the final OS analysis is reached, whichever occurs first. Subjects who experience an event of disease progression or withdraw from study will continue to be followed for survival and post treatment information until the number of OS events required for the final OS analysis is reached.

Survival information and post treatment information will be collected approximately every 12 weeks (or as needed to allow for more frequent data collection) until death, the subject is lost to follow-up, the subject withdraws consent, the number of OS events required for the final OS analysis is reached, or the study is terminated by AbbVie, whichever occurs first. Non-treatment emergent death (those occurring 30 days after the final dose of study drug) information will also be collected until the number of OS events required for the final OS analysis is reached. Subject must request to be withdrawn specifically from survival follow-up.

Diagnosis and Main Criteria for Inclusion/Exclusion:

Main Inclusion:

1. Eastern Collaborative Oncology Group (ECOG) performance score of ≤ 2.
2. Subjects has documented relapsed or progressive multiple myeloma on or after any regimen or is refractory to the most recent line of therapy.
   - Relapsed myeloma is defined as previously treated myeloma that progresses and requires initiation of salvage therapy, but does not meet criteria for refractory myeloma.
   - Refractory myeloma is defined as disease that is nonresponsive (failure to achieve minimal response or development of PD) while on primary or salvage therapy, or progresses within 60 days of last therapy.
3. Subject must have received prior treatment with at least one, but no more than three, prior lines of therapy for multiple myeloma.
   - 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.
4. Prior treatment with bortezomib or other proteasome inhibitor is allowed, provided: ALL of the following criteria are met:
   - Disease is NOT refractory to any proteasome inhibitor, defined as no disease progression (i.e., PD, per IMWG or European Society for Blood and Marrow Transplantation [EBMT] criteria) while receiving proteasome inhibitor therapy or within 60 days after the last dose, AND
   - Best response achieved with any proteasome inhibitor therapy (alone or in combination) was at least a Partial Response (PR), AND
   - Subject did not discontinue any proteasome inhibitor due to intolerance or ≥ Grade 3 related toxicity.
5. Subject has measurable disease at Screening, defined as at least one of the following:
   - Serum M-protein ≥ 0.5 gram (g)/deciliter (dL), OR
   - Urine M-protein ≥ 200 mg in 24 hours, OR
   - Serum immunoglobulin free light chain (FLC) ≥ 10 mg/dL provided serum FLC ratio is abnormal.
6. Subjects must meet the following laboratory parameters, per laboratory reference range:
   - Absolute neutrophil count (ANC) ≥ 1000/microliter (µL) within 2 weeks prior to randomization; subjects may use growth factor support to achieve ANC eligibility criteria.
   - Platelet count ≥ 50,000/millimeter (mm)^3, within 2 weeks prior to randomization. For subjects with > 50% myeloma involvement in the bone marrow, a platelet count of ≥ 30,000/mm^3, within 2 weeks prior to randomization is allowed. Subjects may not have received a platelet transfusion within 72 hours prior to the platelet count used for eligibility.
   - Hemoglobin ≥ 8.0 g/dL, within 2 weeks prior to randomization. Subjects may receive red blood cell (RBC) transfusions in accordance with institutional guidelines to meet this criteria.
   - AST and ALT ≤ 3 × upper limit of normal (ULN).
   - Total bilirubin ≤ 1.5 × ULN. Subjects with documented Gilbert's syndrome may have bilirubin > 1.5 × ULN with the approval of the Primary Therapeutic Area Medical Director (TA MD).
   - Creatinine clearance (CrCl) ≥ 30 milliliter (mL)/minute (min) measured by 24-hour urine collection or calculated using the Cockcroft-Gault formula.

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

Main Exclusion:

1. Subject is refractory to any proteasome inhibitor, defined as progression on or within 60 days of the last dose of a proteasome inhibitor-containing regimen.
2. Subject has had prior treatment with proteasome inhibitor within 60 days prior to first dose of study drug.
3. Subject has any of the following conditions:
   - Non-secretory multiple myeloma
   - Active plasma cell leukemia, i.e., either 20% of peripheral white blood cells or > 2.0×10^9/Liter (L) circulating plasma cells by standard differential
   - Waldenström's macroglobulinemia
   - Amyloidosis
   - Polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes (POEMS syndrome)
   - Known Human Immunodeficiency Viral (HIV) infection
   - Active hepatitis B or C infection based on blood screen tests
   - Significant cardiovascular disease, including uncontrolled angina, hypertension, arrhythmia, recent myocardial infarction within 6 months of randomization, congestive heart failure New York Heart Association (NYHA) Class ≥ 3
   - Major surgery within 4 weeks prior to randomization
   - Acute infections requiring parenteral therapy (antibiotic, antifungal or antiviral) within 14 days prior to randomization
   - Peripheral neuropathy ≥ Grade 3 or ≥ Grade 2 with pain within 2 weeks prior to randomization
   - Uncontrolled diabetes or uncontrolled hypertension within 14 days prior to randomization
   - Any other medical condition that, in the opinion of the Investigator, would adversely affect the subject's participation in the study
4. Subject has a history of other active malignancies, including myelodysplastic syndrome (MDS), within the past 3 years prior to study entry, with the following exceptions:
   - 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 (PSA) levels off treatment,
   - Previous malignancy with no evidence of disease confined and surgically resected (or treated with other modalities) with curative intent and unlikely to impact survival during the duration of the study.
5. If subject had prior stem cell transplant (SCT), subject has evidence of ongoing graft-versus-host disease (GvHD).

Investigational Product:	Venetoclax, 100 mg tablet
Doses:	800 mg QD
Mode of Administration:	Oral

Reference Therapy:	Placebo (to match venetoclax 100 mg tablet)
Doses:	Placebo QD
Mode of Administration:	Oral
Reference Therapy:	Bortezomib powder for solution for injection
Doses:	Cycles 1 – 8: 1.3 mg/m^2 on Days 1, 4, 8 and 11 Cycle 9 and beyond: 1.3 mg/m^2 on Days 1, 8, 15 and 22
Mode of Administration:	Subcutaneous (preferred) or Intravenous
Reference Therapy:	Dexamethasone tablet
Doses:	Cycles 1 – 8: 20 mg on Days 1, 2, 4, 5, 8, 9, 11 and 12 Cycle 9 and beyond: 20 mg on Days 1, 2, 8, 9, 15, 16, 22 and 23
Mode of Administration:	Oral

Duration of Treatment: Subjects will receive venetoclax/placebo plus Bd until documented disease progression, unacceptable toxicity, withdrawal of consent, or the subject meets other criteria for discontinuation per study protocol.

Criteria for Evaluation:

Efficacy:

IMWG assessments for clinical response and progressive disease will be done per IMWG criteria, and will be used to assess PFS, VGPR or better response rate, DOR, TTP, and ORR.

OS will be evaluated according to survival information (i.e., alive or deceased, and if deceased, date and cause of death) and post treatment information (including therapy, dates of therapy and response).

PROs will be evaluated using BPI-SF, EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Multiple Myeloma Module (EORTC QLQ-MY20), PROMIS Cancer Fatigue SF, and EuroQoL EQ-5D-5L (EQ-5D-5L).

Pharmacokinetic:

Pharmacokinetic (PK) samples will be collected and analyzed for venetoclax and bortezomib (and dexamethasone, in subjects enrolled in Japan only). Venetoclax results may be incorporated into a population PK analysis to estimate parameters such as clearance.

Biomarkers:

Biospecimens (serum, plasma, bone marrow aspirate and bone marrow core biopsy tissue) will be collected to investigate biomarkers. Types of biomarkers analyzed may include: BCL-2 family member expression, chromosomal abnormalities (Immunoglobulin [Ig] H translocations, amplifications, or deletions), and MRD negativity. Additional biomarkers analyzed may include nucleic acids, proteins, lipids or metabolites. The samples may be analyzed as part of a multi-study assessment of factors involved in the response to therapy or the disease state.

Pharmacogenetics:

Deoxyribonucleic Acid (DNA) samples may be analyzed for genetic factors contributing to the response to venetoclax in terms of pharmacokinetics, efficacy, tolerability, and safety.

Criteria for Evaluation (Continued):

Safety:

AbbVie will assess adverse events, laboratory data, electrocardiograms (ECG) and vital signs throughout the study. Adverse events intensity and laboratory evaluation changes will be assessed by utilizing National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03.

Statistical Methods:

Efficacy:

Primary Efficacy Endpoint:

The primary efficacy endpoint is PFS. PFS is defined as the time from randomization to the first documented PD or death due to any cause, whichever occurs first. The primary analysis of PFS will be based on data from the IRC's assessment of disease progression.

A stratified two-sided log-rank test will be used to test PFS. Two-sided significance level of this test is 0.05. The hazards ratio for treatment effect will be estimated and its two-sided 95% confidence interval will be provided. In addition, survivorship functions will be estimated by using Kaplan-Meier product-limit method. If reached, median PFS time and its two-sided 95% confidence intervals will be presented by treatment group.

Secondary Efficacy Endpoints:

Secondary efficacy endpoints are as follows: VGPR or better response rate; PROs: Worst Pain (BPI-SF), Physical Functioning (EORTC QLQ-C30); OS; PFS in subjects with high BCL-2 expression; DOR; TTP; ORR; MRD negativity rate; PROs GHS/QoL (EORTC QLQ-C30), and Fatigue (PROMIS Cancer Fatigue SF).

OS is defined as time from randomization to death due to any cause.

VGPR or better response rate is defined as the proportion of subjects with documented Complete Response (CR), stringent Complete Response (sCR), or VGPR.

DOR is defined as the time from first documented response (PR or better) to the date of first documented PD or death due to multiple myeloma, whichever occurs first. TTP is defined as the time from randomization to the date of first documented PD or death due to multiple myeloma, whichever occurs first. ORR is defined as the proportion of subjects with documented PR or better.

A stratified two-sided (cumulative two-sided $\alpha = 0.05$) 3-look group sequential log-rank test will be used to test OS. The hazards ratio (HR) for treatment effect will be estimated and its two-sided 95% confidence interval will be provided.

VGPR or better response rate and ORR will be analyzed by using Cochran-Mantel-Haenszel test. Estimated rates along with corresponding 95% confidence intervals will be presented.

PFS in subjects with high BCL-2 expression, DOR, and TTP will be analyzed by using stratified log-rank test. The hazards ratios for treatment effect will be estimated and two-sided 95% confidence intervals will be provided.

For MRD negativity, estimated rates along with corresponding 95% confidence intervals will be presented.

Patient-Reported Outcomes:

Worst Pain (BPI-SF), Physical Functioning and GHS/QoL (EORTC QLQ-C30), and Fatigue (PROMIS Cancer Fatigue SF) will be analyzed by treatment groups.

Statistical Methods (Continued):

Efficacy (Continued):

Secondary Efficacy Endpoints (Continued):

Statistical Analyses:

The primary analysis of PFS will be performed when approximately 136 PFS events are observed.

Pharmacokinetics:

An analysis of venetoclax plasma concentrations may be performed using a nonlinear mixed effect population PK modeling approach.

Biomarkers:

A pre-defined threshold for BCL-2 expression will be utilized to compare median PFS between treatment arms in subjects with High BCL-2 expression. Additionally, biomarker analyses may be explored based upon the available data and may not be included in the clinical study report. Summary tabulations may be produced if data from a sufficient number of subjects are collected.

Safety:

Safety will be assessed by evaluating study treatment exposure, adverse events, serious adverse events, deaths, and changes in laboratory determinations and vital sign parameters. Subjects who are randomized, but do not receive study drug, will not be included in the analyses of safety.

Sample Size:

For sample size estimation, the median PFS of placebo plus Bd and venetoclax plus Bd is assumed to be 9 months and 16.25 months, respectively (HR = 0.554, under the assumption of proportionality). Two-sided log-rank test with a two-sided type I error rate of $\alpha = 0.05$ and a power of $\geq 90\%$ is used. Under the assumptions above and using a 2:1 randomization ratio to the two arms (venetoclax plus Bd versus placebo plus Bd) a total of 136 PFS events per IRC assessment are required. To observe 136 PFS events per IRC assessment, approximately 280 subjects will be randomized.

1.3 List of Abbreviations and Definition of Terms

Abbreviations

ADL	Activities of Daily Living
AE	Adverse Event
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
aPTT	Activated Partial Thromboplastin Time
ASCO	American Society of Clinical Oncology
AST	Aspartate Aminotransferase
Bd	Bortezomib and dexamethasone
BCL-2	B-cell Lymphoma 2
BMC	Bone Marrow Core
BPI-SF	Brief Pain Inventory – Short Form
BCRP	Breast Cancer Resistance Protein
BUN	Blood Urea Nitrogen
C	Cycle
CBC	Complete Blood Count
CBR	Clinical Benefit Rate
CFR	Code of Federal Regulations
CLL	Chronic Lymphocytic Leukemia
cm	Centimeter
CNS	Central Nervous System
COVID-19	Coronavirus Disease – 2019
CR	Complete Response
CrCl	Creatinine Clearance
CRM	Continual Reassessment Method
CRP	C-Reactive protein
CS	Clinically Significant
CSF	Colony Stimulating Factors
CT	Computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
CYP1A2	Cytochrome P450 1A2

CYP2B6	Cytochrome P450 2B6
CYP2C8	Cytochrome P450 2C8
CYP2C9	Cytochrome P450 2C9
CYP2C19	Cytochrome P450 2C19
CYP2D6	Cytochrome P450 2D6
CYP3A	Cytochrome P450 3A
D	Day
DCR	Disease Control Rate
DDI	Drug Drug interaction
DE	Dose Escalation
dL	Deciliter
DNA	Deoxyribonucleic Acid
DOR	Duration of Response
DSUR	Drug Safety Update Report
DTP	Direct-to-patient
EBMT	European Society for Blood and Marrow Transplantation
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic Data Capture
eCRF	Electronic Case Report Form
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core
EORTC QLQ-MY20	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Multiple Myeloma Module
EQ-5D-5L	EuroQol EQ-5D-5L
FFPE	Formalin-Fixed, Paraffin-Embedded
FISH	Fluorescent In Situ Hybridization
FLC	Free Light Chain
g	Gram
GCP	Good Clinical Practice
G-CSF	Granulocyte colony-stimulating factor
GHS	Global Health Status
GM-CSF	Granulocyte-macrophage colony-stimulating factor
GVHD	Graft-Versus-Host Disease
HBsAg	Hepatitis B Surface Antigen

HCV Ab	Hepatitis C Virus Antibody
HDAC	Histone deacetylase
HDPE	High Density Polyethylene
HIV	Human Immunodeficiency Virus
Hr	Hour
HR	Hazards Ratio
HRQoL	Heath-related Quality of Life
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
Ig	Immunoglobulin
IHC	Immunohistochemistry
IMiD®	Immunomodulatory Thalidomide Derivative Compound
IMP	Investigational Medicinal Product
IMWG	International Myeloma Working Group
INR	International Normalized Ratio
IRB	Institutional Review Board
IRC	Independent Review Committee
IRT	Interactive Response Technology
ISS	International Staging System
ITT	Intent To Treat
IUD	Intrauterine Device
IV	Intravenous
Kg	Kilogram
L	Liter
LD_{50}	Lethal Dose 50%
LDH	Lactate Dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
m	Meter
µg	Microgram
µL	Microliter
MDS	Myelodysplastic Syndrome
Mg	Milligram
Min	Minute

mL	Milliliter
mm	Millimeter
MM	Multiple Myeloma
mmHg	Millimeter mercury
mmol	Millimole
MR	Minimal Response
MRI	Magnetic resonance imaging
MRD	Minimal Residual Disease
mRNA	Messenger Ribonucleic Acid
ms	Milliseconds
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
NCS	Not Clinically Significant
NHL	Non-Hodgkin Lymphoma
nM	Nanomolar
NOAEL	No observed adverse effect level
NYHA	New York Heart Association
OATP	Organic anion transporting polypeptide
ORR	Objective Response Rate
OS	Overall Survival
PD	Progressive Disease
PET	Positron Emission Tomography
PFS	Progression Free Survival
P-gp	P-glycoprotein
PG	Pharmacogenetic
PI	Principal Investigator
PK	Pharmacokinetic
PO	Orally
POEMS	Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal Protein, and Skin Changes
PR	Partial Response
PRO	Patient Reported Outcomes
PROMIS	Patient Reported Outcomes Measurement Information System
PSA	Prostate Specific Antigen
PT	Prothrombin Time

QD	Once Daily
QoL	Quality of Life
qPCR	Quantitative polymerase chain reaction
QTc	QT Interval Corrected for Heart Rate
QTcB	QT Interval Corrected for Heart Rate by Bazett's Formula
QTcF	QT Interval Corrected for Heart Rate by Fridericia's Formula
RBC	Red Blood Cell
RNA	Ribonucleic Acid
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
sβ2M	Serum β2 microglobulin
sCR	Stringent Complete Response
SCT	Stem Cell Transplant
SD	Stable Disease
SE	Safety Expansion
SF	Short Form
sFLC	Serum Free Light Chains
SGOT	Serum glutamic-oxaloacetic transaminase
SGPT	Serum glutamic-pyruvic transaminase
SPEP	Serum Protein Electrophoresis
sQI	Serum Quantitative Immunoglobulins
SmPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
TA MD	Therapeutic Area Medical Director
TCV	Treatment Completion Visit
TLS	Tumor Lysis Syndrome
TNT	Time to Next Treatment
TTP	Time to Disease Progression
TTR	Time to Response
UGTs	UDP-glucuronosyltransferases
ULN	Upper Limit of Normal Range
UPEP	Urine Protein Electrophoresis
VAS	Visual Analog Scale

VGPR	Very Good Partial Response
WBC	White Blood Cell

Pharmacokinetic and Statistical Abbreviations

AUC	Area Under the Plasma Concentration-Time Curve
AUC_{∞}	Area Under the Plasma Concentration-Time Curve from Time Zero to Infinity
CL/F	Apparent Clearance
C_{max}	Maximum Observed Plasma Concentration

Other Clarifications

References to "Study Drug" and "IMP" (Investigational Medicinal Product) are defined as Venetoclax/Placebo and not Bortezomib and/or Dexamethasone.

References to "Study Treatment" are defined as Venetoclax/Placebo, Bortezomib and Dexamethasone.

2.0 Table of Contents

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3.0 Introduction

3.1 Multiple Myeloma (MM)

Multiple myeloma (MM) represents 1% of all cancers and about 13% of all hematologic malignancies. Approximately 86,000 new cases of MM occur annually worldwide.[1] The incidence of MM is 6.7 cases per 100,000 in the United States and 6.0 cases per 100,000 per year in Europe, with an age-adjusted mortality rate of 3.4 cases per 100,000 per year.[2,3] For 2014, it has been estimated that 24,000 new cases of MM would be diagnosed and 11,000 deaths would occur in the United States alone.[4]

Patients with MM experience a number of disease-related symptoms and effects, such as bone destruction and bone pain, bone marrow failure, renal failure, and immunodeficiency, leading to deterioration in health-related quality of life (HRQoL).[5] In a study comparing HRQoL data from survivors of 13 uncommon cancers from individuals without cancer, survivors of MM and pancreatic cancer were among those with the lowest HRQoL scores.[6]

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 overall survival from 3 years to 6 years.[3,7] 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 myeloma 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 Immunomodulatory Thalidomide Derivative Compounds (IMiDs), proteasome inhibitors, histone deacetylase (HDAC) inhibitors, and monoclonal antibodies

(anti-CS1, anti-CD38). Most recommended treatment protocols comprise variable combinations of these drugs. The proteasome inhibitor bortezomib combined with dexamethasone (Bd) has proven therapeutic value and is considered to be one of the standards of care in the treatment of relapsed multiple myeloma.[3,8]

3.2 BCL-2 Family of Proteins in Multiple Myeloma

There are two main pathways of apoptosis or programmed cell death, namely the extrinsic, or death receptor-mediated pathway, and the intrinsic or mitochondrial pathway. The intrinsic pathway is regulated by a delicate balance between anti-apoptotic (BCL-2, BCL-X_L, BCL-W, BFL-1/A1, and MCL-1) and pro-apoptotic (BAX, BAK, BID, BCL-xS, BAD, BIK, BIM, HRK, and NOXA) BCL-2 family proteins. Normally, BAX and BAK are sequestered by the anti-apoptotic proteins BCL-2, BCL-X_L, and/or MCL-1 and prevented from interacting with mitochondria.

Plasma cells are typically geared towards long-term survival and have low apoptotic rates, likely due to high levels of anti-apoptotic proteins such as BCL-2 and MCL-1. Dysregulation of apoptotic pathways in these cells, often via aberrant BCL-2 and/or MCL-1 overexpression, is thought to play a major role in the development and progression of multiple myeloma. Antagonizing BCL-2 and MCL-1 function to induce apoptosis is thus a compelling therapeutic approach in multiple myeloma, and can be achieved by combining the BCL-2-selective inhibitor venetoclax with the proteasome inhibitor bortezomib, which has been demonstrated to upregulate the MCL-1-neutralizing protein NOXA.

3.3 Nonclinical Pharmacology and Clinical Data

Venetoclax Activity

Venetoclax is a novel, orally bioavailable small molecule inhibitor of BCL-2 (K_i < 0.010 nanomolar [nM]) with much lower affinity for BCL-X_L and BCL-W (> 480-fold and > 2,000-fold lower affinity, respectively). *In vitro*, venetoclax has demonstrated cell killing activity against MM cell lines and primary patient samples. The sensitivity of MM

cell lines correlated most closely with their *BCL2/MCL1* messenger ribonucleic acid (mRNA) expression ratio, with the most sensitive cell lines expressing high levels of *BCL2* relative to *MCL1*. MM cell lines bearing the t(11;14) translocation were particularly sensitive to venetoclax (6 of 8 cell lines with a lethal dose 50% [LD_{50}] < 100 nM, median LD_{50} = 10 nM). Similar trends were observed for MM primary samples treated ex vivo with venetoclax, with four of five t(11;14)-positive samples being especially sensitive (LD_{50} < 100 nM).[9]

Venetoclax has also shown efficacy in multiple xenograft models of MM when combined with bortezomib. This combination was clearly more efficacious than either agent alone in the t(14;16) model RPMI-8226 and the t(4;14) models H929, KMS-11 and OPM-2, with improved tumor growth inhibition and tumor growth delay observed in each case. Combination efficacy correlated with an ability of bortezomib to upregulate the MCL-1-inhibiting protein NOXA.

Additional information on venetoclax clinical pharmacology and clinical data (including clinical data with venetoclax in multiple myeloma) can be found in the most current version of the Investigator's Brochure.[12]

Venetoclax Nonclinical Toxicology and Pharmacology

Primary venetoclax-related toxicities were effects on the hematologic system (decreased lymphocytes and red blood cell mass in mice, rats and dogs), the male reproductive system (testicular germ cell depletion in dogs), and embryo-fetal toxicity in mice.

Decreases in lymphocytes and red blood cell (RBC) mass were dose-related and reversible. Lymphocyte decreases are consistent with the expected pharmacology of venetoclax (a selective Bcl-2 inhibitor)[10] and, when sustained over periods of 6 to 9 months in chronic toxicology studies, were not associated with opportunistic infections. B-cells were the most sensitive lymphocyte subtype based on the magnitude of decrease (> 90%) and/or the length of time required for recovery (up to 18 weeks). Decreased RBC mass, typified by decreased hemoglobin, was adverse only at the high dosages

administered (–21% in mice at 600 milligram [mg]/kilogram [kg]/day and –23% in dogs at 150 mg/kg/day). Thrombocytopenia has not been observed in toxicology studies in mice and dogs. These findings are consistent with venetoclax as a BCL-2 specific (BCL-X_L sparing) inhibitor. Venetoclax produced adverse, non-dose-related microscopic findings of testicular germ cell loss in dogs at all dosages tested and did not demonstrate reversibility. In the mouse embryo-fetal development study, increased post-implantation loss and decreased fetal body weights occurred at the highest dosage administered (150 mg/kg/day); the no-observed-adverse-effect-level (NOAEL) was defined at the mid-dose of 50 mg/kg/day. Venetoclax was not teratogenic in mice or rabbits, and there were no other effects on development or fertility.

Other noteworthy findings with venetoclax were epithelial single cell necrosis in multiple tissues and hair coat color change, both in dogs. Single cell necrosis was observed in the gallbladder, exocrine pancreas, epididymides, prostate, and stomach. These findings were not adverse based on minimal to mild severity and no microscopic evidence of loss of mucosal integrity. Partial to complete reversibility was observed.

Venetoclax was tested in a battery of safety pharmacology assays, and produced no effects in the central nervous system (CNS)/neurobehavioral or respiratory studies in mice at oral doses up to and including the highest oral dose of 600 mg/kg. In conscious dogs, venetoclax did not produce any cardiovascular effects up to and including the highest oral dose of 150 mg/kg (maximum observed plasma concentration [C_{max}] = 16 microgram [µg]/milliliter [mL]). At higher plasma concentrations in anesthetized dogs, mild decreases in cardiac contractility and cardiac output, and a small increase in QT Interval Corrected for Heart Rate (QTc) (8 milliseconds [ms]), were observed. These effects occurred at concentrations > 3- to 5-fold above peak clinical concentrations at the maximum dose and were not considered to be clinically relevant due to their small magnitude and lack of a dose-dependent relationship. On the basis of nonclinical safety pharmacology and toxicology evaluations of venetoclax, and on the basis of nonclinical and human studies of related anti-apoptotic BCL-2 family protein inhibitors, potential mechanism-based toxicities may include lymphopenia and neutropenia,[11] signs of tumor

lysis, reduction in red cell mass, decreased spermatogenesis, skin swelling, and hair hypopigmentation.

A detailed discussion of the preclinical toxicology, metabolism, and pharmacology can be found in the most current version of the Investigator's Brochure.[12]

Clinical Pharmacology

Following oral administration, the maximum plasma concentration of venetoclax is generally obtained by 5 to 8 hours. The harmonic mean terminal half-life ranges from 17 to 41 hours following a single oral dose of venetoclax, which supports the proposed daily dosing. In patients with Chronic Lymphocytic Leukemia (CLL), venetoclax showed minimal accumulation, and steady-state Area Under the Plasma Concentration-Time Curve (AUC) increased proportionally over the dose range of 150 to 800 mg.

Venetoclax has been administered with food in all clinical studies, as food increased the bioavailability of venetoclax. In Non-Hodgkin Lymphoma (NHL) patients, administration of venetoclax with low- and high-fat meals increased the venetoclax area under the plasma concentration – time curve from time zero to infinity (AUC_{∞}) by 4.3- and 4.4-fold, respectively, compared to fasting conditions. Similarly, in healthy subjects, venetoclax administration following low-fat and high-fat meals increased venetoclax exposure by approximately 3.4- and 5.1- to 5.3-fold, respectively, compared to fasting conditions. Therefore, venetoclax should be administered with food to ensure adequate bioavailability.

Venetoclax is highly bound to plasma proteins with unbound fraction < 0.01, and it is primarily eliminated as metabolites in feces with negligible renal elimination (< 0.1%). M27 was identified as a major metabolite with an inhibitory activity against Bcl-2 that is at least 58-fold lower than venetoclax *in vitro*. Venetoclax and M27 are predominantly metabolized by cytochrome P450 (CYP) 3A4 (CYP3A4) *in vitro*; UDP-glucuronosyltransferases (UGTs) are not involved in the metabolism of venetoclax. Venetoclax is also substrate for P-glycoprotein (P-gp) and breast cancer resistance protein

(BCRP) transporters. No active uptake of venetoclax was observed in cells overexpressing organic anion transporting polypeptide (OATP) 1B1 or OATP1B3.

The effect of ketoconazole, a potent CYP3A inhibitor, on venetoclax pharmacokinetics (PK) was evaluated in 12 patients with relapsed or refractory NHL. Co-administration of ketoconazole with venetoclax resulted in a 2.3-fold increase in venetoclax maximum observed plasma concentration (C_{max}) and a 6.4-fold increase in AUC_{∞}. The effect of the strong CYP3A inducer rifampin on venetoclax PK was evaluated in 12 female patients of non-childbearing potential. Following co-administration of venetoclax with multiple doses of rifampin when CYP3A induction effects dominate, venetoclax C_{max} and AUC_{∞} decreased by approximately 42% and 71%, respectively, compared to venetoclax administered alone. Comparing the venetoclax exposure following multiple doses of rifampin to that following the first dose of rifampin, venetoclax C_{max} and AUC_{∞} decreased by approximately 72% and 84%, respectively. This comparison isolates the effects of rifampin CYP3A induction effects from its transporter inhibition effects.

Based on *in vitro* results, venetoclax was a P-gp, BCRP, and OATP1B1 inhibitor. It was not a potent *in vitro* inhibitor of CYP3A4, CYP1A2, CYP2B6, or CYP2D6 (IC_{50} > 30 µM); and it did not induce CYP3A4 or CYP1A2 at concentrations up to 10 µM. Venetoclax is also not predicted to cause inhibition of CYP2C19, CYP2C8, CYP2C9, and UGT1A1 at clinically relevant concentrations. It is not an inhibitor of UGT1A4, UGT1A6, UGT1A9 and UGT2B7.

Following co-administration of a single dose of venetoclax with warfarin, R- and S-warfarin C_{max} and AUC_{∞} increased by approximately 18% to 28%. Relatively low variability was observed in warfarin PK.

No specific clinical trials have been conducted in the subjects with hepatic or renal impairment. No dose adjustment is recommended in patients with mild or moderate hepatic or renal (creatinine clearance [CrCl] ≥ 30 mL/min) impairment based on results of the population pharmacokinetic analysis. The analysis indicated no relationship between apparent clearance or apparent volume of distribution and hepatic function. The

contribution of renal processes to the elimination of venetoclax is negligible, with < 0.1% of the dose being recovered in urine. Additionally, the population PK analysis showed no relationship between venetoclax apparent clearance and baseline renal function. Based on the population PK analysis, age, sex, race and weight also do not have an effect on venetoclax clearance.

The potential for venetoclax to affect electrocardiogram parameters was evaluated in patients with relapsed or refractory CLL or relapsed or refractory NHL. Results from this study showed that at doses through 1200 mg once daily (QD), venetoclax had no effect on the QT interval corrected for heart rate using QT Interval Corrected for Heart Rate by Fridericia's formula (QTcF), and there was no relationship between venetoclax exposure and change in QTcF interval.

Venetoclax Clinical Data

As of 17 September 2015, a total of 102 subjects were dosed in two AbbVie oncology Phase 1 studies in multiple myeloma, at doses ranging from 50 mg to 1200 mg.

Study M13-367 is an open-label, multicenter study evaluating the safety, PK and efficacy of venetoclax monotherapy given once daily in subjects with relapsed or refractory MM. In the dose-escalation (DE) cohorts (3 + 3 design), venetoclax was given orally daily at 300, 600, 900, or 1200 mg after a 2-week dose ramp-up. Subjects in the ongoing safety expansion (SE) cohort receive 1200 mg daily after ramp-up. As of 17 September 2015, 57 subjects were dosed with venetoclax in Study M13-367: 30 from DE cohorts and 27 from the SE.

Study M12-901 is an open-label, multicenter study evaluating the safety, PK and efficacy of venetoclax when dosed once daily in combination with bortezomib and dexamethasone in subjects with relapsed or refractory MM. As of 17 September 2015, 45 patients were dosed with venetoclax in the DE cohorts at doses ranging from 50 mg to 1000 mg. Dose escalation followed a continual reassessment method (CRM) design. There is no dose

ramp-up or lead-in period in this study. Subjects (N ~ 12) in the planned SE cohort receive the recommended Phase 3 dose.

Patients in both studies have been heavily pre-treated, with a median (range) number of prior lines of therapy of 4 (1 – 13) and 5 (1 – 13) in Studies M12-901 and M13-367, respectively.

Additionally, a small (n ~ 24) Phase 1 clinical trial is also being conducted in Japan to evaluate the safety and pharmacokinetic profile of venetoclax monotherapy in Japanese subjects with hematological malignancies including multiple myeloma (Study M13-834).

As of 17 September 2015, clinical activity has been observed in both Phase 1 studies using the International Myeloma Working Group (IMWG) criteria.[13,14] In the venetoclax monotherapy Study M13-367, objective responses (partial response [PR] or better) were observed in 5 out of 43 evaluable subjects (11.6%). These responses included 2 complete responses [CR] and 3 very good partial responses [VGPR]. Also, 4 of these responses were observed in subjects with the t(11;14), who comprised 17 of the evaluable subjects.

In Study M12-901, objective responses were reported in 21 of 41 evaluable subjects (51.2%). Importantly, the objective response rate (ORR) was 17% (3/18) in subjects considered refractory to prior bortezomib therapy, but increased to 71% (12/17) in bortezomib-sensitive subjects and 100% (6/6) in bortezomib-naïve subjects, respectively. Furthermore, whereas no VGPR or better responses were reported in bortezomib-refractory patients, 35% and 83% of the bortezomib-sensitive and bortezomib-naïve patients, respectively, experienced VGPR or better responses. Preliminary results also indicate that subjects who had received 1 to 3 prior lines of therapy had higher ORR (83.3%) and VGPR or better (56%), compared to patients who had received 4 – 6 (38.5% ORR) or at least 7 (10% ORR) prior lines of therapy.

As of 17 September 2015, discontinuations in the Phase 1 studies (Studies M13-367 and M12-901) were between 67% – 69%, and mostly related to progressive disease (PD) (61% – 77% of discontinuations). Few discontinuations occurred due to adverse events

(AE) not related to PD (7% – 12% of discontinuations). In Study M12-901, treatment-emergent AEs occurring in ≥ 20% of the subjects were constipation (40%), diarrhea (38%), thrombocytopenia (33%), insomnia (29%), asthenia (27%), peripheral neuropathy (27%), anemia (24%), nausea (24%), dyspnea (22%), peripheral edema (22%), and fatigue (20%). Grade 3 or 4 AEs in ≥ 10% of subjects in Study M12-901 were thrombocytopenia (22%), and anemia (16%). Serious Adverse Events (SAEs) occurred in 19 subjects (42%), none considered related to venetoclax. In ≥ 2 patients, the following SAEs were noted: pneumonia (n = 3), cardiac failure, embolism, pyrexia, sepsis, respiratory failure, and thrombocytopenia (n = 2 each). The safety profile in Study M13-367 was similar, but with fewer sensory peripheral neuropathy (6.3%) and no AE of insomnia reported. In Study M13-367, SAEs occurred in 14 subjects (29%). SAEs in ≥ 2 pts were sepsis (n = 3), cough, pyrexia, pneumonia, and malignant neoplasm progression (2 each). The SAEs of anemia, supraventricular tachycardia and upper abdominal pain (1 of each) were considered possibly related to venetoclax.

Tumor Lysis Syndrome (TLS) was identified as an important risk when initiating venetoclax in CLL patients even with initial doses of 20 and 50 mg doses. To-date, in the dose-finding Phase 1 study, TLS has not been observed in MM patients receiving venetoclax at initial doses of 50 to 1200 mg.

In addition, due to potential mechanism-based toxicities of lymphopenia and neutropenia, serious infections are a potential risk with venetoclax therapy.

All information related to the venetoclax clinical pharmacology and clinical data (including clinical data with venetoclax in multiple myeloma) can be found in the most current version of the Investigator's Brochure.[12]

Rationale for Studying Venetoclax with Bortezomib and Dexamethasone in Multiple Myeloma Subjects

It is hypothesized that multiple myeloma cells expressing high levels of BCL-2 and low levels of MCL-1 would be more susceptible to BCL-inhibition and induction of cell death

by venetoclax. High MCL-1 expression may drive resistance to BCL-inhibition in myeloma cells, as MCL-1 is also an important anti-apoptotic molecule. In this study, the addition of bortezomib is especially attractive due to its ability to upregulate the MCL-1 inhibitor NOXA. Combination efficacy in the nonclinical setting corresponded with bortezomib-mediated NOXA upregulation and disruption of BCL-2-BIM complexes driven by venetoclax. Clinical efficacy data from the Phase 1 combination therapy study of venetoclax plus Bd support the hypothesis, with high rates of PR and better in subjects that are sensitive or naïve to bortezomib therapy.

Additional information on venetoclax clinical pharmacology and clinical data can be found in the most current version of the Investigator's Brochure.[12]

3.4 Differences Statement

The current study is the first randomized, double-blind, multicenter Phase 3 study comparing venetoclax plus Bd versus placebo plus Bd in relapsed or refractory multiple myeloma subjects.

3.5 Benefits and Risks

Despite therapeutic advances, MM remains essentially incurable, associated with high morbidity and mortality, and even with the best available approved agents, all patients will eventually relapse. Furthermore, the remission duration in relapsed myeloma decreases with each regimen.

Based on evidence of clinically meaningful activity observed in Phase 1 studies with venetoclax given as a single agent and when it is combined with the Bd regimen, it is anticipated subjects in the investigational arm may benefit from the combined treatment.

Additionally, all subjects randomized in this trial have already progressed on between 1 to 3 prior lines of therapy and will receive an anti-myeloma regimen of Bd that has proven therapeutic value and is a worldwide standard of care. The safety and efficacy profile of Bd has been established in multiple Phase 3 clinical trials.[15-18]

Guidance on dose management of Bd is based on the bortezomib prescribing information and current standard of care.

As of 17 September 2015, the safety profile of venetoclax as a monotherapy or plus Bd in subjects with relapsed or refractory MM has been consistent with its mechanism of action and the background disease in this population. Based on nonclinical toxicology and clinical studies with venetoclax, toxicities may include lymphopenia, neutropenia, anemia and gastrointestinal adverse events. The rate of peripheral neuropathy in Study M12-901 is in the expected range of a bortezomib-based regimen. Additionally, no cases of TLS have been reported in the Phase 1 studies with venetoclax in MM. An independent data monitoring committee (IDMC) will regularly review safety and efficacy data of treated subjects in this study.

The safety and efficacy data to date of venetoclax plus Bd from the Phase 1 study supports further evaluation of this combination in subjects with relapsed or refractory multiple myeloma.

Following the study's primary analysis, recommendations for antibiotic prophylaxis and dose interruption/reduction for subjects receiving venetoclax/placebo in combination with proteasome inhibitors have been implemented (see Section 5.2.4.1, Section 6.1.7.1 and Section 6.2.1 - Table 8). Additionally, recommendations for pneumococcal and influenza vaccinations applicable for subjects on study treatment have been implemented (see Section 5.2.4.1).

Additional information on venetoclax clinical pharmacology and clinical data (including clinical data with venetoclax in multiple myeloma) can be found in the most current version of the Investigator's Brochure.[12]

Considering the coronavirus (COVID-19) pandemic, the benefit and risk to subjects participating in this study has been re-evaluated. Subjects receiving venetoclax, bortezomib, and dexamethasone may be at an increased risk for COVID-19 infection or experience serious illness if infected. Management of these adverse events will be made

on a case-by-case basis with consideration of benefit/risk. However, based on the population and disease being studied and the anticipation that COVID-19 related risks are not expected to differ substantially between study subjects and the broader population of subjects receiving treatment for multiple myeloma, no change to the benefit/risk balance for subjects in this study is expected.

4.0 Study Objectives

The primary objective of the study is to compare PFS based on the IMWG Criteria,[13,14] as determined by an Independent Review Committee (IRC) between treatment arms in subjects with relapsed or refractory multiple myeloma who are considered sensitive or naïve to proteasome inhibitors and received 1 to 3 prior lines of therapy for multiple myeloma.

The secondary objectives are to compare, between treatment arms, the following: VGPR or better response rate; progression free survival (PFS) in subjects with high BCL-2 expression; duration of response (DOR); patient reported outcomes (PRO) including Worst Pain (Brief Pain Inventory – Short Form [BPI-SF]), Physical Functioning and Global Health Status (GHS)/Quality of Life (QoL) (European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core [EORTC QLQ-C30]), and Fatigue (Patient Reported Outcomes Measurement Information System [PROMIS] Cancer Fatigue Short Form [SF]); overall survival (OS); time to progression (TTP); ORR; minimal residual disease (MRD) negativity rate; and safety.

The tertiary objectives of the study are to assess clinical benefit rate (CBR), disease control rate (DCR), time to response (TTR), time to next treatment (TNT), other PRO endpoints (remaining subscales/items from BPI-SF, EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Multiple Myeloma Module [EORTC QLQ-MY20], and Euroqol EQ-5D-5L), and a preliminary assessment of potential biomarkers for association with PK, safety and efficacy.

5.0 Investigational Plan

5.1 Overall Study Design and Plan: Description

This is a Phase 3, multicenter, randomized, double blind, placebo-controlled, parallel group study. This study is designed to evaluate the efficacy and safety of venetoclax plus Bd in subjects with relapsed or refractory multiple myeloma who are considered sensitive or naïve to proteasome inhibitors and received 1 to 3 prior lines of therapy for MM.

Approximately 280 subjects at approximately 120 sites will be randomized in a 2:1 ratio to receive an oral daily dose of either venetoclax 800 mg or placebo plus Bd, respectively. The study is designed to meet scientific and regulatory objectives without enrolling an undue number of subjects in alignment with ethical considerations. Therefore, if the target number of subjects has been enrolled, there is a possibility that additional subjects in screening will not be enrolled.

The study will consist of the following three phases:

- **Screening:** Study assessments performed prior to randomization, including randomization;
- **Treatment:** Study assessments performed from first dose through the Treatment Completion Visit (TCV);
- **Follow-Up:** Includes the 30 Day Safety Follow-Up Visit. Also includes IMWG assessments performed after the TCV and survival and post-treatment information collected from the date of disease progression until death, subject is lost to follow-up, the number of OS events required for the final OS analysis is reached, or until study termination by AbbVie.

Screening

Unless otherwise specified, screening assessments must be performed within 21 days prior to randomization (see Appendix D and Appendix H for all screening assessments). Procedures that are completed as standard of care within 7 days prior to consent may be

considered for screening. Laboratory tests not meeting eligibility criteria can be repeated during the screening period to confirm eligibility.

Subjects who do not randomize within 21 days of screening will be screen-failed.

Subjects who are screen-failed may be re-screened one additional time. Subjects who are re-screened will be re-consented. Re-screened subjects will keep their original screening number and will begin the screening period once again.

Once screening procedures are completed and eligibility is confirmed, subjects will be randomized 2:1 to one of the following two arms:

- Arm 1: Venetoclax plus Bd;
- Arm 2: Placebo plus Bd.

Subjects will be stratified based on prior exposure to bortezomib or other proteasome inhibitors (proteasome inhibitor-naïve versus proteasome inhibitor-sensitive) and the number of prior lines of therapy (1 versus 2 or 3).

Treatment

Subject treatment must start within 5 days after randomization. Unless otherwise noted, cycle visits may be completed within a window of ± 1 day provided the 72-hour bortezomib requirement is kept. If unable to dose with bortezomib within this allowed window, then the cycle visit must be skipped. A delay of up to 7 days is acceptable for Cycle X Day 1 visits, beginning at Cycle 2 Day 1, due to toxicity or scheduling issues.

During Treatment, all assessments must be performed on the day of the specified visit unless a time window is specified in the schedule of assessments (Appendix E, Appendix F, and Appendix H). Allowed modifications due to COVID-19 are detailed in Section 5.3.1.1.

All eligible subjects will receive venetoclax/placebo orally (PO) once daily (QD) plus Bd as follows beginning on Cycle 1 Day 1. Subjects will be provided with dosing diaries to document Venetoclax/Placebo and Dexamethasone dosing compliance beginning at Cycle 1 and continuing until discontinuation. Subjects in Arm 2 (Placebo + Bd) who remain on study after being unblinded, will only need to document Dexamethasone dosing compliance in their subject dosing diaries. The subject dosing diaries should be reviewed by the Investigator at each clinic visit to assess compliance. Compliance is defined as adhering to the study treatment dosing at least 80% of the time. Subjects who are noncompliant will need to be re-educated by the Investigator and documentation of the re-education added to the source documents.

Due to the COVID-19 pandemic, subject visits may be conducted via phone or video conference. In these situations, subject diaries can be couriered to subjects along with study drug. Adverse events, concomitant medications and dosing compliance listed in the diaries shall be verbally shared with site if a phone or video conference visit occurs Diaries should be returned to the study site when the subject is able to visit the site next, and appropriately filed with the subject's source documents for this study.

Cycles 1 – 8, 21-day cycle length

- Venetoclax 800 mg/Placebo QD on Days 1 – 21
- Bortezomib 1.3 mg/meter $(m)^2$ on Days 1, 4, 8, and 11
- Dexamethasone 20 mg on Days 1, 2, 4, 5, 8, 9, 11, and 12

Cycles 9 and beyond, 35-day cycle length

- Venetoclax 800 mg/Placebo QD on Days 1 – 35*
- Bortezomib 1.3 mg/m^2 on Days 1, 8, 15, and 22**
- Dexamethasone 20 mg on Days 1, 2, 8, 9, 15, 16, 22 and 23***

* Placebo tablet administration will be discontinued for subjects in Arm 2 (Placebo + Bd) once subjects are unblinded.

** Bortezomib dosing frequency may be reduced or discontinued per investigator's decision and institutional guidelines once subjects are unblinded.

*** Dexamethasone dosing (frequency and/or dose) may be reduced or discontinued per investigator's decision and institutional guidelines once subjects are unblinded.

When unblinding occurs, if subjects from Arm 1 (Venetoclax + Bd) and Arm 2 (Placebo + Bd) are on dexamethasone monotherapy, they must be discontinued from the study treatment and from the study once the Safety Follow-Up Visit is completed.

Venetoclax/Placebo will be administered as described in Section 5.5.1. Note: Consider TLS prophylaxis with oral hydration (at least 1 – 2 liters, as tolerable, each day) in all subjects at least 72 hours prior to the first day of dosing with venetoclax/placebo plus Bd and continue as appropriate (refer to Section 6.1.7.2).

Venetoclax/Placebo dose modifications guidelines are provided in Section 6.2.1 and Section 6.2.2, Table 8, and Table 9.

Bortezomib will be administered as described in Section 5.5.1. Bortezomib dose modifications guidelines are provided in Section 6.2.3 and Table 10.

Dexamethasone will be administered as described in Section 5.5.1. Dexamethasone dose modifications guidelines are provided in Section 6.2.3 and Table 11.

Subjects will continue their study treatment assignment until disease progression, unacceptable toxicity or the subject meets other protocol criteria for discontinuation (whichever occurs first). All subjects will have a TCV performed when treatment is discontinued.

Baseline IMWG assessments should be completed at Cycle 1 Day 1 prior to first dose of study treatment, unless the Screening IMWG assessments were completed within 7 days of Cycle 1 Day 1. Post-baseline IMWG assessments will be performed on Day 1, ± 7 days of every cycle starting on Cycle 2 Day 1 (Section 5.3.7.1, Appendix E, Appendix F, and per the guidelines of Appendix J).

Disease assessment for each post-baseline IMWG assessment will be performed by the Investigator and independently reviewed by a team of multiple myeloma experts (IRC). Details regarding the Investigator and IRC assessment progression are provided in Section 5.3.7.3. **Interpretations from the IRC will not be sent to sites.**

With the completion of the PFS analysis, post-baseline IMWG assessments are no longer required to be sent to the IRC and will be reviewed only by the Investigator and/or qualified medical site staff.

An IDMC will periodically review safety and efficacy data. Once the final Overall Survival (OS) analysis is complete (refer to Section 8.1.5.5.2), a final IDMC meeting will be held to review safety and efficacy data. Details regarding the IDMC's review are provided in Section 5.5.5.2.

Follow-Up

All subjects should have one Safety Follow-Up Visit approximately 30 days following the last dose of study treatment.

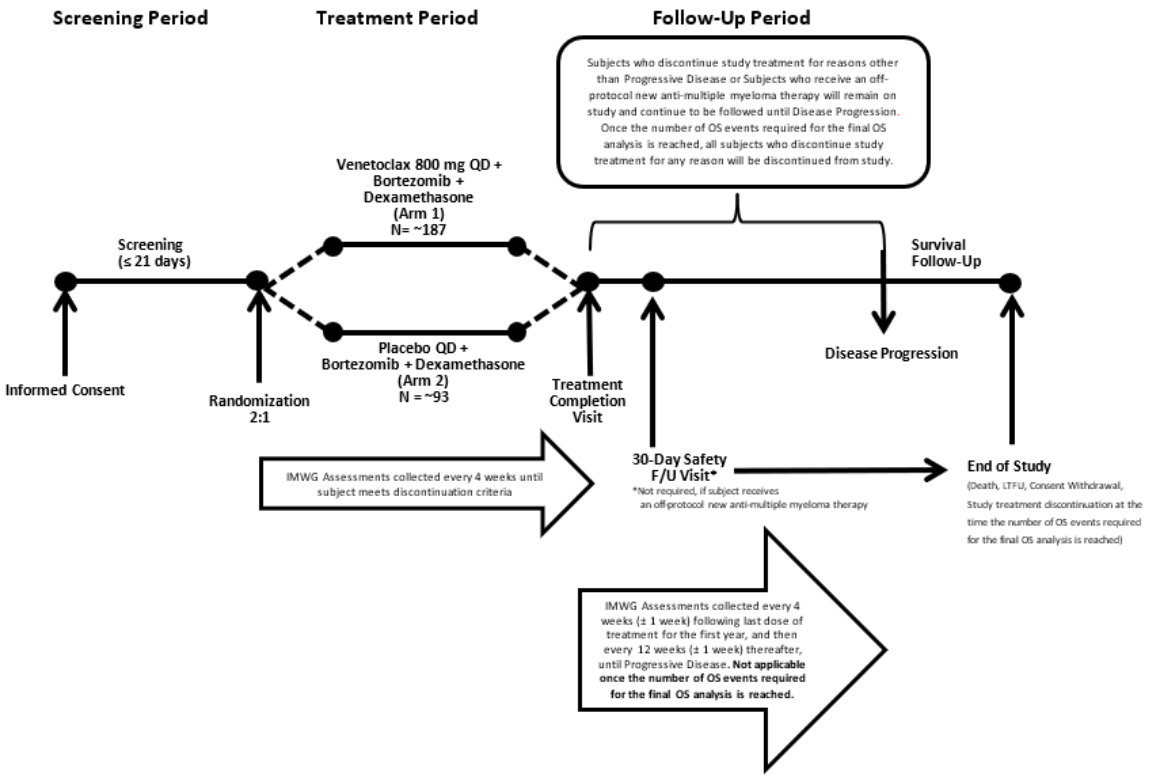
Subjects who discontinue study treatment for reasons other than PD (e.g., toxicity, non-compliance, etc.) or subjects who receive an off protocol new anti-multiple myeloma therapy, will remain on study and continue to be followed for progressive disease per IMWG criteria every 4 weeks (± 1 week) following last dose of treatment for the first year, and then every 12 weeks (± 1 week) thereafter until PD or until the number of OS events required for the final OS analysis is reached, whichever occurs first.

Subjects who experience an event of progressive disease per the IMWG criteria[13,14] or withdraw from the study will continue to be followed for survival and post-treatment information. Survival information and post-treatment information will be collected approximately every 12 weeks (or as needed to allow for more frequent data collection) until the endpoint of death, the subject is lost to follow-up, the number of OS events required for the final OS analysis is reached, or the study is terminated by AbbVie, whichever occurs first.

Subjects who experience an event of progressive disease per the IMWG criteria[13,14] or withdraw from the study treatment once the number of OS events required for the final OS analysis is reached, will be discontinued from the study.

Study visits and assessments are detailed in Section 5.3.1.1.1 and Appendix G.

Figure 1. Study Schema



5.2 Selection of Study Population

Adult male and female subjects with relapsed or refractory multiple myeloma who are sensitive or naïve to proteasome inhibitors, have received 1 to 3 prior lines of therapy for multiple myeloma, and who meet all inclusion criteria and none of the exclusion criteria will be eligible for enrollment into the study.

5.2.1 Inclusion Criteria

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

1. Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2.
2. Subject has documented relapsed or progressive multiple myeloma on or after any regimen or is refractory to the most recent line of therapy.
   - Relapsed myeloma is defined as previously treated myeloma that progresses and requires initiation of salvage therapy, but does not meet the criteria for refractory myeloma.
   - Refractory myeloma is defined as disease that is nonresponsive (failure to achieve minimal response or development of PD) while on primary or salvage therapy, or progresses within 60 days of last therapy.
3. Subject must have received prior treatment with at least one, but no more than three, prior lines of therapy for multiple myeloma (refer to Section 5.2.3).
   - A line of therapy consists of ≥ 1 complete cycle of a single agent, a regimen consisting of combination of several drugs, or a planned sequential therapy of various regimens.
4. Prior treatment with bortezomib or other proteasome inhibitor is allowed, provided ALL of the following criteria are met:
   - Disease is NOT refractory to any proteasome inhibitor, defined as no disease progression (i.e., PD, per IMWG or European Society for Blood and Marrow Transplantation [EBMT] criteria) while receiving proteasome inhibitor therapy or within 60 days after the last dose, AND
   - Best response achieved with any proteasome inhibitor therapy (alone or in combination) was at least a PR, AND
   - Subject did not discontinue any proteasome inhibitor due to intolerance or ≥ Grade 3 related toxicity.
5. Subject has measurable disease at Screening, defined as at least one of the following:

- Serum M-protein ≥ 0.5 g/dL, OR
- Urine M-protein ≥ 200 mg in 24-hours, OR
- Serum immunoglobulin free light chain (FLC) ≥ 10 mg/dL provided serum FLC ratio is abnormal.

6. Subject must meet the following laboratory parameters, per laboratory reference range:

   - Absolute neutrophil count (ANC) ≥ 1000/microliter (µL) within 2 weeks prior to randomization. Subjects may use growth factor support to achieve ANC eligibility criteria.
   - Platelet count ≥ 50,000/millimeter $(mm)^3$, within 2 weeks prior to randomization. For subjects with > 50% myeloma involvement in the bone marrow, a platelet count of ≥ 30,000/mm^3, within 2 weeks prior to randomization is allowed. Subjects cannot receive a platelet transfusion within 72 hours prior to the platelet count used for eligibility.
   - Hemoglobin ≥ 8.0 gram (g)/deciliter (dL), within 2 weeks prior to randomization. Subjects may receive RBC transfusions in accordance with institutional guidelines to meet this criterion.
   - Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 3 × upper limit of normal range (ULN).
   - Total bilirubin ≤ 1.5 × ULN. Subjects with documented Gilbert's syndrome may have bilirubin > 1.5 × ULN with the approval of the AbbVie TA MD or designee (refer to Section 6.1.5).
   - CrCl ≥ 30 mL/minute (min), measured by 24-hour urine collection or calculated using Cockcroft-Gault formula.

     CrCl = ((140 – age in years) × weight in kg × 0.85 if female) / (72 × serum creatinine in mg/dL)

7. France and Japan Subjects Only: PaO_2 ≥ 60 millimeter mercury (mmHg) by arterial blood gas analysis or SpO_2 ≥ 93% by percutaneous oxygen saturation.

8. Subject must be ≥ 18 years of age.

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

10. If female, subject is either not of childbearing potential, defined as postmenopausal for at least 1 year or surgically sterile (bilateral tubal ligation at least 3 months before study participation, bilateral oophorectomy and/or hysterectomy) or is of childbearing potential and is practicing at least one of the following highly effective methods of birth control on Study Day 1 (or earlier) through at least 90 days after last dose of study treatment.

    Examples of approved methods of birth control in this study include the following:

    - Intrauterine device (IUD);
    - Intrauterine hormone-releasing system (IUS);
    - Combined (estrogen and progestogen containing) hormonal contraception (oral, intravaginal, transdermal) associated with the inhibition of ovulation, initiated at least 3 months prior to Study Day 1. Also, barrier method must be used during this study from initial study drug administration to 90 days after the last dose of study drug as drug-drug interaction with venetoclax upon the hormonal contraception is unknown;
    - Progestogen-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation, initiated at least 3 months prior to Study Day 1. Also, barrier method must be used during this study from initial study drug administration to 90 days after the last dose of study drug as drug-drug interaction with venetoclax upon the hormonal contraception is unknown;
    - Bilateral tubal occlusion/ligation at least 3 months before study participation;
    - Bilateral tubal occlusion via hysteroscopy (i.e., Essure), provided a hysterosalpingogram confirms success of the procedure at least 3 months before study participation
    - A vasectomized partner(s) provided the vasectomized partner verbally confirms receipt of medical assessment of the surgical success, and is the sole sexual partner of the WOCBP trial participant;

- Total abstinence: Refraining from heterosexual intercourse when this is in line with the preferred and usual lifestyle of the subject [periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable].

Note: If male, subject agrees to inform their partner(s) that the effects of venetoclax on an unborn fetus or embryo in humans are unknown.

11. Females of childbearing potential must have negative results for pregnancy test performed:
    - At Screening on a serum sample obtained within 21 days prior to randomization.
    - Prior to dosing on a urine sample obtained on the first day of study drug administration, if it has been > 24 hours since obtaining the serum pregnancy test results.
    - Females with documented non-childbearing potential (either postmenopausal or permanently surgically sterile as defined above) at Screening do not require pregnancy testing.

Rationale for Inclusion Criteria

1 – 5, 8	To select the subject population
6 – 7	For the safety of the subjects
9	In accordance with Harmonized Good Clinical Practice (GCP)
10 – 11	The impact of venetoclax on pregnancy is unknown

5.2.2 Exclusion Criteria

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

1. Subject is refractory to any proteasome inhibitor, defined as progression on or within 60 days of the last dose of a proteasome inhibitor-containing regimen.

2. Subject has had prior treatment with proteasome inhibitor within 60 days prior to first dose of study drug.
3. Subject has any of the following conditions:
   - Non-secretory multiple myeloma
   - Active plasma cell leukemia i.e., either 20% of peripheral white blood cells comprised of plasma cells or > 2.0×10^9/liter (L) circulating plasma cells by standard differential
   - Waldenström's macroglobulinemia
   - Amyloidosis
   - POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes)
   - Known Human Immunodeficiency Viral (HIV) infection
   - Active hepatitis B or C infection based on screening blood testing
   - Significant cardiovascular disease, including uncontrolled angina, severe or uncontrolled arrhythmia, recent myocardial infarction within 6 months of randomization, or congestive heart failure New York Heart Association (NYHA) Class ≥ 3
   - France only: Significant cardiovascular or pericardial disease, including uncontrolled angina, severe or uncontrolled arrhythmia, recent myocardial infarction within 6 months of randomization, congestive heart failure New York Heart Association (NYHA) Class ≥ 3
   - Major surgery within 4 weeks prior to randomization
   - Acute infections requiring parenteral therapy (antibiotic, antifungal, or antiviral) within 14 days prior to randomization
   - Peripheral neuropathy ≥ Grade 3 or ≥ Grade 2 with pain within 2 weeks prior to randomization
   - Uncontrolled diabetes or uncontrolled hypertension within 14 days prior to randomization
   - Any other medical condition that, in the opinion of the Investigator, would adversely affect the subject's participation in the study

4. Subject has a history of other active malignancies, including myelodysplastic syndrome (MDS), within the past 3 years prior to study entry, with the following exceptions:
   - 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 (PSA) levels off treatment
   - Previous malignancy with no evidence of disease, confined and surgically resected (or treated with other modalities) with curative intent and unlikely to impact survival during the duration of the study
5. If subject had prior stem cell transplant (SCT), subject has evidence of ongoing graft-versus-host disease (GvHD).
6. Subject has a hypersensitivity or allergy to any of the components of study treatment including bortezomib, boron, mannitol, or dexamethasone.
7. Subject has received prior treatment with a BCL-2 family inhibitor.
8. Subject has been treated or received any of the following:
   - Allogeneic or syngeneic SCT within 16 weeks prior to randomization.
   - Autologous SCT within 12 weeks prior to randomization.
   - Immunization with live vaccine within 8 weeks prior to randomization.
   - Anti-myeloma monoclonal antibodies within 6 weeks prior to randomization.
   - Any anti-myeloma therapy (other than monoclonal antibodies), including chemotherapy, biological, immunotherapy or an investigational therapy, including targeted small molecule agents within 2 weeks prior to randomization.
   - Anti-myeloma radiotherapy within 14 days prior to randomization.
   - Corticosteroid therapy at a dose equivalent to > 4 mg/day of dexamethasone or a single dose of corticosteroid greater than or equal to the equivalence of 40 mg/day dexamethasone within 2 weeks prior to randomization.

- A strong or moderate CYP3A inhibitor or inducer within 1 week prior to randomization (refer to Section 5.3.1.2).

9. Japan Subjects Only: Clinically indicated interstitial pneumonitis, pulmonary fibrosis, or abnormal (e.g., ground glass opacity or linear) interstitial shadow bilaterally by a chest-computerized tomography (CT) scan (high resolution) regardless of symptom, or high value of KL-6, SPA or SP-D, to be consulted with chest physician or other expert as necessary.
10. Female subject who is pregnant, breastfeeding or is considering becoming pregnant during the study or for approximately 90 days after the last dose of study treatment.
11. Male subject who is considering fathering a child or donating sperm during the study or for approximately 90 days after the last dose of study drug.

Rationale for Exclusion Criteria

1 – 2	To select the appropriate subject population
3 – 9	For the safety of the subjects
10	The impact of venetoclax on pregnancy is unknown

5.2.3 Determination of the Number of Prior Lines of Therapy

A line of therapy consists of at least 1 complete cycle of a single agent, a regimen consisting of combination of several drugs, or a planned sequential therapy of various regimens.[19]

A treatment is considered a new line of therapy if any of these 3 following conditions are met:

- Start of a new line of treatment after discontinuation of a previous line: If a treatment regimen is discontinued for any reason and a different regimen is started, it should be considered a new line of therapy. A regimen is considered

to have been discontinued if all the drugs in that given regimen have been stopped. A regimen is not considered to have been discontinued if only some of the drugs of the regimen, but not all, have been discontinued.

- The unplanned addition or substitution of 1 or more drugs in an existing regimen: Unplanned addition of a new drug or switching to a different drug (or combination of drugs) due to any reason is considered a new line of therapy.
- SCT: In patients undergoing > 1 SCT, except in the case of a planned tandem SCT with a predefined interval (such as 3 months), each SCT (autologous, allogeneic, or syngeneic) should be considered a new line of therapy regardless of whether the conditioning regimen used is the same or different. Data on type of SCT should also be captured.

5.2.4 Prior and Concomitant Therapy

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

The AbbVie TA MD or designee (refer to Section 6.1.5) should be contacted if there are any questions regarding prior and concomitant therapies.

5.2.4.1 Pretreatment Requirements

All subjects must start the following treatment at least 24 hours prior to dosing with bortezomib:

- Acyclovir (400 mg orally [PO] twice a day or local standard dosing) or valacyclovir (500 mg PO once a day or local standard dosing) or other equivalent antiviral during treatment with bortezomib (additional prophylaxis is at the Investigator's discretion).

Prophylaxis for Grade 3 or Serious Infections

All subjects receiving treatment with venetoclax/placebo in combination with a proteasome inhibitor **must** receive antibiotic prophylaxis as outlined in Section 6.1.7.1, Management of Cytopenias and Infection.

Pneumococcal and Influenza Vaccination

All subjects **must** be vaccinated against pneumococcus and receive a yearly influenza vaccination (live attenuated vaccines are not allowed), while on study treatment. It is mandated that pneumococcal and yearly influenza vaccinations be administered after signing the updated informed consent for all subjects who have not previously received the influenza and/or pneumococcal vaccine within the recommended time frame per local and/or institutional vaccination guidelines, unless contraindicated, not available, or not applicable per local standard of care.

It is recommended that subjects in Progression Follow-up and/or Survival Follow-up remain vaccinated against pneumococcus and receive a yearly influenza vaccination at the discretion of the investigator.

Please refer to local label and/or institutional guidelines for additional information (e.g., vaccination/booster schedules) and contraindications regarding pneumococcal and influenza vaccinations. Local and/or institutional vaccination references must be recorded in the site source documents.

Pneumococcal and Influenza vaccination information must be recorded on the Vaccination eCRF.

COVID-19 Pandemic-Related Acceptable Protocol Modification:

A delay in pneumococcal and/or influenza vaccination may take place per PI discretion if the subject tests positive for COVID-19 until such time that the subject has clinically

recovered or per institutional guidelines. In all other cases, pneumococcal and/or Influenza vaccinations should continue as scheduled per protocol.

5.2.4.2 Allowed Treatments

The following concomitant medications **are allowed** during study treatment. Please refer to Table 1 for a list of restricted medications due to potential drug-drug interaction (DDI) when considering the use of the following:

- Hormonal contraceptives (examples include birth control pills, vaginal rings, or patches), associated with inhibition of ovulation for at least 3 months prior to taking study treatment.
- Colony stimulating factors (granulocyte colony-stimulating factor [G-CSF], granulocyte-macrophage colony-stimulating factor [GM-CSF]) will be allowed per American Society of Clinical Oncology (ASCO) guidelines.[20]
- Bisphosphonates intravenous (IV) or PO as indicated per Institutional guidelines.
- Oral proton-pump inhibitor (lansoprazole, omeprazole, esomeprazole, etc.) as prophylactic therapy for peptic ulcer disease during treatment with dexamethasone.
- Antimicrobial (including anti-fungal) prophylaxis.
- Anticoagulants to prevent or treat thromboembolic events.
- Best supportive care and treatment (e.g., antiemetics, antibiotics, transfusions, nutritional support, pain control, etc.).
- Only low dose corticosteroids (e.g., prednisone ≤ 10 mg PO QD or its equivalent), inhaled steroids and topical preparations for reasons other than multiple myeloma (e.g., asthma) are allowed during study treatment. Systemic corticosteroids > 10 mg PO QD of prednisone (or its equivalent) should not be given on the same day as dexamethasone is administered. Systemic corticosteroids > 10 mg PO QD of prednisone (or its equivalent) are allowed when dexamethasone has not been interrupted provided that the dose of prednisone (or its equivalent) was given for less than 7 days and the cumulative dose was < 120 mg. For additional guidance and to determine the equivalent

dose of systemic corticosteroid, please refer to the Corticosteroid Conversion Table, Appendix M.

- Surgery and radiation:
  - Localized radiation therapy to a site of pre-existing disease may be permitted while on study. Following approval by the AbbVie TA MD or designee (refer to Section 6.1.5), the subject may initiate or continue with protocol therapy without interruption during the course of palliative radiation therapy if the Investigator believes that the risk of excessive bone marrow suppression or other toxicity is acceptable, and it is in the best interest of the subject to do so.
  - If the subject develops a definite increase in the size of existing bone lesions or soft tissue plasmacytomas that meets the criteria for progressive disease, treatment must be discontinued for progressive disease 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 Case Report Form.

5.2.4.3 Excluded and Cautionary Medications

General guidelines regarding excluded and cautionary medications are summarized in Table 1.

Table 1. Excluded and Cautionary Medications

Excluded
• Any systemic anti-myeloma therapies other than bortezomib, dexamethasone and venetoclax while on study treatment. • Biologic agents (e.g., monoclonal antibodies) for anti-neoplastic intent.
Cautionary, Additional Guidance Noted
• **Strong and Moderate CYP3A inhibitors** Consider alternative medications. If subject requires use of these medications, use with caution and reduce the venetoclax dose by 2-fold for moderate inhibitors and 4-fold for strong inhibitors during co-administration. Patients should be monitored more closely for signs of toxicities and the dose may need to be further adjusted. After discontinuation of CYP3A inhibitor, wait for 3 days before venetoclax dose is increased back to the previous dose level. • **Strong and Moderate CYP3A inducers** Consider alternative medications. If subject requires use of these medications, use with caution and contact AbbVie TA MD or designee (refer to Section 6.1.5) for guidance.
Cautionary
• Warfarin and coumadin derivatives • P-gp substrates • BCRP substrates • OATP1B1/1B3 substrates • P-gp inhibitors • BCRP inhibitors • High Dose Corticosteroids[a]

a. Refer to Appendix M for additional guidance.

A sample list of excluded medications and cautionary medications that fall into the categories within Section 5.2.4.3 is contained in Appendix I. It is not possible to produce a 100% exhaustive list of medications that fall into these categories, so if in question, please refer to the appropriate product label.

5.3 Efficacy, Pharmacokinetic, Biomarker, Exploratory Research and Safety Assessments/Variables

5.3.1 Efficacy and Safety Measurements Assessed

The study visit and procedure schedules for each phase of the study are outlined in Appendix D (Schedule of Assessments – Screening), Appendix E (Schedule of Assessments – Treatment: Cycles 1 – 8), Appendix F (Schedule of Assessments – Treatment: Cycles 9 and Beyond Through TCV), and Appendix G (Schedule of Assessments – Follow-Up). Additional information regarding pharmacokinetic, pharmacogenomics, and biomarker collections can be found in Appendix H.

Japan Subjects Only: The safety of the first 12 subjects enrolled in the run-in phase will be assessed. Based on the safety results of the first 12 subjects and it is determined that enrollment can continue, the study will proceed to the randomized phase. All of the subjects in the run-in phase will be hospitalized during Cycle 1. Operational details are described in the Japan run-in phase manual.

COVID-19 Pandemic-Related Acceptable Protocol Modification:

Pharmacokinetic, biomarker, and exploratory research samples (Appendix H) may only be collected at the study site and are not to be collected if travel restrictions or other changes in local regulations in light of the COVID-19 pandemic prevent the subject from visiting the study site at a sample collection time point.

5.3.1.1 Study Procedures

The study procedures are discussed in detail in this section, with the exception of treatments administered and timing of dose (Section 5.5.1), monitoring of treatment compliance (Section 5.5.6) and adverse event information (Section 6.1.1.1). All study data will be recorded on eCRFs.

Study visits may be impacted due to the COVID-19 pandemic. This may include changes such as phone or virtual visits, visits at alternative locations, or changes in the visit

frequency and timing of study procedures, among others. Every effort should be made to ensure the safety of subjects and site staff, while maintaining the integrity of the study. Additional details are provided in the following sections of the protocol, in case visits cannot be conducted onsite due to travel restrictions or other pandemic-related reasons:

- Section 3.5, Benefits and Risks
- Section 5.1, Overall Study Design and Plan: Description
- Section 5.2.4.1, Pretreatment Requirements
- Section 5.3.1, Efficacy and Safety Measurements Assessed
- Section 5.3.1.1, Study Procedures
- Section 5.3.1.1.1, Screening and Treatment Assessments:
  - Informed Consent
  - Concomitant Medications and AE Assessments
  - Physical Examination
  - Vital Signs
  - ECOG Performance Status
  - Patient Reported Outcome (PRO) Assessments
  - Cardiac Assessments
  - Clinical Laboratory Tests
- Section 5.3.1.1.2, Follow-Up
- Section 5.3.1.3, Collection and Handling of Biomarker and Exploratory Research Samples
- Section 5.3.7.1, Disease Assessments:
  - Laboratory Tests for Multiple Myeloma
  - Skeletal Survey
  - Plasmacytoma Evaluation
  - Bone Marrow Aspirate and Biopsy
- Section 5.3.7.3, Evaluation of Disease
- Section 5.4.1, Discontinuation of Individual Subjects from Treatment
- Section 5.4.2, Withdrawal from Study Visits

- Section 5.5.1, Treatments Administered
- Section 6.1.5, Adverse Event Reporting
- Section 6.2, Guidelines for Dose Modifications and Treatment
- Section 7.0, Protocol Deviations
- Section 9.2, Ethical Conduct of the Study
- Section 10.1, Source Documents
- Section 11.0, Data Quality Assurance

5.3.1.1.1 Screening and Treatment Assessments

Subjects will undergo screening procedures within 21 days prior to randomization. For procedures performed at screening and repeated prior to dosing on Cycle 1 Day 1, the later procedure(s) will serve as baseline for clinical assessment. Procedures that are completed as standard of care within 7 days of consent may be considered for screening.

Informed Consent

Signed informed consent will be obtained from the subject or the subject's legally acceptable representative before any study-specific procedures are undertaken or before any prohibited medications are withheld from the subject in order to participate in this study. Informed consent is also required for optional exploratory research sampling. Details about how informed consent will be obtained and documented are provided in Section 9.3.

COVID-19 Pandemic-Related Acceptable Protocol Modification:

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

Medical and Oncology History

The medical history includes complete medical history, including documentation of any clinically significant medical condition(s); history of tobacco and alcohol use.

Detailed Oncology History

The following will be documented:

- Date of multiple myeloma diagnosis
- Histopathology and Cytogenetic information
- Staging/Grading
- Any surgical procedures
- Prior treatments administered (including dates, type of modality, response to treatment and reason for treatment discontinuation)
- Proteasome inhibitor naiveté/sensitivity must be assessed and documented per the definitions in Inclusion Criterion 2
- The number of prior lines of therapy must be assessed and documented per the definition provided in Inclusion Criterion 3 and Section 5.2.3.

On Cycle 1 Day 1, any changes observed (i.e., abnormal laboratory or vital sign assessment) from the screening assessments, prior to dosing, and not considered related to study-specific required procedures will be recorded in the subject's medical or oncology history, as applicable and will serve as the subject's baseline. At each subsequent visit, the subject's condition will be reviewed and any clinically significant changes from baseline will be recorded in the source documents and on the adverse event eCRF.

Additional guidance for IMWG diagnostic criteria can be found in Appendix C.

Concomitant Medication and AE Assessments

Concomitant medication and AE assessments will be performed prior to the initial dose at each subject visit, per Appendix D, Appendix E, Appendix F, and Appendix G.

COVID-19 Pandemic-Related Acceptable Protocol Modification:

Due to the COVID-19 pandemic, concomitant medication and adverse event assessment visits may be conducted via phone or video conference. Additional guidance for the reporting of COVID-19 adverse events (including the capture of specific signs/symptoms of infection and testing results) can be found in Section 6.1.5.

Physical Examination

Physical examinations (full and targeted exams), including body weight, will be performed per Appendix D, Appendix E, Appendix F, and Appendix G. The targeted physical exam includes an assessment of heart, lung, and abdomen, and any body system, guided by the examiner's observations or subject complaints on new or changed conditions, symptoms, or concerns. Target exams can be performed by the Principal Investigator (PI) or delegated to qualified medical staff (e.g., a sub-Investigator, nurse, etc.).

If the screening physical examination is performed within 7 days of Cycle 1 Day 1, it is not required to repeat the exam on Cycle 1 Day 1 unless clinically indicated. Physical examinations after screening may be performed within 72 hours before or after the scheduled visit. Clinically significant changes from baseline will be documented in the source documentation and eCRFs as adverse events.

Height will be measured at the Screening Visit only. For height and weight, subject should not wear shoes.

COVID-19 Pandemic-Related Acceptable Protocol Modification:

Due to the COVID-19 pandemic, subject visits may be conducted via phone or video conference. In these situations, body weight may be collected by the subject or caregiver as needed, and physical exam may be performed by another licensed practitioner.

Vital Signs

Vital signs will be performed at each visit, per Appendix D, Appendix E, Appendix F, and Appendix G. Vital sign determinations include sitting blood pressure, heart rate, respiratory rate, and body temperature. Vital signs should be measured prior to blood collections and prior to dosing with venetoclax/placebo and Bd. It is recommended that vitals should be assessed after the subject has been seated quietly for at least 5 minutes.

COVID-19 Pandemic-Related Acceptable Protocol Modification:

Due to the COVID-19 pandemic, subject visits may be conducted via phone or video conference. In these situations, vital signs may be obtained by another licensed practitioner, or collected by the subject or caregiver as needed.

ECOG Performance Status

The ECOG performance status will be assessed per Appendix D, Appendix E, Appendix F, and Appendix G using the following criteria:

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.

COVID-19 Pandemic-Related Acceptable Protocol Modification:

Due to the COVID-19 pandemic, subject visits may be conducted via phone or video conference. If subjects are unable to be assessed by the study site, ECOG performance status may be performed by another licensed practitioner.

Patient-Reported Outcome (PRO) Assessments

PRO assessments include BPI-SF, EORTC QLQ-C30, EORTC QLC-MY20, PROMIS Cancer Fatigue SF, and EQ-5D-5L. These assessments will be collected per Appendix D, Appendix E, and Appendix F throughout the trial until the final OS analysis. Once the number of OS events required for the final OS analysis is reached, PRO assessments will no longer be collected.

Subjects may complete all baseline PRO assessments within 72 hours prior to the first dose of venetoclax/placebo. It is required that PRO assessments be completed prior to any other clinical assessments and prior to dosing for subsequent cycle visits. If a PRO assessment is collected on a non-protocol required visit date, as requested per Appendix D, Appendix E and Appendix F, this PRO assessment may be reclassified.

BPI-SF

The BPI-SF is a pain-specific measure developed to assess patient-reported severity (or intensity) of pain (4 items) and the impact of pain on daily functioning (7 items) in patients with cancer pain.[21] The four pain severity items assess pain at its "worst," "least," "average," and "now" (current pain). For these items, patients are asked to rate their pain on an 11-point numeric rating scale with anchors of 0 (no pain) and 10 (pain as bad as you can imagine). The BPI "worst" pain severity item has been shown to be reliable and valid for use as a single item.[22] The BPI-SF also includes questions to measure the interference of pain in the patient's daily life, including general activity, mood, ability to walk, normal work both outside the home and housework, relations to other people, sleep, as well as enjoyment of life. For these items, patients are asked to describe the extent to which pain

has interfered on an 11-point numeric rating scale with anchors of 0 (does not interfere) to 10 (completely interferes).

EORTC QLQ-C30

HRQoL and symptoms will be assessed with the EORTC-QLQ-C30 version 3.[23] The QLQ-C30 is a 30-item subject self-report questionnaire composed of both multi-item and single scales, including five functional scales (physical, role, emotional, social, and cognitive), three symptom scales (fatigue, nausea and vomiting, and pain), a global health status/quality of life scale, and six single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). Subjects rate items on a four-point scale, with 1 as "not at all" and 4 as "very much." The QLQ-C30 was developed and validated for use in a cancer patient population, and its reliability and validity is highly consistent across different language-cultural groups.

EORTC QLQ-MY20

The EORTC QLQ-MY20 was developed as an additional module for the QLQ-C30 and is composed of 20 multiple myeloma specific items.[24] The QLQ-MY20 includes scales for disease symptoms, side effects of treatment, future perspective, and body image. Values for each scale range from 0 to 100. Subjects rate items on a four-point scale, with 1 as "not at all" and 4 as "very much." The QLQ-MY20 is a reliable and valid instrument for measuring quality of life in myeloma patients.

PROMIS Cancer Fatigue SF

The PROMIS® is a system of highly reliable, precise measures of patient-reported health status for physical, mental, and social well-being.[25] PROMIS instruments measure concepts such as pain, fatigue, physical function, depression, anxiety and social function. Fatigue will be assessed using the PROMIS Cancer Fatigue SF that has been developed for use in oncology populations.[26,27] PROMIS Cancer Fatigue SF is a seven item questionnaire that assesses the impact and experience of fatigue over the past 7 days. All

questions employ the following five response options: 1 = Not at all, 2 = A little bit, 3 = Somewhat, 4 = Quite a bit, and 5 = Very much.

EQ-5D-5L

The EQ-5D-5L is a generic preference instrument that has been validated in numerous populations.[28] The EQ-5D-5L has five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. These dimensions are measured on a five level scale: no problems, slight problems, moderate problems, severe problems, and extreme problems. The EQ-5D-5L also contains a visual analog scale (VAS) to assess the subject's overall health.

Table 2. Patient-Reported Outcome Assessments

Administration Order	Test	Administration Time
1	BPI-SF	Approximately 5 minutes
2	PROMIS Cancer Fatigue SF	Approximately 5 minutes
3	EORTC QLQ-C30	Approximately 12 minutes
4	EORTC QLQ-MY20	Approximately 5 minutes
5	EQ-5D-5L	Approximately 5 minutes
		Total Admin Time: Approximately 32 minutes

COVID-19 Pandemic-Related Acceptable Protocol Modification:

Due to the COVID-19 pandemic, subject visits may be conducted via phone or video conference. All PROs are eligible for completion by interview at such visits; however, if it is not possible to complete all PROs during the telephone interview, the PRO completion prioritization is as follows (highest to lowest priority): EORTC QLQ-C30, EORTC QLQ-MY20, EQ-5D-5L, PROMIS and BPI-SF. In this situation, the interviewer properly delegated for this assessment will read the PRO questions and response options to the subject and record the subject responses either on paper or directly into the electronic web-based system. If subject responses are recorded on paper, the Subject ID number, visit identification, date and time that each PRO was started and completed

should be recorded along with the interviewer's name on each page of the paper screen report and recorded in the source. In both cases, the site must also record in the source that the PRO data collection was performed remotely along with who collected the information. The subject's ability to view the PRO to understand the questions and response options should be preserved. Sites may share the questionnaire by videoconference or send the questionnaires (email or hard copy) to the subjects to allow them to read/understand the questions and responses when the subject is providing responses over the phone.

Cardiac Assessments

Cardiac assessments will be performed using a 12-lead electrocardiogram. Data from the cardiac assessment will be entered into the electronic data capture (EDC) eCRF within 5 days of report availability.

12-Lead Electrocardiogram (ECG)

A resting 12-lead ECG will be performed per Appendix D and Appendix F. An appropriately qualified physician at the study site (local reader) will determine if any findings outside normal physiological variation are clinically significant. The local reading of the ECG will be used by the Investigator for subject safety assessments, including adverse event determination and management, and termination of subjects from the study. The local reader will sign and date the ECG tracing and provide a global interpretation using the following categories:

- normal ECG
- abnormal ECG – not clinically significant (NCS)
- abnormal ECG – clinically significant (CS)
- unable to evaluate

All ECGs will be entered into the eCRF. If the global interpretation is abnormal (CS), the Investigator will provide specifics pertaining to the abnormality (e.g., sinus bradycardia,

arrhythmias). The corrected QT interval measurement will be documented only if the Investigator selects the "prolonged QT" box for an abnormal ECG. Correction by the Bazett formula (QTcB) is suggested for consistency across sites; however, correction by other methods may be acceptable based on discussion with the AbbVie TA MD or designee. A copy of any other ECGs will sent to AbbVie, if requested. The original ECG tracing will be retained in the subject's records at the study site.

COVID-19 Pandemic-Related Acceptable Protocol Modification:

In the event the ECG cannot be performed at the study site due to study modifications related to the COVID-19 pandemic, the ECG may be completed at other centers providing the modality/technique is equivalent.

Lung Disease Risk Assessment – JAPAN and FRANCE ONLY

All subjects enrolled in Japan and France are required to complete the following assessments below:

- a PaO_2 by arterial blood gas analysis or SpO_2 by percutaneous oxygen saturation at screening will be performed
- a chest CT (high resolution) scan at screening

Tests may be followed during the study visits at the discretion of the investigator.

Pregnancy Test

For female subjects of childbearing potential, pregnancy testing will be performed per Appendix D and Appendix E (if necessary). Pregnancy tests must have a minimal sensitivity of ≥ 25 IU/L.

Subjects considered not of childbearing potential must be surgically sterile or postmenopausal for at least 1 year.

Clinical Laboratory Tests

All subjects will undergo the laboratory assessments listed in Table 3 per the schedule in Appendix D, Appendix E, and Appendix F.

Certified local laboratories will be utilized to process and provide results for the hematology and chemistry labs listed in Table 3. These data will be used for all data analysis. The appropriate certifications will be collected from the local laboratories.

A certified central laboratory will be utilized to process and provide results for coagulation, viral serologies, urinalysis, and special chemistry labs listed in Table 3. These data will be used for all data analysis. The central laboratory will provide instructions regarding the collection, processing, handling, and shipping of samples.

Qualified medical staff at the study site will review, initial, and date all central and local laboratory results. Any laboratory value outside the reference range that is considered clinically significant by the Investigator will be followed as appropriate.

COVID-19 Pandemic-Related Acceptable Protocol Modification:

If travel restrictions or other changes in local regulations in light of the COVID-19 pandemic prevent the subject from having blood drawn for laboratory testing at the study site, if possible, arrange for subjects to have laboratory work done at a local laboratory, hospital, or other facility. Local lab results should be obtained along with reference ranges and kept within the subjects' source documentation. Local lab results should be reviewed by the investigator as soon as possible and prior to study drug dispensation.

At minimum, safety lab samples [hematology, chemistry, urine pregnancy testing (women of childbearing potential), and coagulation panel (when applicable)] should be collected and reviewed by the investigator at least once per cycle to have venetoclax/placebo and dexamethasone dispensed.

In case of bortezomib, safety lab samples [hematology, chemistry, urine pregnancy testing (women of childbearing potential), and coagulation panel (when applicable)] must be collected and reviewed by the investigator prior to each bortezomib administration. If this is not possible, bortezomib cannot be dispensed to the subject.

If safety lab samples cannot be collected and related results reviewed by the investigator as described above, venetoclax/placebo, dexamethasone or bortezomib cannot be dispensed to the subject.

Coagulation

Prothrombin time (PT)/Activated Partial Thromboplastin Time (aPTT) and International Normalized Ratio (INR) will be performed per Appendix D.

Coagulation tests will be done for all subjects at screening and only in subjects being treated with medication for thromboembolic prophylaxis thereafter on Day 1 of each cycle. Subjects who are not on vitamin K antagonists do not require coagulation tests after screening.

Hepatitis Serologies

Samples will be collected to identify Hepatitis B surface antigen (HBsAg), and Hepatitis C Virus antibody (HCV ab) antibody and ribonucleic acid (RNA) if HCV ab is positive per Appendix D.

Table 3. Clinical Laboratory Tests

Hematology – Local Lab	**Serum Chemistry – Local Lab**	**Urinalysis – Central Lab**
Hematocrit Hemoglobin RBC count White blood cell (WBC) count Neutrophils Lymphocytes Monocytes Basophils Eosinophils Platelet count (estimate not acceptable) Reticulocyte Count (Screening, Day 1 of each cycle, and TCV only)	Blood urea nitrogen (BUN) or urea Creatinine Total bilirubin Serum glutamic-pyruvic transaminase (SGPT/ALT) Serum glutamic-oxaloacetic transaminase (SGOT/AST) Alkaline phosphatase Sodium Potassium Calcium Inorganic phosphorus Uric acid[a] Total protein Glucose Albumin Lactate dehydrogenase (LDH) Magnesium Chloride	Specific gravity Ketones pH Protein Blood Glucose Microscopic examination (as indicated)
Coagulation – Central Lab		**Special Chemistry Labs – Central Lab**
PT aPTT INR		Amylase Lipase Serum β2 Microglobulin (Sβ2M) C-Reactive protein (CRP)
Viral Serologies – Central Lab	**Viral Serology – Local Lab**	
HBsAg HCV ab or RNA	SARS-CoV-2[b] testing	

a. For samples analyzed locally, at room temperature, rasburicase causes enzymatic degradation of the uric acid in blood/plasma/serum samples potentially resulting in spuriously low plasma uric acid readings. The following special sample handling procedure must be followed to avoid *ex vivo* uric acid degradation.

1. Uric acid must be analyzed in plasma. Blood must be collected into pre-chilled 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 pre-cooled centrifuge (4°C). Finally, the plasma must be maintained in an ice water bath and analyzed for uric acid within 4 hours of collection.

b. SARS-CoV-2 testing performed at local lab for all subjects on study treatment, as clinically indicated per Investigator's discretion.

SARS-CoV-2 serology testing (preferred molecular testing e.g., PCR) to be done at any timepoint if clinically indicated, per Investigator's decision. Testing will be performed locally. All COVID-19 test results (both positive and negative), regardless of reason administered, must be inserted into EDC on the COVID-19 Status eCRF.

Randomization and Subject (Screening) Number Assignment

Interactive Response Technology (IRT) will be utilized to register (screen, re-screen and randomize) subjects on study. The site will contact the IRT to obtain a screening (subject) number once the subject has signed the informed consent and a study-specific procedure has been performed (e.g., labs are drawn). Once the screening number is assigned, if the subject is not randomized into the study, the reason for screen failure will be documented in the source document and will be captured in the IRT and eCRF. If the subject is randomized into the study, the site will contact the IRT to complete the randomization process and obtain the study treatment assignment. Subject treatment must start within 5 days after randomization. All subsequent drug assignments and changes in subject status (e.g., treatment completion) will be registered in the IRT.

See Section 5.5.3 for further information.

Dispensing Venetoclax/Placebo

Randomized subjects will receive sufficient quantities of venetoclax/placebo for 21 days in each 21-day cycle during the Cycles 1 – 8, and sufficient quantities for 35 days in each 35-day cycle for Cycles 9 and beyond. The IRT will assign every bottle of venetoclax/placebo to be dispensed to a subject. Prior to each drug dispensation, site personnel must contact IRT for bottle number assignment. **Venetoclax/placebo cannot be dispensed without contacting the IRT**. AbbVie or designee will provide specific instructions on the use of IRT.

Subjects will be provided with venetoclax/placebo self-administration instructions. Subjects will be instructed to store venetoclax/placebo according to specific directions included in Section 5.5.2.2. Subjects are required to return bottles of venetoclax or placebo (empty, partially filled, or full) to the study site prior to each cycle and at the TCV.

Subjects in Arm 2 (Placebo + Bd) who remain in the study once unblinded, will no longer be required to take placebo tablets.

5.3.1.1.2 Follow-Up

After treatment has ended, subjects will be followed for post-therapy information, overall survival, non-treatment emergent death information, and progressive disease (if applicable).

At the time the number of OS events required for the final OS analysis is reached, subjects will not be followed for post-therapy information, overall survival, non-treatment emergent death information, and progressive disease (if applicable) after treatment has ended and will be discontinued from the study.

Overall Survival

Survival (i.e., alive or deceased, and if deceased, the date and cause of death) and post treatment information will be collected on the appropriate eCRF approximately every 12 weeks (or as requested by sponsor to support data analysis) beginning on the date of progression or discontinuation and continuing either until the endpoint of death, until the subject is lost to follow-up, subject withdraws consent, the number of OS events required for the final OS analysis is reached, or until study termination by AbbVie, whichever occurs first. The following will be collected for post treatment information:

- Name(s) of post-therapy regimens
- Post-therapy dates of initiation and completion

Non-Treatment Emergent Death Collection

After the end of the AE reporting period (in this instance 30 days after the final dose of study drug), all deaths reported until the number of OS events required for the final OS analysis is reached, including any relevant clinical information leading to the death, regardless of cause, should be reported through use of the Non-Treatment Emergent Death eCRFs.

Additionally, retrospective relevant clinical information on non-treatment emergent deaths which already occurred will be collected from sites that have obtained IRB/EC approval to use a waiver of consent to collect such information. Non-Treatment Emergent Death information collected retrospectively should also be recorded on Non-Treatment Emergent Death eCRFs.

Non-Treatment Emergent Death information related to deaths reported immediately after the number of OS events required for the final OS analysis is reached will no longer be collected.

Progressive Disease Assessment

Subjects who discontinue the study treatment for reasons other than PD, even after receipt of new anti-multiple myeloma treatment, will be assessed for disease progression (IMWG assessment) every 4 weeks (± 1 week) for 1 year following the last dose of study treatment, and then every 12 weeks (± 1 week) thereafter until PD. After PD, the subject will continue to be followed for Overall Survival until the number of OS events required for the final OS analysis is reached.

COVID-19 Pandemic-Related Acceptable Protocol Modification:

In the event the subject cannot visit the study site for central laboratory and/or research sample collection for reasons related to the COVID-19 pandemic, a local accredited laboratory may be used to manage subject disease assessment. Local lab results should be obtained along with reference ranges and kept within the subjects' source documentation. Local lab results should be reviewed by the investigator as soon as possible. Additionally, the study site should contact the subject by phone or video conference to assess for post-study myeloma therapy as per Appendix G. This discussion shall be documented in the source documents.

5.3.1.2 Meals and Dietary Requirements

Each dose of venetoclax/placebo will be taken orally once daily with approximately 240 mL of water within 30 minutes after the completion of breakfast or subject's first meal of the day. Tablets must be swallowed whole and must not be broken, chewed, or crushed.

On days that pre-dose PK sampling is required, venetoclax/placebo dosing will occur in the morning at the clinic to facilitate PK sampling.

Subjects may not consume the following: grapefruit or grapefruit products, Seville oranges (including marmalade containing Seville oranges) or starfruit within the 3-day period prior to the first study treatment administration and until the last day of treatment is completed due to possible CYP3A mediated metabolic interaction. It is expected that sites record if grapefruit products are consumed by the subject during the study.

5.3.1.3 Collection and Handling of Biomarker and Exploratory Research Samples

Serum, plasma, bone marrow aspirate and bone marrow core biopsy tissue will be collected per Appendix H. Subjects will also have the option to provide samples for exploratory research. Subjects may still participate in the main study even if they decide not to participate in the optional exploratory research. Samples may be utilized to evaluate known and/or novel markers (nucleic acids, peptides/proteins and/or metabolites) of disease status, related conditions or to evaluate the association with pharmacokinetics, safety or efficacy. All samples should be prepared, labeled, and shipped as outlined in the study-specific laboratory manual. The biomarker rationale is discussed in the Biomarker Research Variables Section (Section 5.3.6).

AbbVie (or people or companies working with AbbVie) will store the biomarker and exploratory research samples in a secure storage space with adequate measures to protect confidentiality. The samples will be retained while research on venetoclax (or drugs of this class) or this disease and related conditions continues, but for no longer than 20 years

after study completion, or per local requirements. The procedure for obtaining and documenting informed consent is discussed in Section 9.3.

COVID-19 Pandemic-Related Acceptable Protocol Modification:

Biomarker and exploratory research samples may only be collected at the study site and are not to be collected if travel restrictions or other changes in local regulations in light of the COVID-19 pandemic prevent the subject from visiting the study site at a sample collection time point.

5.3.1.3.1 Samples for Mandatory Biomarker Analysis

A summary table of biomarker samples is found in Appendix H.

Blood Collection for Plasma Markers

Approximately 12 mL of blood will be collected at the following time points:

- Cycle 1 Day 1 (Pre-dose)
- Cycle 5 Day 1 (Pre-dose)
- Disease Progression or TCV

Blood Collection for Serum Markers

Approximately 3.5 mL of blood will be collected at the following time points:

- Cycle 1 Day 1 (Pre-dose)
- Cycle 5 Day 1 (Pre-dose)
- Disease Progression or TCV

Pre-Treatment Bone Marrow Core (BMC) Biopsy Tissue Collection for Immunohistochemistry (IHC)

One of the following forms of pre-therapy tumor tissue (newly collected tissue or archived tissue) should be collected at Screening:

- **Fresh tumor tissue:** It is strongly encouraged that BMC biopsies be collected for all subjects to enable biomarker assessments as outlined in the study objectives. BMC biopsies should be performed during screening, unless not recommended per Institution guidelines. Tissue should be fixed in formalin, decalcified, and embedded in paraffin according to institutional procedures. While sending Formalin-Fixed, Paraffin-Embedded (FFPE) blocks is preferred, slides prepared and stored 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 all the subject identifying information redacted, should be submitted along with the tissue sample.
- **Archived BMC 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. 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 all the subject identifying information redacted, should be submitted along with the tissue sample.

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:

1. Assessment of Disease Response by IMWG Criteria (Appendix J)[13,14]
2. Quantitative polymerase chain reaction (qPCR) and MRD, 6 mL
3. Fluorescent In Situ Hybridization (FISH), 4 mL

qPCR and MRD Sample Collection

A 6 mL aspirate sample will be collected at the following time point for qPCR and baseline assessment of disease using MRD assay:

- Screening (preferred) or prior to first dose of study treatment (Cycle 1 Day 1)

MRD Assessment

A 3 mL aspirate sample will be collected at the following time points for MRD assessment:

- At the time of suspected CR/stringent complete response (sCR) for confirmation of clinical response
- At approximately 6 months and 12 months after confirmation of CR/sCR for subjects who maintain this response

Fluorescent In Situ Hybridization (FISH)

A 4 mL aspirate sample will be collected at the following time point for baseline assessment of chromosomal abnormalities, including t(11;14), t(4;14), t(14;16), del 17p, 5+, 9+, 15+:

- Screening (preferred) or prior to first dose of study treatment (Cycle 1 Day 1). If the bone marrow aspirate collected is not sufficient for FISH analysis, data from a historical FISH result may be entered into the EDC eCRF as long as results are within 12 weeks from date of first dose.

5.3.1.3.2 Samples for Exploratory Research

For all subjects in the study that consent to optional exploratory research, blood, bone marrow core and bone marrow aspirate samples will be collected per Appendix H. Please contact the AbbVie TA MD or designee if necessary for additional information.

Bone Marrow Core (BMC) Biopsy Tissue Collection for IHC

Sample may be collected at the time of Disease Progression or TCV (prior to the initiation of a new anti-myeloma treatment), if deemed feasible by the Investigator. Tissue should be fixed in formalin, 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 and stored as described in the study-specific laboratory manual. In addition, a pathology report, with all the subject identifying information redacted, should be submitted along with the tissue samples.

Bone Marrow Aspirate Collection for FISH and qPCR/MRD

Sample may be collected at Disease Progression or TCV, if deemed feasible by the Investigator. Priority of the bone marrow aspirate sample split is as follows:

1. qPCR/MRD, 6 mL
2. FISH, 4 mL

Pharmacogenetic Sample (Optional JPMA Category B)

An optional 4 mL whole blood sample for deoxyribonucleic acid (DNA) isolation will be collected on Cycle 1 Day 1 (prior to the first dose of study treatment), Cycle 5 Day 1 and TCV from each subject who consents to provide samples for exploratory research.

5.3.2 Drug Concentration Measurements

5.3.2.1 Collection of Samples for Analysis

Blood samples for venetoclax, bortezomib (and dexamethasone, only in Japanese subjects), and possible metabolite(s) will be collected by venipuncture per Appendix H.

The timing of blood collections will take priority over all other scheduled study activities except for dosing.

The date and time (to the nearest minute) of each dose of venetoclax/placebo and whether or not the venetoclax/placebo dose was taken within approximately 30 minutes after the completion of breakfast (or subject's first meal of the day) will be recorded on the appropriate eCRF within Medidata RAVE for each scheduled venetoclax or placebo PK day and for the 2 days prior to every scheduled venetoclax/placebo PK day. The date and time (start time and end time) of each bortezomib injection/infusion will be recorded to the nearest minute. Sites will ensure that all information is captured through source documents. FOR JAPAN SUBJECTS ONLY: the date and time (to the nearest minute) of each dexamethasone dose will be recorded for the scheduled dexamethasone PK day and for the doses immediately prior to and after the scheduled dexamethasone PK day.

Refer to the study specific laboratory manual for detailed instructions on sample collection, processing, and shipment.

Blood Samples for Venetoclax Assay

Blood samples (3 mL) for venetoclax assay will be collected at the following times:

- Cycle 1 Day 1: 6 hour post dose (optional)
- Cycles 2, 4, 6 and 8 (Day 1): 0 hour (pre-dose)

A total of 4 – 5 blood samples are planned to be collected per subject for venetoclax PK analysis.

Blood Samples for Bortezomib Assay

Blood samples (4 mL) for bortezomib assay will be collected at the following times:

- Cycle 1 Day 1: 0.5 hour post dose
- Cycles 2, 4, 6 and 8 (Day 11): 0 hour (pre-dose)

A total of 5 blood samples are planned to be collected per subject for bortezomib PK analysis.

Blood Samples for Dexamethasone Assay (Japan Subjects Only)

Japanese subjects enrolled in the run-in phase, blood samples (3 mL) for dexamethasone assay will be collected at the following times:

- Cycle 1 Day 1: 0.5 and 6 hour post dose
- Cycle 1 Day 11: 0 (pre-dose), 0.5, 1, 2, 4, 8 and 24 (Day 12 pre-dose) hours post dose

A total of 9 blood samples are planned to be collected per subject enrolled in the run-in phase for dexamethasone PK analysis.

For the remaining Japanese subjects enrolled after the run-in phase, blood samples (3 mL) for dexamethasone assay will be collected at the following times:

- Cycle 1 Day 1: 0.5 and 6 hour post dose

A total of 2 blood samples are planned to be collected per subject enrolled after the run-in phase for dexamethasone PK analysis.

5.3.2.2 Measurement Methods

Plasma concentrations of venetoclax will be determined by the Drug Analysis Department at AbbVie using validated method. Plasma concentrations of other possible metabolites from venetoclax may be determined with validated or non-validated methods.

Plasma concentrations of bortezomib and dexamethasone will be determined under the supervision of the Drug Analysis Department at AbbVie.

5.3.3 Efficacy Variables

The primary endpoint is PFS based on IMWG criteria for multiple myeloma (Appendix J).[13,14]

Secondary efficacy endpoints are as follows: VGPR or better response rate; PROs: Worst Pain (BPI-SF), Physical Functioning (EORTC QLQ-C30); OS; PFS in subjects with high BCL-2 expression; DOR; TTP; ORR; MRD negativity rate; PROs GHS/QoL (EORTC QLQ-C30), and Fatigue (PROMIS Cancer Fatigue SF).

Tertiary efficacy endpoints are CBR, DCR, TTR, TNT, and PROs based on the remaining subscales of BPI-SF, EORTC QLQ-C30, EORTC QLQ-M20, and EQ-5D-5L.

Efficacy endpoints and analyses of efficacy are described in Section 8.1.3 and Section 8.1.5.

5.3.4 Safety Variables

The following safety evaluations will be performed during the study: adverse event monitoring, vital signs, physical examination, 12-lead ECG and laboratory assessments.

5.3.5 Pharmacokinetic Variables

Values for the PK parameters of venetoclax, including the apparent clearance (CL/F), may be determined using a population PK approach. Additional parameters may be calculated if useful in the interpretation of the data.

5.3.6 Biomarker and Exploratory Research Variables

Biospecimens (blood, serum, plasma, bone marrow aspirate and bone marrow core biopsy tissue) will be collected to conduct biomarker and exploratory analyses. The types of biomarkers to be analyzed may include, but are not limited to, nucleic acids, proteins, lipids or metabolites. The samples may be analyzed as part of a multi-study assessment of factors influencing the subjects' response to the study treatment (or drugs of the same or similar class) or the development and progression of the subjects' disease or related conditions. The information learned from analyzing these samples may be used to investigate factors influencing response to the study treatment, scientific questions related to multiple myeloma, and/or in the development of new therapies and diagnostic tests, or technologies. The results from these analyses may not be included with the study report.

Biospecimens (serum, plasma, bone marrow aspirate and bone marrow core biopsy tissue) will be collected to support biomarker objectives of the study. These include assessment of BCL-2 expression at baseline as a predictive biomarker of response to the combination of venetoclax with bortezomib and dexamethasone. BCL-2 protein expression will be determined by IHC analysis in bone marrow core biopsy samples. A pre-defined threshold for BCL-2 expression status (high/low) will be utilized to compare median PFS between treatment arms in subjects with High BCL-2 expression as a secondary endpoint in the study. Furthermore, BCL-XL and MCL-1 protein expression will be assessed as exploratory markers. Additionally, BCL-2, BCL-XL and MCL-1 gene expression may be evaluated in CD138-enriched bone marrow aspirate samples by sequencing-based methodologies, including qPCR. The ratio of target expression (BCL-2) to resistance factors (MCL-1/BCL-XL) was found to associate with tumor responses to single agent venetoclax treatment in pre-clinical studies of multiple myeloma.[9] Clinically, higher BCL-2 mRNA expression levels were associated with improved overall response rate in the Study M12-901.

Additional biomarker objectives include the assessment of FISH markers that are known to be prognostic in MM. These include, but not limited to, t(11;14), t(4;14), t(14;16), del17p, and 5+, 9+, or 15+. Patient multiple myeloma tumor cells that possess the t(11;14) translocation were found to associate with increased sensitivity to venetoclax in preclinical studies of MM.[9] t(11;14) positive samples also demonstrated a high median BCL-2/MCL-1 mRNA ratio.[9] FISH analysis will be performed on CD138-enriched samples from bone marrow aspirates.

MRD negativity is an emerging component of response assessment in multiple myeloma patients who have achieved complete responses. Recent reports have demonstrated the potential prognostic value of MRD detection in multiple myeloma with sensitive assays that define immunophenotypic disease specific (via flow cytometry) and/or molecular (Allelle Specific Oligonucleotide – Polymerase Chain Reaction [ASO-PCR] or Next Generation Sequencing [NGS]) abnormalities.[29-32] MRD negativity in bone marrow aspirates will be defined at 10^{-5} threshold as assessed by NGS 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. Exploratory analysis of MRD negativity at 10^{-4} and 10^{-6} thresholds may additionally be performed.

Additional exploratory evaluations may include biomarkers related to pathway(s) targeted by the study treatment, those believed to be related to the disease or to drug response evaluation or association with genetic factors. Plasma and serum samples may be analyzed for mutational status of circulating tumor 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 qPCR-based assays for BCL-2 family members and other nucleic acids or proteins known to regulate the expression of these molecules. Gene sequencing- and hybridization-based techniques may also be used on any of the above specimens for exploratory biomarker research.

Pharmacogenetic samples may also be analyzed for genetic factors contributing to the disease or to the subject's response to venetoclax, or other study treatment in terms of pharmacokinetics, efficacy, tolerability, and safety. Pharmacogenetic research on samples from Japan will be restricted to the subject's response to treatment. Such genetic factors may include sequencing and epigenetic testing on genes associated with 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 in the clinical study report.

5.3.7 Disease Assessments and IMWG Criteria for Response and Progression

5.3.7.1 Disease Assessments

Analysis of serum protein electrophoresis (SPEP), serum protein immunofixation, serum quantitative immunoglobulins (sQI), serum free light chains (sFLC), urine protein

electrophoresis (UPEP), urine protein immunofixation, corrected serum calcium, plasmacytoma evaluation (if applicable), skeletal survey, and bone marrow aspirate and biopsy, will be utilized for disease assessment. Subjects will be evaluated using the IMWG[13,14] criteria for disease response and progression.[45]

Laboratory Tests for Multiple Myeloma:

All serum and urine laboratory tests for multiple myeloma must be sent to a certified central laboratory. Corrected serum calcium will be based off the serum calcium and albumin levels obtained from the local laboratory.

Serum protein immunofixation, SPEP, sQI, sFLC, urine protein immunofixation, and UPEP may be performed up to 1 week prior to the scheduled visit day.

Serum Protein Electrophoresis (SPEP), Serum Protein Immunofixation, Serum Quantitative Immunoglobulins (sQI)

Blood samples for SPEP, serum protein immunofixation, and sQI testing will be collected per Table 4 and Appendix D, Appendix E, Appendix F, and Appendix G.

SPEP and serum immunofixation will be collected for all subjects at baseline and throughout the study until PD or withdrawal of consent, regardless of SPEP being measurable or M-protein presence at baseline.

Once the number of OS events required for the final OS analysis is reached, SPEP and serum immunofixation will continue to be collected only from the subjects on treatment.

At the time that subjects are unblinded, subjects in Arm 1 (Venetoclax + Bd) or Arm 2 (Placebo + Bd) may continue on study treatment per PI decision, unless PD is presented, provided that subjects are benefiting from treatment.

Serum Free Light Chains (sFLC)

Blood samples for sFLC testing will be collected for all subjects per Table 4 and Appendix D, Appendix E, Appendix F, and Appendix G.

Subjects with measurable disease in either SPEP and/or UPEP will be assessed for clinical response only based on these two tests and not by the sFLC assay. sFLC response criteria are only applicable to subjects without measurable disease in the serum or urine and to fulfill the requirements of sCR per IMWG criteria.

Corrected Serum Calcium

Blood samples for corrected serum calcium testing will be collected for all subjects per Table 4 and Appendix D, Appendix E, Appendix F, and Appendix G.

The determination of corrected serum calcium levels is required to perform disease assessment. If corrected serum calcium is used as a criterion for disease progression, it must be confirmed by a second value. The correction will be done according to the following formula:

Corrected Serum Calcium [mg/dL] = Measured serum calcium [mg/dL] + 0.8 × (4 – serum albumin [g/dL]).

Urine Protein Immunofixation and Urine Protein Electrophoresis (UPEP), 24-Hour Urine

Twenty-four-hour urine samples for urine protein immunofixation and UPEP for M-protein testing will be collected for all subjects at each Cycle Day 1 visit per Table 4 and Appendix D, Appendix E, Appendix F, and Appendix G.

Importantly, assessment of UPEP M-protein and urine immunofixation at the time of possible VGPR or CR/sCR is mandatory, even in subjects without measurable values at baseline.

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

COVID-19 Pandemic-Related Acceptable Protocol Modification:

If travel restrictions or other changes in local regulations in light of the COVID-19 pandemic prevent the subject from visiting the study site for the collection and shipping of IMWG laboratory assessments to the central laboratory, a local laboratory, hospital, or other facility may be used to manage subject disease assessment of IMWG (Serum M-Protein, Urine M-Protein, Serum Free Light Chains). Local lab results should be obtained along with reference ranges and kept within the subject's source documentation. Local lab results should be reviewed by the investigator as soon as possible and prior to study drug dispensation.

Skeletal Survey

Skeletal survey using conventional radiography (X-Ray) will be done at screening. Use of conventional or low dose CT scan or magnetic resonance imaging (MRI) bone survey is acceptable. If imaging is done on treatment for assessment of progression, the site must use the same modality of imaging as used in screening. Historical skeletal survey results obtained within 30 days prior to randomization may be used for Screening provided that the images meet the requirements in the Image Acquisition Guidelines. 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 per Table 4 and Appendix D, Appendix E, Appendix F and Appendix G. After the screening procedure, 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 of or size of lytic lesions, as well as the number and location of any new skeletal or lytic lesions.

COVID-19 Pandemic-Related Acceptable Protocol Modification:

In the event the skeletal survey cannot be performed at the study site due to study modifications related to the COVID-19 pandemic, the skeletal survey may be completed at other centers providing the modality/technique is equivalent.

Plasmacytoma Evaluation

Plasmacytoma evaluation should be assessed for all subjects with a history of plasmacytomas or if clinically indicated at Screening, via physical examination or imaging, and should be completed per Table 4, and Appendix D, Appendix E, Appendix F, and Appendix G. Positron emission tomography (PET) scan or ultrasound tests are not acceptable to document the size of extramedullary plasmacytomas.

CT, PETCT (CT component) or MRI (same 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, and to confirm MR or better responses if plasmacytoma is present at baseline.

In addition to be reviewed by the Investigator and/or qualified medical site staff, imaging scans should be sent within 5 business days of imaging acquisition to an independent central imaging vendor. The central imaging vendor will provide instructions regarding the preparation and shipment/upload of the images.

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 tumor measurements must be made in millimeters. 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, PET/CT or MRI scanning are the preferable methods of assessment. Conventional CT, PET/CT or 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, PET/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. Skin lesions must be documented by a photograph with a ruler.

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. Non-measurable 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.

With the completion of the PFS analysis, imaging scans are no longer required to be sent to an independent central imaging vendor and will be reviewed only by the Investigator and/or qualified medical site staff.

COVID-19 Pandemic-Related Acceptable Protocol Modification:

In the event the imaging for plasmacytoma assessment cannot be performed at the study site due to study modifications related to the COVID-19 pandemic, the imaging may be completed at other centers providing the modality/technique is equivalent.

Bone Marrow Aspirate and Biopsy

Bone marrow aspirate and biopsy should be completed per Table 4 and Appendix D, Appendix E, Appendix F, and Appendix G. 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 local laboratory as well as for shipment of a portion to AbbVie (or designee) for the biomarker analyses (including BCL-2 expression, qPCR/MRD assessment, and FISH subtyping) as described in Section 5.3.1.3 per Appendix H.

Assessment of bone marrow for percentage plasma cells performed locally is required within 21 days prior to randomization for baseline assessment and while on study to confirm sCR/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 locally at the time of CR (< 5% plasma cells) to assess for sCR, if applicable. Flow cytometry is preferred over IHC for assessment of plasma cell clonality. Flow cytometry will be performed to assess for sCR locally per institution standard practice. If local flow cytometry to assess plasma cell clonality is not available at the time of CR, a core biopsy and/or clot section should be evaluated by IHC staining for kappa (κ) or lambda (λ) or light chain restriction. To

confirm a suspected CR, a second confirmation bone marrow analysis for CR is not needed.

A bone marrow aspirate collection is mandatory. Bone marrow biopsy 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).

COVID-19 Pandemic-Related Acceptable Protocol Modification:

Bone marrow samples may only be collected at the study site and are not to be collected if travel restrictions or other changes in local regulations in light of the COVID-19 pandemic prevent the subject from visiting the study site at a sample collection time point.

Table 4. Assessments for IMWG Response Criteria

	Screening	Cycle 1 Day 1[a]	Day 1 of Each Subsequent Cycle	To Confirm sCR, CR or VGPR	TCV	Post-Treatment[b]
Serum protein electrophoresis	X	X	X	X	X	X
Serum protein immunofixation	X	X	X	X	X	X
Serum quantitative immunoglobulins	X	X	X		X	X
Serum free light chains	X	O	O	X (CR/sCR only)	O	O
Corrected Serum Calcium	X	X	X		X	X
Urine protein immunofixation	X	X	X[c]	X	X[c]	X[c]
Urine protein electrophoresis	X	X	X[c]	X	X[c]	X[c]
Skeletal survey	X	If clinically indicated				
Plasmacytoma evaluation	all subjects with history of plasmacytomas or if clinically indicated	Performed during treatment only to confirm response of a Minimal Response (MR) or better in subjects with plasmacytoma at baseline, or to confirm PD, or as clinically indicated.				
Bone marrow aspirate and biopsy	X			X (sCR or CR only)	X[d]	

CR = Complete Response; sCR = Stringent Complete Response; VGPR = Very Good Partial Response

X Collect for all subjects.

O Collect only for subjects without measurable M-protein in Screening serum or urine.

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

b. Only for subjects who went off study for reasons other than progressive disease and is to be collected every approximately 4 weeks following last dose of treatment for 1 year and then approximately every 12 weeks thereafter until progression. Additional IMWG assessments may be performed during treatment based on the clinical judgment of the Investigator. Once the number of OS events required for the final OS analysis is reached, IMWG assessments will no longer be collected for subjects in the Progression Follow up period.

c. UPEP and urine immunofixation should be collected at each Cycle Day 1 visit. UPEP 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 PD or TCV is optional.

Cross reference: Rajkumar 2011,[13] Durie 2007[14]

5.3.7.2 IMWG Criteria for Response and Progression

Subjects will be assessed for response using the IMWG response criteria (Appendix J).[13,14] Disease status categories include sCR, CR, VGPR, PR, MR, defined per EBMT criteria, stable disease (SD) and PD.

All response categories (i.e., sCR, CR, VGPR, PR, MR and PD) require two consecutive assessments completed by the central lab to be considered confirmed. 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.

Subjects with measurable disease in both serum (SPEP) and urine (UPEP) at study entry are required to meet response criteria in both UPEP and SPEP to qualify for a MR or better. On the other hand, criteria for PD only need to be met and confirmed in one parameter.

At the time that subjects are unblinded, subjects in Arm 1 (Venetoclax + Bd) or Arm 2 (Placebo + Bd) may continue on study treatment per PI decision, unless PD is presented, provided that subjects are benefiting from treatment.

Stringent Complete Response (sCR)

sCR requires that all of the following criteria be met:

- Negative immunofixation on 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 (confirmation with repeat bone marrow aspirate or biopsy not needed), AND
- Normal FLC ratio of 0.26 to 1.65 or per laboratory reference range, AND

- Absence of clonal plasma cells in bone marrow by immunohistochemistry or immunofluorescence or 2 to 4 color flow cytometry (confirmation with repeat bone marrow biopsy not needed).

Presence or absence of clonal plasma cells is based upon the k/λ ratio. An abnormal k/λ ratio by immunohistochemistry, and/or flow cytometry and/or immunofluorescence 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.

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 (CR)

CR requires that all of the following criteria be met:

- Negative immunofixation on 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 (confirmation with repeat bone marrow aspirate or biopsy not needed), AND
- For subjects in whom the only measurable disease is by serum FLC levels, a normal FLC ratio of 0.26 to 1.65 (or per laboratory reference range) is required, in addition to all the CR criteria listed above.

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

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.

Very Good Partial Response (VGPR)

VGPR is defined as follows:

- Serum and urine M-protein detectable by immunofixation but not on electrophoresis OR
- 90% or greater reduction in serum M-protein plus urine M-protein level < 100 mg/24-hour

For subjects in whom the only measurable disease is by serum FLC levels, VGPR is defined as follows:

- 90% or greater decrease in the difference between involved and uninvolved FLC levels

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.

Partial Response (PR)

PR is defined as follows:

- ≥ 50% reduction of serum M-protein AND
- Reduction in 24-hour urinary M-protein by ≥ 90% or to < 200 mg/24-hour, AND
- ≥ 50% reduction in size of soft tissue plasmacytomas, if present at baseline

If serum and urine M-protein levels are unmeasurable, a ≥ 50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria.

Minimal Response (MR)

Subjects who have reduction in M-protein or plasmacytoma but do not meet the criteria for PR are classified as MR if they meet all the following definition:

- 25% – 49% reduction of serum M-protein AND
- 50% – 89% reduction in 24-hour urinary M-protein AND

- 25% – 49% reduction in size of soft tissue plasmacytomas, if present at baseline AND
- If a skeletal survey is done, no increase in size or number of lytic bone lesions (development of compression fracture does not exclude response)

Stable Disease (SD)

SD is defined as not meeting the criteria for sCR, CR, VGPR, PR, MR, or PD.

Subjects with confirmed sCR, CR, VGPR, and PR will be considered to have achieved an objective response. Subjects with objective response and those with MR will be considered to have achieved clinical benefit. Additionally, subjects with clinical benefit and those with stable disease lasting at least 8 weeks will be considered to have achieved disease control.

Progressive Disease (PD)

PD is determined using the IMWG criteria (Appendix J),[13,14] and is defined as any one or more of the following:

- Increase of ≥ 25%* from lowest response level in any of the following:
  - Serum M-protein with an absolute increase of ≥ 0.5 g/dL
  - Serum M-protein increases of ≥ 1 g/dL are sufficient to define relapse if starting M-protein is ≥ 5 g/dL
  - Urine M-protein with an absolute increase of ≥ 200 mg/24-hour
  - For subjects without measurable serum and urine M-protein levels, the difference between involved and uninvolved FLC levels with an absolute increase of > 10 mg/dL
- Definite development of new bone lesions or soft tissue plasmacytomas
- Definite increase in the size of bone lesions or soft tissue plasmacytomas
  - A definite increase in size of bone lesions and/or plasmacytomas is defined as ≥ 50% increase from nadir in the sum of the product of the cross-

diameters (SPD) of > 1 lesion, or ≥ 50% increase in the longest diameter of a previous lesion > 1 cm in short axis.[45]

- Development of hypercalcemia (corrected serum calcium > 11.5 mg/dL) that can be attributed solely to the plasma cell proliferative disorder
  * Note: The "25% increase" refers to M-protein and, FLC results and does not refer to bone lesions, soft tissue plasmacytomas, or hypercalcemia. The "lowest response value" does not need to be a confirmed value.

Two consecutive assessments, made at any time before the start of new therapy, are required for confirmation of PD per IMWG criteria. 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), two 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. SPEP and UPEP are also required.

If PD is suspected based on hypercalcemia attributed solely to the plasma cell proliferative disorder, the laboratory values for corrected serum calcium should be greater than 11.5 mg/dL (2.875 millimole [mmol]/L) and a confirmatory reading should be obtained.

The following assessments are not sufficient to determine progressive disease:

- Rising sFLC or quantitative immunoglobulins. In this situation, SPEP and UPEP should be performed and progressive disease determination should be made based on central lab readings.
  - 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, increase in serum creatinine, hyperviscosity), and relapse from CR categories should not be considered progressive disease.
- 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 progressive disease by at least one of the following assessments prior to the initiation of new therapy: SPEP, UPEP, bone marrow biopsy, plasmacytoma evaluation, skeletal survey, or hypercalcemia (attributed solely to myeloma).

Due to delays in receiving response information from the central laboratory and also the possible lag time in the manifestation of clinical efficacy, 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 J)[13,14] as requiring one or more of the following direct indicators of increasing disease and/or end organ dysfunction (CRAB features [increased **c**alcium level, kidney (**r**enal) failure, **a**nemia, and destructive **b**one lesions]) that are considered related to the underlying plasma cell proliferative disorder:

- Development of new soft tissue plasmacytomas or bone lesions on skeletal survey, MRI or other imaging
- Definite increase in size of existing plasmacytomas or bone lesions. A definite increase is defined as a 50% (and at least 1 cm) increase as measured serially by the sum of the products of the cross-diameters of the measurable lesion
- Hypercalcemia > 11.5 mg/dL (> 2.875 mM/L)
- Decrease in hemoglobin of > 2 g/dL (> 1.25 mM) or to < 10 g/dL
- Rise in serum creatinine by ≥ 2 mg/dL (≥ 177 mM/L)
- Hyperviscosity

5.3.7.3 Evaluation of Disease

IMWG assessments will be reviewed by the Investigator per the IMWG criteria (Appendix J)[13,14] outlined in Section 5.3.7.2. If the Investigator confirms the subject meets the criteria for progressive disease, 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.

IMWG assessments will be performed by the central laboratory. Investigators may choose to submit additional samples to their local laboratory for testing. All local lab results must be entered into the eCRF.

Disease assessment for each post-baseline IMWG assessment will be performed by a team of independent multiple myeloma experts (IRC). The IRC will review subject data in a blinded fashion to provide the overall response assessment and associated response assessment date. The IRC will only review clinical data and imaging relevant for the disease assessment. **Interpretations from the IRC will not be sent to the site.**

A charter will outline the review process for IRC determination of overall response.

With the completion of the PFS analysis, post-baseline IMWG assessments are no longer required to be sent to the IRC and will be reviewed only by the Investigator and/or qualified medical site staff.

COVID-19 Pandemic-Related Acceptable Protocol Modification:

If travel restrictions or other changes in local regulations in light of the COVID-19 pandemic prevent the subject from visiting the study site for the collection and shipping of IMWG laboratory assessments to the central laboratory, a local laboratory, hospital, or other facility may be used to manage subject disease assessment of IMWG (Serum M-Protein, Urine M-Protein, Serum Free Light Chains). Local lab results should be obtained along with reference ranges and kept within the subject's source documentation.

Local lab results should be reviewed by the investigator as soon as possible and prior to study drug dispensation.

5.4 Removal of Subjects from Therapy or Assessment

5.4.1 Discontinuation of Individual Subjects from Treatment

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

- Disease progression confirmed through IMWG assessments;
- Subjects who are just on dexamethasone monotherapy;
- The subject experiences toxicities related to study treatment that requires more than a 3-week dose interruption of the study treatment;
- The subject receives an anti-myeloma treatment not specified in the protocol and prior to documented disease progression;
- The subject becomes pregnant or begins breastfeeding;
- Unacceptable toxicity;
- Noncompliance with the protocol.

If a subject is discontinued from treatment or the study with an ongoing adverse event, the Investigator will attempt to provide follow-up until a satisfactory clinical resolution of the adverse event is achieved.

At the end of the subject's treatment, a TCV will be completed.

A Safety Follow-Up Visit should be performed for all subjects approximately 30 days following last dose of treatment.

A separate Safety Follow-Up Visit does not need to be performed for subjects who had a Treatment Completion Visit conducted ≥ 30 days after discontinuation of the study treatment and did not require additional follow-up visits for disease or safety assessment. If the subject refuses or is unable to attend the Safety Follow-Up Visit, this should be noted in the subject's source documentation.

In the event that a positive result is obtained on a pregnancy test for a subject or a subject reports becoming pregnant during the study, the administration of the study treatment must be discontinued immediately. The Investigator must report a pregnancy within 1 working day of the site being aware to one of the AbbVie representatives listed in Section 6.1.5.

COVID-19 Pandemic-Related Acceptable Protocol Modification:

The investigator should contact the AbbVie TA MD or designee before discontinuing a subject from the study for reasons other than those identified above to ensure all acceptable mitigation steps have been explored.

All efforts should be made to obtain safety and disease response information at the Treatment Completion visit prior to the subject initiating another therapy. If travel restrictions or other changes in local regulations in light of the COVID-19 pandemic prevent the subject from having blood drawn for laboratory testing at the study site at the TCV and/or Safety Follow-Up Visit, if possible, arrange for subjects to have laboratory work done at a local laboratory, hospital, or other facility. Local lab results should be obtained along with reference ranges and kept within the subject's source documentation. Local lab results should be reviewed by the investigator as soon as possible.

Non-Treatment Emergent Death Collection

Refer to Section 5.3.1.1.2 for more information on Non-Treatment Emergent Death Collection.

Importantly, if a subject discontinues treatment for a reason other than PD, the subject will still be considered "on study" until the number of OS events required for the final OS analysis is reached, and followed for diseases assessments until the events of PD, death or withdrawal of consent. Once the number of OS events required for the final OS analysis is reached, if a subject discontinues treatment for any reason, the subject will be discontinued from the study.

5.4.2 Withdrawal from Study Visits

A subject may decide to discontinue participation in study visits and procedures. If subject withdraws from study visits, the subject must discontinue treatment, and the reason for withdrawal must be documented in the subject's medical record and signed by the Investigator. Subject will be followed for OS.

If withdrawal from study visits occurs at the time the number of OS events required for the final OS analysis is reached, subject will be discontinued from treatment and from the study.

COVID-19 Pandemic-Related Acceptable Protocol Modification:

During the COVID 19 pandemic, it has been necessary to employ mitigation strategies to enable the investigator to ensure subject safety and continuity of care. Additional guidance regarding the location of COVID-19 pandemic-related acceptable protocol modifications can be found in Section 5.3.1.1.

The investigator should contact the AbbVie TA MD or designee before discontinuing a subject from the study for reasons other than those identified in Section 5.4.1 to ensure all acceptable mitigation steps have been explored.

5.4.3 Withdrawal from Follow-Up

Subject must request to be withdrawn specifically from survival follow-up; this request must be documented in the subject's medical record and signed by the Investigator. If the subject withdraws from survival follow-up, the site staff may use a public information

source (such as county records) to obtain information about survival status only, as appropriate per local regulations.

Once the number of OS events required for the final OS analysis is reached, subjects will no longer be followed for progression or survival, and survival follow up withdrawal will no longer apply.

5.4.4 Discontinuation of Entire Study

AbbVie may terminate this study prematurely, either in its entirety or at any study site, for reasonable cause provided that written notice is submitted in advance of the intended termination. An Investigator may also terminate the study at his/her site for reasonable cause, after providing written notice to AbbVie in advance of the intended termination. Advance notice is not required by either party if the study is stopped due to safety concerns. If AbbVie terminates the study for safety reasons, AbbVie will immediately notify the Investigators by telephone and subsequently provide written instructions for study termination.

If, in the judgment of the Investigators and AbbVie, the continued exposure to the study treatment represents a significant risk to subjects, the study will be stopped. The following procedures for discontinuation will be followed:

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

5.5 Treatments

5.5.1 Treatments Administered

Subjects will take daily venetoclax/placebo 800 mg orally in combination with Bd. Venetoclax/placebo should always be given before other agents administered on the same day, if applicable. Subjects will self-administer venetoclax/placebo by mouth QD. Each dose of venetoclax/placebo should be taken all at one time with approximately 240 mL of water within 30 minutes after completion of breakfast or the subject's first meal of the day. Tablets must be swallowed whole and must not be broken, chewed, or crushed. On days that pre-dose PK sampling is required, dosing will occur at the clinic to facilitate PK sampling.

In cases of vomiting, the subject should not take any additional dose that day and next dose should be taken at usual time the next day. In cases where a dose is missed or forgotten, the subject should take the dose as soon as possible, ensuring the dose is taken within 8 hours of the missed dose with food. Otherwise, the dose should not be taken.

Placebo tablet administration will no longer be required for subjects in Arm 2 (Placebo + Bd) who remain in the study at the time subjects are unblinded.

Bortezomib (1.3 mg/m^2 subcutaneous injection [preferred] or IV) will be given following administration of venetoclax/placebo in Cycles 1 – 8 on Days 1, 4, 8 and 11, and for Cycles 9 and beyond, on Days 1, 8, 15 and 22 and should be administered per the prescribing information.[33] Dose capping and dose rounding of bortezomib is permitted per institutional guidelines. The route of administration should not change during the study.

Bortezomib dosing frequency may be reduced or discontinued per investigator's decision and institutional guidelines once subjects are unblinded.

Dexamethasone (20 mg) will be given orally in Cycles 1 – 8 on Days 1, 2, 4, 5, 8, 9, 11 and 12, and in Cycles 9 and beyond, Days 1, 2, 8, 9, 15, 16, 22, and 23. Dexamethasone

should be administered per the prescribing information. Dexamethasone should be administered the day of bortezomib dosing and the following day, given the protocol defined dosing window (bortezomib dosing window is ± 1 day) is maintained. If bortezomib is interrupted or a dose is skipped, dexamethasone should still be administered as scheduled per protocol (unless dexamethasone is interrupted due to toxicity). When bortezomib is discontinued and venetoclax/placebo and/or dexamethasone dosing continues, adverse events and concomitant medications need only be evaluated on Day 1 of each cycle visit.

Dexamethasone dosing (frequency and/or dose) may be reduced or discontinued per investigator's decision and institutional guidelines once subjects are unblinded.

When unblinding occurs, if subjects from Arm 1 (Venetoclax + Bd) and Arm 2 (Placebo + Bd) are on dexamethasone monotherapy, they must be discontinued from the study treatment and from the study once the Safety Follow-Up Visit is completed.

TLS prophylaxis should be considered as discussed in Section 6.1.7.2.

COVID-19 Pandemic-Related Acceptable Protocol Modification:

If a subject is unable to come to the study site to pick up their study drug due to COVID-19, a direct-to-patient (DTP) study drug shipment can be made, for venetoclax/placebo and dexamethasone only, from the study site to the subject, if allowed by local regulations. DTP shipments of venetoclax/placebo or dexamethasone may also include additional non-drug study supplies (e.g., patient diaries, 24-hour urine collection containers, etc.). AbbVie will submit any required notifications to the regulatory authority as applicable. Prior to DTP shipping, the study site must confirm it is still safe for the subject to continue treatment via onsite (preferred), phone or video conference visit, or local assessments as permitted through COVID-19 Pandemic-Related Acceptable Protocol Modifications. These assessments should be documented in the subject's source documents accordingly.

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

- Direct-to-patient (DTP) shipment of study drug is allowed by local regulations and the relevant ethics committee
- Study drug can be administered by the subject at home
- Subject agrees to have the study drug shipped directly to his/her home
- Assessment of the following procedures prior to dispensing venetoclax/placebo to subjects: hematology, chemistry, urine pregnancy testing (women of childbearing potential), coagulation panel (when applicable), IMWG disease assessment (central lab collection preferred, local laboratory acceptable if not possible to collect centrally), AE and Concomitant Medication reviews, and continuation of TLS prophylaxis and infections (as applicable).
- Instructions will be provided by AbbVie as to how a study site can initiate a DTP shipment using Marken, a global vendor selected by AbbVie to provide this service when necessary.
    - Marken is the preferred courier for DTP shipping; however, in extenuating circumstances, alternate local couriers may be allowed with prior approval from the AbbVie Clinical Contact (or designee) identified in Section 7.0. If Marken is not utilized, the study site is responsible for ensuring the courier will transport the study drug under appropriate temperature controlled conditions and require a signature for delivery.
- Shipments may also include other non-drug study supplies (e.g., drug dosing diaries, 24-hour urine collection containers, etc.). Subjects should provide dosing updates to study site staff during remote phone or video conference visits, and return diaries to the study site at the time of the next onsite visit.
- Prior to arranging shipment, the study site should contact the subject to confirm the subject will be available to accept delivery of the shipment.
- Shipments of study drugs from the study site to a subject's home will be appropriately temperature controlled (qualified shipper or temperature monitoring) within the labeled storage conditions. Signature is required upon delivery; due to COVID-19 related social distancing, this may be provided by

the courier after delivery. Documentation of the shipment is to be retained by the clinical site.

- The site should contact the subject to confirm delivery of the shipment and the date and time of the next dose, and document this in the source documents.
- AbbVie will not receive subject identifying information related to these shipments, as the study site will work directly with the courier.

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

The study site must keep records of all shipments within the subject source documentation.

When DTP shipping is utilized, subjects are not to discard any study drug bottles and/or unused study drug. The subject should return the study drug bottles and any unused study drug to the site at the time of the next onsite study visit unless the study site is directed otherwise by AbbVie.

Bortezomib should be administered at the study site; however, trained staff (site staff or home health) may administer subcutaneous bortezomib in the home setting when permitted by the country's regulations and after discussion and approval of the TA MD.

5.5.2 Identity of Investigational Products

Information about the venetoclax/placebo formulations and standard therapy drugs, bortezomib and dexamethasone, to be used in this study are presented in Table 5 and Table 6.

Table 5. Identity of Investigational Product

Study Drug	Trademark	Formulation	Route of Administration
Venetoclax	N/A	100 mg Tablet, film coated	Oral
Matching Placebo for Venetoclax	N/A	Tablet, film coated	Oral

Note: AbbVie will supply venetoclax tablets and a matching placebo for venetoclax.

Table 6. Identity of Non-Investigational Products

Non-Investigational Products	Trademark	Formulation	Route of Administration
Bortezomib	Velcade® Or NA[a]	3.5 mg/vial	Subcutaneous (preferred) or IV
Dexamethasone	NA	Tablet[b]	Oral

a. Generic or branded bortezomib may be used.

b. Dexamethasone dosage strength may vary based on the source.

Sites are responsible for obtaining bortezomib and dexamethasone. For operational or regulatory purposes, AbbVie may provide non-investigational products depending on local requirements. Bortezomib and dexamethasone should be obtained from a licensed pharmacy or wholesaler. Each site will be responsible for maintaining drug accountability records including product description, manufacturer, and lot numbers for all non-investigational products dispensed by the site.

5.5.2.1 Packaging and Labeling

Venetoclax/Placebo

The venetoclax/placebo tablets will be packaged in high density polyethylene (HDPE) plastic bottles to accommodate the study dosing requirements. Each bottle will be labeled per local regulatory requirements.

Bortezomib

Bortezomib is supplied as a vial containing 3.5 mg powder for solution for injection. Each vial must be reconstituted and administered per the applicable Summary of Product Characteristics (SmPC)[34] or the bortezomib prescribing information.[33] Bortezomib will be labeled as per country requirements. Labels must remain affixed to the supplies.

Dexamethasone

Dexamethasone tablets will be labeled as per country requirements. Labels must remain affixed to the supplies.

5.5.2.2 Storage and Disposition of Study Drug and Non-Investigational Products

Venetoclax/Placebo

Venetoclax/placebo study drug must be stored at 15° to 25°C (59° to 77°F). The investigational products (venetoclax/placebo) are for investigational use only and are to be used only within the context of this study. The study drug supplied for this study must be maintained under adequate security and stored under the conditions specified on the label.

Bortezomib

Bortezomib must be stored per locally approved label or SmPC.

Dexamethasone

Dexamethasone must be stored per locally approved label or SmPC.

5.5.3 Method of Assigning Subjects to Treatment Groups

The IRT will randomize subjects into the 2 treatment arms in a 2:1 ratio (Venetoclax:Placebo). Subject randomization will be stratified by prior exposure to bortezomib or other proteasome inhibitors (proteasome inhibitor-naïve versus proteasome

inhibitor-sensitive) and number of prior lines of therapy (1 versus 2 or 3). The stratification factors used for the randomization should be the most recent values on the date of randomization.

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

Japan Subjects Only: The first 12 subjects in Japan will be enrolled in the run-in phase. Separate randomization will be used for the first 12 subjects in the run-in phase in Japan, the remaining subjects in Japan and subjects in all countries expect Japan. An identical procedure will be used in the three groups of subjects. Subjects will be stratified based on prior exposure to bortezomib or other proteasome inhibitors (proteasome inhibitor naïve versus sensitive) and the number of prior lines of therapy (1 versus 2 or 3). There will be separate randomization lists for 4 strata within each of the three groups (Japan run-in, the rest of the Japan and the rest of the world). Subjects within a stratum will be randomized to venetoclax and placebo arms in 2:1 ratio. This procedure of randomization will ensure at least 6 subjects in Japan to be allocated in venetoclax arm in run-in phase.

5.5.4 Selection and Timing of Dose for Each Subject

Selection of the dose of venetoclax is discussed in Section 5.6.4. Timing of doses is discussed in Section 5.5.1.

5.5.5 Blinding

5.5.5.1 Blinding of Investigational Product

The Investigator, the study site personnel and the subject will remain blinded to each subject's treatment with venetoclax/placebo throughout the course of the study.

All subjects will be treated with open-label bortezomib and dexamethasone.

The IRT system can provide access to blinded subject treatment information during the study if identification of the study drug is required for medical emergency, i.e., situation in which the knowledge of the specific blinded treatment will affect the immediate management of the subject/subject's conditions (e.g., antidote is available). AbbVie must then be notified within 24 hours of the blind being broken. The date and reason that the blind was broken must be recorded in the source documentation and eCRF, as applicable. Un-blinding of subject treatment information in other exceptional circumstances will require approval from the AbbVie TA MD or designee.

5.5.5.2 Blinding of Data for Independent Data Monitoring Committee (IDMC)

An IDMC will periodically review the safety and efficacy data for this study in an un-blinded fashion. Aggregate blinded clinical safety and efficacy data will be reviewed on a real-time basis throughout the course of the study. Once the final Overall Survival (OS) analysis is complete (refer to Section 8.1.5.5.2), a final review of safety and efficacy data will be conducted by the IDMC. AbbVie will continue to monitor subjects' safety data after the final IDMC meeting.

Details of the IDMC review will be outlined in the IDMC Charter.

5.5.5.3 Unblinding Process

Once the final OS analysis is complete, an unblinding letter will be sent from the AbbVie TA MD to the Principal Investigator of each site taking part in the study. The PI should notify study subjects of treatment allocation by preferred method (e.g., phone, letter) and document in the subject’s chart that the subject has been informed of treatment allocation and applicable safety information.

5.5.6 Treatment Compliance

The Investigator or his/her designated and qualified representatives will administer/dispense the study treatment only to subjects enrolled in the study in

accordance with the protocol. The study treatment must not be used for reasons other than that described in the protocol.

5.5.7 Drug Accountability

The Investigator or his/her designated representatives will administer study treatment only to subjects enrolled in the study. Documentation of the receipt of supplies will be supported by a signed and dated Proof of Receipt or similar document. A current (running) and accurate inventory of study treatment will be kept by the site and will include lot number, Proof of Receipt number(s), bottle numbers, and the date on which the study treatment is dispensed or administered to the subject.

An overall accountability of the study treatment will be performed and verified by AbbVie or the designated monitor(s) throughout the study and at the study site Closeout Visit. Upon completion or termination of the study, all original containers (containing partially used or unused study treatment) will be returned to AbbVie according to instructions from AbbVie or the designated monitor(s). If prearranged between AbbVie and the site, destruction of used and unused study treatment will be performed at the site. Empty containers will be destroyed at the site. Labels must remain attached to the containers.

5.6 Discussion and Justification of Study Design

5.6.1 Discussion of Study Design and Choice of Control Groups

This is a Phase 3, multicenter, randomized, double blind study to evaluate the efficacy and safety of venetoclax plus Bd compared to an active control of placebo plus Bd. The choice of the control group allows for a double blinded assessment of the contribution of venetoclax to the safety and efficacy of the backbone regimen of Bd.

The proteasome inhibitor bortezomib combined with dexamethasone has proven therapeutic value and is considered to be a standard of care listed in the National Comprehensive Cancer Network and the European Society for Medical Oncology (ESMO) guidelines as a recognized treatment for patients with previously treated

MM.[13,16,35] Given that bortezomib combined with dexamethasone is one of the standard of care therapies in the treatment of relapsed or refractory MM, it makes an ideal therapeutic regimen to be used as an active comparator in a randomized, controlled study designed to evaluate the therapeutic value of an investigational drug added to the bortezomib plus dexamethasone regimen.

5.6.2 Appropriateness of Measurements

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

5.6.3 Suitability of Subject Population

Adult male and female subjects with relapsed or refractory MM who are considered sensitive or naïve to proteasome inhibitor and received 1 to 3 prior lines of therapy for multiple myeloma will be selected to participate in this study. Due to the expected mechanism-based lymphopenia, subjects will be monitored to assess risk for infection. As a preventative measure, prophylaxis for viral, fungal, bacterial or Pneumocystis infections will be implemented when appropriate.

5.6.4 Selection of Doses in the Study

The dosage regimen of bortezomib and dexamethasone are the doses specified in relapsed or refractory multiple myeloma subjects on the bortezomib US package insert and the EU SmPC. For the initial 8 cycles, the currently approved regimen of bortezomib with dosing on Days 1, 4, 8 and 11 every 21 days is used. For extended therapy beyond 8 cycles, bortezomib is used per the US package insert on a maintenance schedule of weekly dosing on Days 1, 8, 15, 22 every 35 days. This regimen allows patients who are responding to continue their treatment beyond 8 cycles with the less intense and better tolerated weekly regimen, which decreases the incidence of peripheral neuropathy, a key limiting toxicity with bortezomib. Similar regimens have been used in other Phase 3 clinical studies with bortezomib-based therapies.[36-38]

The selected 800 mg dosage of venetoclax is based on the results from Study M12-901, a Phase 1b study of venetoclax plus Bd in relapsed or refractory multiple myeloma subjects.

In this study venetoclax was administered until progression or unacceptable toxicity occurred and the maximum tolerated dose (MTD) of venetoclax plus Bd was not reached at the highest tested venetoclax dose of 1200 mg QD. Exposure-response analyses of the efficacy and safety from Study M12-901 were conducted based on the available PK, best response (per the International Myeloma Working Group [IMWG] criteria), and safety (grade ≥ 3 anemia, thrombocytopenia, and neutropenia). Anemia, thrombocytopenia, and neutropenia were selected as they are the toxicities relevant to the venetoclax experience to date. At the time of the analysis, the venetoclax doses ranged from 50 to 1200 mg QD in these subjects and the duration of treatment ranged from 9 to 664 days.

Using a population PK exposure-response model, the dose-response relationships of efficacy and neutropenia were determined for subjects with typical PK in the population that will be enrolled in Study M14-031 (non-refractory to bortezomib and received 1 to 3 prior treatments). There was a high predicted probability of achieving MR (or better) across all venetoclax dosages in this population, while the probability of VGPR or better was predicted to increase with increasing doses through 1200 mg QD. Similarly, neutropenia (grade ≥ 3) rates were generally low through doses of 800 mg QD, increasing thereafter. No relationship between venetoclax exposure and anemia or thrombocytopenia was observed. Based on these preliminary efficacy and safety results, and considering treatment compliance considerations, a venetoclax dose of 800 mg QD was selected in combination with BD.

6.0 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/device after it is released for distribution.

Complaints associated with any component of this investigational product must be reported to the Sponsor (Section 6.3.2). For adverse events, please refer to Section 6.1 through Section 6.1.5. For product complaints, please refer to Section 6.3.

6.1 Medical Complaints

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

All adverse events will be followed to a satisfactory conclusion.

6.1.1 Definitions

6.1.1.1 Adverse Event

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

Such an event can result from use of the drug as stipulated in the protocol or labeling, as well as from accidental or intentional overdose, drug abuse, or drug withdrawal. Any worsening of a pre-existing condition or illness is considered an adverse event. Worsening in severity of a reported adverse event should be reported as a new adverse event. Laboratory abnormalities and changes in vital signs are considered to be adverse events only if they result in discontinuation from the study, necessitate therapeutic

medical intervention, meet protocol specific criteria (see Section 6.1.7 regarding toxicity management) or if the Investigator considers them to be adverse events.

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

A treatment-emergent adverse event is defined as any adverse event with onset or worsening reported by a subject from the time that the first dose of venetoclax/placebo, bortezomib, or dexamethasone is administered until 30 days have elapsed following discontinuation of venetoclax/placebo, bortezomib, and dexamethasone administration.

6.1.1.2 Serious Adverse Events

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

Death of Subject	An event that results in the death of a subject.
Life-Threatening	An event that, in the opinion of the Investigator, would have resulted in immediate fatality if medical intervention had not been taken. This does not include an event that would have been fatal if it had occurred in a more severe form.
Hospitalization or Prolongation of Hospitalization	An event that results in an admission to the hospital for any length of time or prolongs the subject's hospital stay. This does not include an emergency room visit or admission to an outpatient facility.
Congenital Anomaly	An anomaly detected at or after birth, or any anomaly that results in fetal loss.

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

For serious adverse events with the outcome of death, the date and cause of death will be recorded on the appropriate case report form. Deaths related to disease progression will not be recorded as adverse events (see Section 6.1.1.3).

6.1.1.3 Adverse Events Expected Due to Study Related Endpoints

6.1.1.3.1 Deaths

For this protocol, overall survival is an efficacy endpoint. Deaths that occur during the protocol specified adverse event collection period (Section 6.1.4 and Figure 2) that are attributed by the investigator solely to progression of multiple myeloma should be recorded only on the Death eCRF and the Study Completion Form eCRF. All other on-study deaths, regardless of relationship to study treatment, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (Section 6.1.5).

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

6.1.1.3.2 Lack of Efficacy or Worsening of Disease

Events that are clearly consistent with the expected pattern of progression of the underlying disease are also considered an expected outcome for this study and will not be subject to expedited reporting.

6.1.2 Adverse Event Severity

The Investigator will rate the severity of each adverse event according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE Version 4.03).[39] If a reported adverse event increases in severity, the initial adverse event should be given an outcome date and a new adverse event reported to reflect the change in severity. For all reported serious adverse events that increase in severity, the supplemental eCRFs also need to be updated to reflect the change in severity.

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

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

Grade 3	The adverse event causes considerable interference with the subject's usual activities and may be incapacitating (moderate to severe).
Grade 4	The adverse event is life threatening requiring urgent intervention (severe).
Grade 5	The adverse event resulted in death of the subject (severe).

6.1.3 Relationship to Study Treatment

The Investigator will use the following definitions to assess the relationship of the adverse event to the use of the study treatment:

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

The Investigator will assess the relationship of each adverse event to venetoclax, to bortezomib, and to dexamethasone. Some events may be reasonably related to more than one drug or to none. For causality assessments, events assessed as having a reasonable possibility of being related to the study treatment will be considered "associated." Events assessed as having no reasonable possibility of being related to study treatment 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 to study treatment.

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

6.1.4 Adverse Event Collection Period

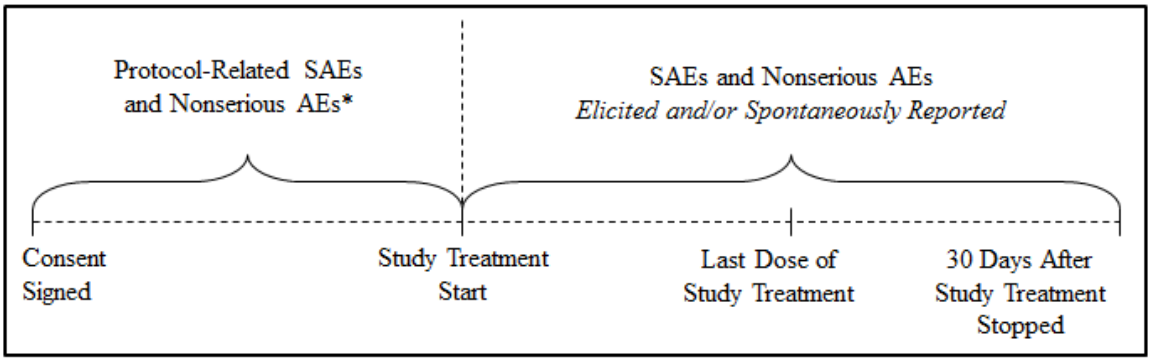
All protocol-related serious adverse events and nonserious adverse events must be collected from the signing of the study specific informed consent until study treatment administration.

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

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

Adverse event information will be collected as shown in Figure 2.

Figure 2. Adverse Event Collection



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

6.1.5 Adverse Event Reporting

In the event of a serious adverse event, whether associated with the study treatment or not, the Investigator will notify Clinical Pharmacovigilance **within 24 hours** of the site being made aware of the serious adverse event by entering the serious adverse event data into EDC RAVE® system. Serious adverse events that occur prior to the site having access to the RAVE® system, or if RAVE® is not operable, should be documented on the SAE Non-CRF forms and emailed (preferred route) or faxed to Clinical Pharmacovigilance within 24 hours of the site or Investigator being made aware of the serious adverse event.

Email: PPDINDPharmacovigilance@abbvie.com

FAX to: +1 (847) 938-0660

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

Oncology Safety Team
Bldg. AP51
AbbVie
1 North Waukegan Road
North Chicago, IL 60064-6146

Safety Phone: +1 (847) 935-2609
Safety Email: SafetyManagement_Oncology@abbvie.com

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

Primary Therapeutic Area Medical Director:

[redacted]
Medical Director
Pharmacyclics Switzerland GmbH (An AbbVie Company)
Mühlentalstrasse 36
CH-8200 Schaffhausen

Office: [redacted]
Cell:
Fax:
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 re-directed to a designated backup AbbVie TA-MD:

Phone: +1 (973) 784-6402

AbbVie will be responsible for Suspected Unexpected Serious Adverse Reactions (SUSAR) reporting for the Investigational Medicinal Product (IMP) in accordance with Global and Local Regulation, and Appendix A of the Investigator Brochure will serve as the Reference Safety Information (RSI) for the AbbVie IMP. The RSI in effect at the start of a Drug Safety Update Report (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. For comparator products being used as non-AbbVie IMPs, the SmPC will serve as the Reference Safety Information (RSI) for those non-AbbVie products.

The following definitions will be used for Serious Adverse Reactions (SAR) and Suspected Unexpected Serious Adverse Reaction (SUSAR):

SAR	Defined as all noxious and unintended responses to an IMP related to any dose administered that result in death, are life-threatening, require inpatient hospitalization or prolongation of existing hospitalization, result in persistent or significant disability or incapacity, or are a congenital anomaly or birth defect.
SUSAR	A suspected SAR: refers to individual SAE case reports from clinical trials where a causal relationship between the SAE and the IMP was suspected by either the sponsor or the investigator, is not listed is the applicable Reference Safety Information, and meets one of the following serious criteria: results in death, is life-threatening, requires hospitalization or prolongation of an existing hospitalization, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect. All individually reported SARs are considered suspected.

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

COVID-19 Pandemic-Related Acceptable Protocol Modification:

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

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

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

Subjects with a confirmed (viral test positive) or suspected COVID-19 infection **must interrupt all study drugs** until the COVID-19 viral clearance criteria in Section 6.2 are met. There are no time limits for study drug interruption as long as no permanent study discontinuation criteria have been met. The investigator should notify the AbbVie TA MD or designee listed above before reintroducing any study drugs in subjects with confirmed or suspected COVID-19 infection.

6.1.6 Pregnancy

Pregnancy in a study subject must be reported to an AbbVie representative (Section 6.1.5) within 1 working day of the site becoming aware of the pregnancy. Subjects who become pregnant during the study must be discontinued (Section 5.4.1).

All subjects should be informed that contraceptive measures (refer to Inclusion Criteria for the details on contraception) should be taken throughout the study and for at least 90 days post last dose of study treatment. Male subjects should inform their partner(s) that the effects of Venetoclax on an unborn fetus or embryo in humans are unknown. Information regarding a pregnancy occurrence in a study subject and the outcome of the pregnancy will be collected. In the event of a pregnancy occurring in the partner of an

enrolled subject, written informed consent for release of medical information from the partner must be obtained prior to the collection of any pregnancy-specific information, and the pregnancy will be followed to outcome.

Pregnancy in a study subject is not considered an adverse event. The medical outcome for either mother or infant, meeting any serious criteria including an elective or spontaneous abortion, is considered a serious adverse event and must be reported to AbbVie within 24 hours of the site becoming aware of the event.

6.1.7 Toxicity Management

6.1.7.1 Management of Cytopenias and Infection

Venetoclax could lead to suppression of lymphocytes (B and T sub-types). In addition, clinically significant neutropenia may also be observed in this study. Both lymphopenia and neutropenia could increase the risk for infections, including opportunistic infections. All subjects receiving treatment with venetoclax/placebo in combination with a proteasome inhibitor **must** receive antibiotic prophylaxis with Bactrim forte® (1 tablet 3 times a week) or equivalent therapy while on treatment. Additionally, Levofloxacin (500 mg daily, adjusted for renal function as necessary) or equivalent antibiotic therapy per institutional guidelines **must** be administered for the first 90 days on study and when Grade 4 neutropenia develops (ANC < 500 cells/µL) and continued until the neutropenia improves to Grade 3 or better (ANC > 500 cells/µL). Subjects may receive antibiotic prophylaxis for at least 30 days upon disease progression or after the discontinuation of the proteasome inhibitor and/or venetoclax/placebo at the discretion of the investigator. Furthermore, it is recommended that subjects deemed at high risk of infection may receive immunoglobulin replacement therapy (i.e., IV immunoglobulin) per institutional guidelines or at the Investigator's discretion.

If the patient has hypersensitivity to these agents or develops unacceptable toxicity or intolerance, and a suitable alternative agent is not available, the subject may be removed from this treatment in consultation with the AbbVie Medical Monitor.

The use of antibiotics that are moderate or strong CYP3A4 inhibitors should be avoided or used with caution and with appropriate dose modification as per protocol.

For all other subjects on venetoclax/placebo (not in combination with a proteasome inhibitor), prophylaxis should be considered at the Investigator's discretion. Anti-infective prophylaxis and G-CSF for the management of neutropenia may be considered per institutional guidelines. **Note:** Potential for drug-drug interactions should be considered. Please refer to Appendix I for a description of excluded and cautionary medications.

All antibiotic and supportive therapies are not required but may be continued at the discretion of the investigator for subjects in Arm 2 (Placebo + Bd) once unblinded.

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

Note: Please refer to Table 8 for guidance on dose interruptions and/or reductions related to hematological and non-hematological toxicities.

All anti-infective prophylaxis measures and growth factor use should be appropriately recorded in the eCRF.

6.1.7.2 Management of Tumor Lysis Syndrome

TLS has been reported in patients with multiple myeloma with significant disease burden when treated with bortezomib or dexamethasone because of the potential for rapid onset of cell lysis with this agent.[40] TLS has also been reported in patients with chronic lymphocytic leukemia with significant tumor burden when initiating venetoclax (initial 5 weeks period of tumor debulking)[12,13] No TLS event has been reported in the Phase 1 studies with venetoclax plus Bd in multiple myeloma.

Subjects with high tumor burden (e.g., Durie-Salmon or International Staging System [ISS] Stage II/III), rapidly increasing M-protein or light chains or high proliferative activity, plasmablastic morphology, unfavorable karyotype or compromised renal function (CrCl < 50 mL/minute) may be at higher risk of developing TLS.[41]

Consider TLS prophylaxis with oral hydration (at least 1 – 2 liters, as tolerable, each day) in all subjects at least 72 hours prior to the first day of dosing with venetoclax/placebo. 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, and manage abnormalities in serum creatinine, uric acid and electrolytes promptly. For subjects at higher risk, more intensive measures (e.g., intravenous hydration, frequent monitoring of labs, hospitalization, etc.) should be considered at the Investigator discretion. All TLS prophylaxis measures should be appropriately recorded in the eCRF.

6.2 Guidelines for Dose Modifications and Treatment

If the dose of one drug in the study treatment (i.e., bortezomib, dexamethasone, or venetoclax/placebo) is delayed outside of the protocol allowed window or interrupted for any reason (i.e., – subject missed dose, dose held due to toxicity, etc.), the dose will be considered missed and the subject will continue on in the cycle (i.e., – if Cycle 2 Day 1 dose of bortezomib is held and not completed with ±1 day window, Cycle 2 Day 1 would be considered missed and subject would continue to be evaluated for dosing at Cycle 2 Day 4). If a dose is held, all assessments listed for that day would still be completed, with the exception of PK samples. Every effort should be made to follow the planned dosing schedule; however, delays of up to 7 days in the initiation of a cycle, beginning at Cycle 2 Day 1, due to toxicity or scheduling issues will be allowed.

The subject will be considered still on protocol treatment as long as at least one of the specified drugs in the study treatment is being administered.

Subjects experiencing a 21-day delay in all drugs that are part of the study treatment (bortezomib, dexamethasone, and venetoclax/placebo) due to an AE(s) related to study

treatment should be discontinued from study treatment. Subjects experiencing delays unrelated to study treatment, for example due to radiation therapy may delay study treatment up to 42 days. Delays greater than 21 days must be discussed with the TA MD or designee (refer to Section 6.1.5).

Interruption/Discontinuation of Study Drug Due to Confirmed or Suspected COVID-19 Infection:

Subjects with a confirmed (viral test positive) or suspected COVID-19 infection must interrupt all study drugs until the following COVID-19 viral clearance criteria are met and COVID-19 related complications do not change the subject's risk/benefit ratio per Investigator assessment.

Confirmed COVID-19 infection:

- Symptomatic subjects: At least 2 negative viral tests in a row, ≥ 24 hours apart after at least 14 days have passed since recovery, defined as resolution of fever without use of antipyretics and improvement in respiratory symptoms (e.g., cough, shortness of breath)
- Asymptomatic subjects: At least 2 negative viral tests in a row, ≥ 24 hours apart after at least 14 days have passed since prior positive result (note: subjects who develop symptoms will follow guidance above for symptomatic subjects)

Suspected COVID-19 infection:

- Subjects with suspected COVID-19 infection should interrupt treatment with study drugs while viral testing is pending. Treatment may be reinitiated upon confirmation of negative viral test result and notification to the AbbVie TA MD or designee.

The TA MD should be notified by the PI of any modification in planned study drug administration due to COVID-19. In addition, the investigator should contact the

AbbVie TA MD before reintroducing any study drugs in subjects with confirmed or suspected COVID-19 infection.

Interruptions in study drug dosing due to the above COVID-19 testing guidance for subjects must be discussed with the AbbVie TA MD, along with the possibility of premature discontinuation from the study drug dosing period. There are no time limits for study drug interruption if no permanent study discontinuation criteria have been met. For subjects that experienced study drug interruptions greater than 42 days, two IMWG samples must be taken in order to rule out progressive disease prior to restarting study drug. Follow protocol Section 5.3.7.1, Section 5.4.1, and Appendix G for subjects who discontinue study drug.

Frequency or timing of COVID-19 testing and intervals between testing for the above viral clearance criteria may be adjusted to account for epidemiologic trends, updated information regarding infectivity, and local/institutional guidelines.

COVID-19 Pandemic-Related Acceptable Protocol Modification:

Subjects who cannot attend an onsite visit to receive scheduled administration of bortezomib should interrupt treatment with bortezomib until the subject is able to attend the study visit for treatment upon further discussion with AbbVie TA MD or designee.

At this time, dose holds are not recommended, unless for infections or other AEs according to the protocol. The Investigator should evaluate the benefit risk for each study patient and treat accordingly, even if this results in temporarily withholding treatment.

- Subject restart after interruption may be allowed following the instructions under "Interruption/Discontinuation of Study Drug Due to Confirmed or Suspected COVID-19 Infection" in Section 6.2 above.
- Permanent discontinuation is not recommended, even if a longer treatment free interval will occur. These cases should be assessed on a case-by-case basis with the AbbVie TA MD or designee.

- Any dose hold or interruption that is due to COVID-19 pandemic, should be thoroughly documented within the subject source documentation.

6.2.1 Dose Modifications or Delays for Venetoclax/Placebo Toxicities

Dose modifications and treatment guidelines for venetoclax/placebo-related toxicities are provided in Table 7 and Table 8.

Table 7. Venetoclax/Placebo* Dose Levels

Dose Level	Venetoclax/Placebo
Dose Level 1	800 mg QD
Dose Level –1	600 mg QD
Dose Level –2	400 mg QD
Dose Level –3	200 mg QD

* Once subjects are unblinded, venetoclax toxicity management will no longer apply for subjects in Arm 2 (Placebo + Bd).

If the dose of venetoclax/placebo at dose level –3 is not tolerable, then no further reductions will be allowed and venetoclax/placebo should be discontinued. Upon resolution of the AE leading to dose reduction, the dose of venetoclax/placebo can be increased once following Table 7 guidelines, based on the Investigator's clinical judgment. If the AE recurs upon increasing the dose of venetoclax/placebo, then the subject should remain at the reduced and tolerated dose level. Guidelines in Table 9 should also be followed for venetoclax/placebo-toxicity related dose reductions when moderate or strong CYP3A inhibitors are concomitantly administered.

Table 8. Hematological and Non-Hematological Toxicities Related to Venetoclax/Placebo*

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 may be administered with venetoclax/placebo if clinically indicated. • For Grade 4 neutropenia without infection, anti-infective prophylaxis with Levofloxacin (500 mg once daily, adjusted for renal function) or equivalent antibiotic therapy, per institutional guidelines must be administered until the neutropenia improves to Grade 3 or better (ANC > 500 cells/μL) (See Section 6.1.7.1). • First episode: Interrupt venetoclax/placebo and once the toxicity has resolved to Grade 1 or baseline level, venetoclax/placebo may be resumed at the same dose. • For subsequent episodes: Interrupt venetoclax/placebo. Consider using G-CSF as clinically indicated. Follow dose reduction guidelines in Table 7 when resuming treatment with venetoclax/placebo after resolution. A larger dose reduction may occur at the discretion of the physician and according to the dose reduction guidelines in Table 7.
Grade ≥ 3 or Serious Infections	• Interrupt venetoclax/placebo and upon resolution, treatment can be resumed at a reduced dose or discontinued, depending on Investigator's clinical judgment.
Grade 3 or 4 non-hematologic events	• First episode: Interrupt venetoclax/placebo. Once toxicity has resolved to Grade ≤ 1 or baseline, venetoclax/placebo may be resumed at the same dose. No dose modification is required. • For subsequent episodes: Interrupt venetoclax/placebo. Follow dose reduction guidelines in Table 7 when resuming treatment with venetoclax/placebo after resolution. A larger dose reduction may occur at the discretion of the physician and according to the dose reduction guidelines in Table 7.
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 (see Table 7). • For any events of clinical TLS, resume at a reduced dose following resolution.

* Once subjects are unblinded, venetoclax toxicity management will no longer apply for subjects in Arm 2 (Placebo + Bd).

6.2.2 Dose Modifications for Moderate or Strong CYP3A Inhibitors Used with Venetoclax/Placebo

Use of venetoclax/placebo with moderate or strong CYP3A4 inhibitors should be avoided and the investigator should consider alternative medications. If the administration of a moderate or strong CYP3A4 is absolutely necessary based on the investigator's clinical judgment, then the venetoclax/placebo dose should be reduced during the period it is co-administered with a moderate or strong CYP3A4. Dose reductions for venetoclax/placebo dose levels used with moderate and strong CYP3A inhibitors are provided on Table 9. Subjects should be monitored more closely for signs of toxicities and the dose may need to be further adjusted. After discontinuation of CYP3A inhibitor, wait for 3 days before venetoclax/placebo dose is increased back to previous dose level.

Table 9. Dose Modifications for Venetoclax/Placebo:* Moderate or Strong CYP3A Inhibitor Use

	Venetoclax/Placebo Dose		
Dose Level (From Table 7)	**No Moderate or Strong CYP3A Inhibitor**	**With Moderate CYP3A Inhibitor**	**With Strong CYP3A Inhibitor**
Dose Level 1	800 mg QD	400 mg QD	200 mg QD
Dose Level –1	600 mg QD	300 mg QD	100 mg QD
Dose Level –2	400 mg QD	200 mg QD	100 mg QD
Dose Level –3	200 mg QD	100 mg QD	Interrupt venetoclax/placebo temporarily

* Once subjects are unblinded, moderate or strong CYP3A inhibitors dose modification will no longer apply for subjects in Arm 2 (Placebo + Bd).

6.2.3 Toxicities Related to Bortezomib/Dexamethasone

The following serious adverse events have been reported in subjects treated with bortezomib as a single agent in a study of bortezomib versus dexamethasone in subjects with relapsed multiple myeloma: pyrexia, diarrhea, dyspnea, pneumonia, and vomiting. In another study comparing subcutaneous and intravenous formulations of bortezomib in subjects with relapsed multiple myeloma, additional serious adverse events were reported

in the intravenous bortezomib treatment arm: peripheral sensory neuropathy, and renal failure. A full description of all adverse events associated with bortezomib can be found in the bortezomib prescribing information.[33]

Dose reductions and treatment guidelines for bortezomib and dexamethasone-related toxicities are provided in Table 10 and Table 12 and represent general recommendations. Please refer to the bortezomib[33] and dexamethasone[42] prescribing information for additional information.

Table 10. Dose Reductions and Treatment Guidelines for Toxicity Related to Bortezomib

Toxicity	Recommended Action
Grade 3 non-hematological or Grade 4 hematological (other than neuropathy)	Withhold bortezomib therapy until the symptoms of the toxicity resolve. When toxicity resolves, bortezomib therapy may be reinitiated at a 25% reduced dose. (1.3 mg/m^2 reduces to 1 mg/m^2/dose; 1 mg/m^2/dose reduces to 0.7 mg/m^2/dose).
Peripheral Neuropathy:[a] • Grade 1 (asymptomatic; loss of deep tendon reflexes or parasthesia) without pain or loss of function	No action
• Grade 1 with pain or Grade 2 (moderate symptoms; limiting instrumental Activities of Daily Living [ADL][b])	For subjects receiving twice-weekly bortezomib, only, change treatment schedule to 1.3 mg/m^2 once per week (Day 1, 8 and 15 in a 21-day cycle) OR Reduce bortezomib current dose by one level (1.3 mg/m^2 to 1 mg/m^2 to 0.7 mg/m^2)
• Grade 2 with pain or Grade 3 (severe symptoms; limiting self care ADL[c])	Withhold bortezomib therapy until toxicity resolves to baseline or ≥ Grade 1. When toxicity resolves, reinitiate with a reduced dose of bortezomib at 0.7 mg/m^2 once per week.
• Grade 4 (life-threatening consequences; urgent intervention indicated)	Discontinue bortezomib

a. Grading based on NCI Common Terminology Criteria CTCAE v4.0.

b. Instrumental ADL: refers to preparing meals, shopping for groceries or clothes, using telephone, managing money, etc.

c. Self-care ADL: refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications and not bedridden.

Dose reduction levels and treatment guidelines for dexamethasone-related toxicities are provided in Table 11 and Table 12.

Table 11. Dose Reductions for Dexamethasone

	Reduced Dexamethasone Doses		
Dexamethasone	**Dose –1**	**Dose –2**	**Dose –3**
20 mg	12 mg	8 mg	4 mg

Table 12. Treatment Guidelines for Toxicity Related to Dexamethasone

Body System	Symptom	Recommended Action
Gastrointestinal	Dyspepsia, gastric or duodenal ulcer, gastritis Grades 1 – 2 (requiring medical management)	Treat with H_2 blockers, sucralfate, or proton pump inhibitor. If symptoms persist despite above measures, decrease dexamethasone dose by 1 dose level.
Gastrointestinal	≥ Grade 3 (requiring hospitalization or surgery)	Hold dexamethasone until symptoms adequately controlled. Restart at 1 dose decrement along with concurrent therapy with H_2 blockers, sucralfate, or proton pump inhibitor. If symptoms persist despite above measures, reduce to dose level –3 or discontinue dexamethasone permanently.
Gastrointestinal	Acute pancreatitis	Discontinue dexamethasone permanently.
Cardiovascular	Edema ≥ Grade 3 (limiting function and unresponsive to therapy or anasarca)	Diuretics as needed, and restart dexamethasone at 1 dose decrement; if edema persists despite above measures, decrease dose by another level. Discontinue dexamethasone permanently if symptoms persist despite second reduction.
Neurology	Confusion or mood alteration > Grade 2 (interfering with function ± interfering with activities of daily living)	Hold dexamethasone until symptoms resolve. Restart at 1 dose decrement. If symptoms persist despite above measures, decrease by another level or discontinue dexamethasone permanently.
Musculoskeletal	Muscle weakness > Grade 2 (symptomatic and interfering with function ± interfering with activities of daily living)	Decrease dexamethasone by 1 dose level. If weakness persists, decrease dose by 1 more dose level. Discontinue dexamethasone permanently if symptoms persist.
Metabolic	Hyperglycemia ≥ Grade 3	Treatment with insulin or oral hypoglycemic agents as needed. If uncontrolled despite above measures, decrease dose by 1 dose level until levels are satisfactory.

6.3 Product Complaint

6.3.1 Definition

A Product Complaint is any Complaint (see Section 6.0 for the definition) related to the biologic or drug component of the product.

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 (example: printing illegible), missing components/product, or packaging issues.

Any information available to help in the determination of causality to the events outlined directly above should be captured.

6.3.2 Reporting

Product Complaints concerning the investigational product must be reported to the Sponsor within 1 business day of the study site's knowledge of the event via the Product Complaint form. Product Complaints that occur during the study will be followed-up to a satisfactory conclusion. All follow-up information is to be reported to the Sponsor (or an authorized representative) and documented in source as required by the Sponsor. Product Complaints associated with adverse events will be reported in the study summary. All other complaints will be monitored on an ongoing basis.

Product Complaints may require return of the product with the alleged complaint condition. In instances where a return is requested, every effort should be made by the Investigator to return the product within 30 days. If returns cannot be accommodated within 30 days, the site will need to provide justification and an estimated date of return.

The description of the complaint is important for AbbVie in order to enable AbbVie to investigate and determine if any corrective actions are required.

7.0 Protocol Deviations

AbbVie does not allow intentional/prospective deviations from the protocol unless when necessary to eliminate an immediate hazard to study subjects. The Principal Investigator is responsible for complying with all protocol requirements, and applicable global and local laws regarding protocol deviations. If a protocol deviation occurs (or is identified, including those that may be due to the COVID-19 pandemic) after a subject has been enrolled, the Principal Investigator is responsible for notifying IEC/IRB regulatory authorities (as applicable), and their assigned Clinical Monitor or the following AbbVie Clinical Monitor(s):

Primary Contact:

[redacted]
Study Project Manager I
AbbVie
[redacted]
1 North Waukegan Road
North Chicago, IL 60064

Office: [redacted]
Fax:
Email: [redacted]

Alternate Contact:

[redacted]
Medical Director
Pharmacyclics Switzerland GmbH
(An AbbVie Company)
Mühlentalstrasse 36
CH-8200 Schaffhausen

Office: [redacted]
Cell:
Fax:
Email:

Alternate Contact:

[redacted]
Study Management Associate III
AbbVie
Av Jornalista Roberto Marinho,
85 8°Andar - Cidade Monções
São Paulo - Brazil – 04576-010

Office: [redacted]
Cell:
Email:

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

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

8.0 Statistical Methods and Determination of Sample Size

Unless otherwise noted, for all statistical tests, statistical significance will be determined by a two-sided P value ≤ 0.05. The date of randomization (enrollment) is defined as the date that the IRT issued a randomization number. The following stratification factors will be considered in efficacy analyses when applicable:

1. Prior exposure to bortezomib or other proteasome inhibitors (proteasome inhibitor-naïve versus proteasome inhibitor-sensitive), and
2. Number of prior lines of therapy (1 versus 2 or 3).

Stratification will be based on strata captured at randomization.

8.1 Statistical and Analytical Plans

8.1.1 Definition for Analysis Populations

Intent-To-Treat (ITT) analysis set consists of all randomized subjects. The data from the ITT population will be analyzed by the treatment group assignment given at the time of randomization, even if the subject does not receive the correct treatment or is not compliant to the protocol procedures.

Unless otherwise noted, the ITT analysis set will be used for baseline characteristics and efficacy analyses.

Safety analysis set consists of all randomized subjects who take at least one dose of study drug. Patients who received venetoclax at the first actual dosing day will be considered as venetoclax plus Bd group and otherwise they will be considered as placebo plus Bd group.

The safety analysis set will be used for safety analyses.

8.1.2 Baseline Characteristics

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

Continuous demographic data (e.g., age, height, and weight) will be summarized with means, standard deviation, minimum, maximum, and range. Frequencies and percentages will be computed for categorical data (e.g., sex, race, number of prior therapies [1 versus 2 versus 3], prior exposure to bortezomib or other proteasome inhibitors [proteasome inhibitor-sensitive versus proteasome inhibitor-naïve], MM stage [I versus II versus III], biomarkers, geography [North America versus EU versus Rest of World]), and baseline ECOG performance status.

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

8.1.3 Efficacy Endpoints

8.1.3.1 Primary Efficacy Endpoint

The primary endpoint is PFS based on IMWG criteria for multiple myeloma (Appendix J) [13,14] per IRC assessment.

For a given subject, PFS is defined as the number of days from the date the subject was randomized to the date of the first documented PD or death due to any cause, whichever occurs first. All events of PD will be included, regardless of whether the event occurred while the subject was still taking study drug or had previously discontinued study drug. Events of death will be included for subjects who had not experienced an event of PD. If the subject does not have an event of PD and the subject has not died, the subject's data will be censored. Detailed event and censoring information for PFS are provided in Table 13.

Table 13. Event and Censoring Date Used in PFS

Situation	Option for End-Date	Outcome
No baseline assessment	Date of randomization	Censor
PD or death at scheduled assessment date or before the next scheduled assessment	If there is documented PD then date of PD. Otherwise date of death	Event
PD or death after exactly one missing assessment	If there is documented PD then date of PD. Otherwise date of death	Event
PD or death after two or more consecutive missing assessments	If no adequate assessment is available prior to PD/death then date of randomization. Otherwise, date of the last adequate assessment prior to PD/death	Censor
No PD and no death	If no adequate assessment is available then date of randomization. Otherwise, date of the last adequate assessment	Censor
Start of new anti-cancer therapy prior to PD/death	If no adequate assessment is available prior to start of new anti-cancer therapy then date of randomization. Otherwise, date of the last adequate assessment prior to start of new anti-cancer therapy	Censor

8.1.3.2 Secondary Efficacy Endpoints

Secondary efficacy endpoints are as follows: VGPR or better response rate; PROs: Worst Pain (BPI-SF), Physical Functioning (EORTC QLQ-C30); OS; PFS in subjects with high BCL-2 expression; DOR; TTP; ORR; MRD negativity rate; PROs GHS/QoL (EORTC QLQ-C30), and Fatigue (PROMIS Cancer Fatigue SF). The patient-reported outcome instruments area described in detail in Section 5.3.1.1.1.

VGPR or better response rate is defined as the proportion of subjects with documented CR, sCR, or VGPR.

For a given subject, DOR is defined as the number of days from the subject's date of first documented response (PR or better) to the date of first documented PD or death due to multiple myeloma, whichever occurs first. If the subject does not have an event of PD

and the subject has not died due to multiple myeloma, the subject's data will be censored. Detailed event and censoring information for DOR are provided in Table 14.

Table 14. Event and Censoring Date Used in DOR

Situation	Option for End-Date	Outcome
No baseline assessment	Date of randomization	Censor
PD or death due to multiple myeloma at scheduled assessment date or before the next scheduled assessment	If there is documented PD then date of PD. Otherwise date of death	Event
PD or death due to multiple myeloma after exactly one missing assessment	If there is documented PD then date of PD. Otherwise date of death	Event
PD or death due to multiple myeloma after two or more consecutive missing assessments	Date of the last adequate assessment prior to PD/death	Censor
No PD and no death due to multiple myeloma	Date of the last adequate assessment	Censor
Start of new anti-cancer therapy prior to PD/Death	Date of the last adequate assessment prior to start of new anti-cancer therapy	Censor

For subjects who never achieve a documented response (PR or better), the subject's data will not be included in the analysis of DOR.

For a given subject, time to death (OS) is defined as the number of days from the date the subject was randomized to the date of the subject's death due to any cause. All events of death will be included, regardless of whether the event occurred while the subject was still taking study drug or after the subject discontinued study drug. If a subject has not died, the data will be censored at the date last known to be alive.

For a given subject, TTP is defined as the number of days from the date the subject was randomized to the date of first documented PD or death due to multiple myeloma, whichever occurs first. If the subject does not have an event of PD and the subject has not died due to multiple myeloma, the subject's data will be censored. Detailed event and censoring information for TTP are provided in Table 15.

Table 15. Event and Censoring Date Used in TTP

Situation	Option for End-Date	Outcome
No baseline assessment	Date of randomization	Censor
PD or death due to multiple myeloma at scheduled assessment date or before the next scheduled assessment	If there is documented PD then date of PD. Otherwise date of death	Event
PD or death due to multiple myeloma after exactly one missing assessment	If there is documented PD then date of PD. Otherwise date of death	Event
PD or death due to multiple myeloma after two or more consecutive missing assessments	If no adequate assessment is available prior to PD/death then date of randomization. Otherwise, date of the last adequate assessment prior to PD/death	Censor
No PD and no death due to multiple myeloma	If no adequate assessment is available then date of randomization. Otherwise, date of the last adequate assessment	Censor
Start of new anti-cancer therapy prior to PD/death	If no adequate assessment is available prior to start of new anti-cancer therapy then date of randomization. Otherwise, date of the last adequate assessment prior to start of new anti-cancer therapy	Censor

ORR is defined as the proportion of subjects with documented PR or better.

MRD negativity will be defined at 10^{-5} threshold as described in Section 5.3.6.

8.1.3.3 Tertiary Efficacy Endpoints

Tertiary efficacy endpoints are CBR, DCR, TTR, TNT, and PROs based on the remaining subscales of BPI-SF, EORTC QLQ-C30, EORTC QLQ-MY20, and EQ-5D-5L.

CBR is defined as the proportion of subjects with documented MR or better. DCR is defined as the proportion of subjects with documented MR or better or SD lasting at least 8 weeks.

For a given subject, TTR is defined as the number of days from the date the subject was randomized to the date of first documented response (PR or better).

Detailed event and censoring information for TTR are provided in Table 16.

Table 16. Event and Censoring Date Used in TTR

Situation	Option for End-Date	Outcome
No baseline assessment	Date of randomization	Censor
Documented response at scheduled assessment date or before the next scheduled assessment	Date of response	Event
Documented response after exactly one missing assessment	Date of response	Event
Documented response after two or more consecutive missing assessments	If no adequate assessment is available prior to response then date of randomization. Otherwise, date of the last adequate assessment prior to response	Censor
No documented response	If no adequate assessment is available then date of randomization. Otherwise, date of the last adequate assessment	Censor
Start of new anti-cancer therapy prior to response	If no adequate assessment is available prior to start of new anti-cancer therapy then date of randomization. Otherwise, date of the last adequate assessment prior to start of new anti-cancer therapy	Censor

For a given subject, TNT is defined as the number of days from the date the subject was randomized to the date of receiving new anti-cancer therapy. If the subject does not receive new anti-cancer therapy, the subject's data will be censored at the subject's last known date of follow-up for new anti-cancer therapy.

PROs based on subscales of the BPI-SF, EORTC QLQ-C30, EORTC QLC-MY20, and EQ-5D-5L will be statistically analyzed. Details will be provided in the statistical analysis plan (SAP).

8.1.4 Timing of Efficacy Analyses and Safety Evaluations

Efficacy and safety analyses will be performed when approximately 136 PFS events per IRC assessment are observed. If the observed treatment benefit with respect to PFS is both statistically and clinically significant, patients will still continue to be followed for overall survival with no treatment cross-over.

8.1.5 Statistical Analyses of Efficacy

8.1.5.1 Primary Analysis of Efficacy

The study is designed to test the following primary statistical hypothesis:

$$H_0: S(t)_{\text{Venetoclax + Bd}} = S(t)_{\text{Placebo + Bd}} \quad \text{vs.} \quad H_1: S(t)_{\text{Venetoclax +Bd}} \neq S(t)_{\text{Placebo + Bd}},$$

where S(t) is the survivorship function of PFS at time t.

For PFS, a stratified two-sided log-rank test with two-sided type-I error rate of $\alpha = 0.05$ (one-sided type I error rate of $\alpha = 0.025$) will be used to test the primary null hypothesis.

The hazards ratio (HR) for treatment effect will be estimated and its two-sided 95% confidence interval will be provided. The estimation will be based on a Cox's proportional hazards model with treatment and stratification factors included.

In addition, survivorship functions will be estimated by using Kaplan-Meier product-limit method. Estimated survival curves will be presented. The estimations will be performed by treatment group. If reached, median PFS time and its two-sided 95% confidence intervals will be presented by treatment group.

8.1.5.2 Secondary Analyses of Efficacy

VGPR or better response rate and ORR will be analyzed by using Cochran-Mantel-Haenszel test. Estimated rates along with corresponding 95% confidence intervals will be presented.

To assess PFS in subjects with high BCL-2 expression, a subgroup analysis will be performed for the primary endpoint PFS by BCL-2 expression levels (high/low).

The cutoff used for categorization of BCL-2 expression levels and alternative and additional supportive biomarker research on BCL-2 expression levels, if deemed necessary and helpful in understanding the drug effect, will be specified in the SAP.

DOR and TTP will be analyzed by using stratified log-rank test.

The hazards ratios for treatment effect will be estimated and two-sided 95% confidence intervals will be provided. The estimation will be based on a Cox's proportional hazards model with treatment and stratification factors in it.

In addition, survivorship functions will be estimated by using Kaplan-Meier product-limit method. Estimated survival curves will be presented. The estimations will be performed by treatment group. If reached, median time to event and its two-sided 95% confidence intervals will be presented by treatment group.

The OS will be analyzed by using a stratified two-sided 3-look group sequential log-rank test with a cumulative two-sided type-I error rate of $\alpha = 0.05$ (one-sided type I error rate of $\alpha = 0.025$). The hazards ratio for treatment effect will be estimated and its two-sided 95% confidence interval will be provided. The estimation will be based on a Cox's proportional hazards model with treatment and stratification factors in it.

In addition, survivorship functions will be estimated by using Kaplan-Meier product-limit method. Estimated survival curves will be presented. The estimations will be performed by treatment group. If reached, median OS time and its two-sided 95% confidence intervals will be presented by treatment group.

DOR will be analyzed only based on data from responders (PR or better) out of the ITT analysis set.

For PROs, change in score from baseline will be compared between treatment arms for the following domains: Worst Pain (BPI-SF), Physical Functioning (EORTC QLQ-C30), Fatigue (PROMIS-Fatigue), and Global Health Status/QoL (EORTC QLQ-C30).

MRD negativity rate will be analyzed by using Cochran-Mantel-Haenszel test. Estimated rates along with corresponding 95% confidence intervals will be presented.

Statistical analysis of secondary endpoints will be described in detail in the SAP.

8.1.5.3 Tertiary Analyses of Efficacy

CBR and DCR will be analyzed by using Cochran-Mantel-Haenszel test. Estimated rates along with corresponding 95% confidence intervals will be presented.

TTR and TNT will be analyzed by using stratified log-rank test.

The hazards ratios for treatment effect will be estimated and two-sided 95% confidence intervals will be provided. The estimation will be based on a Cox's proportional hazards model with treatment and stratification factors in it.

In addition, survivorship functions will be estimated by using Kaplan-Meier product-limit method. Estimated survival curves will be presented. The estimations will be performed by treatment group. If reached, median time to event and its two-sided 95% confidence intervals will be presented by treatment group.

Descriptive statistics will be used to summarize patient-reported outcomes based on the remaining subscales of BPI-SF, EORTC QLQ-C30, EORTC QLC-MY20, and EQ-5D-5L.

Alternative tertiary efficacy statistical analyses may be performed if deemed necessary and helpful in understanding the drug effect, which will be specified in the SAP.

8.1.5.4 Additional Sensitivity and Supportive Efficacy Analyses

As sensitivity analysis, the primary endpoint PFS will be analyzed with the following changes:

1. PFS based on assessment by Investigator.
2. Using the actual event date of PD or death as event date, regardless of the number of preceding missing assessments.
3. Not considering taking new anticancer therapy as a reason for censoring.
4. A robustness analysis will be performed using a stratified, adjusted Cox model, i.e., the MODEL statement will include the treatment group variable; and, e.g., age group (< 65 years/≥ 65 years), renal function, cytogenetic (high risk/standard risk), prior stem cell transplant (yes/no), BCL-2 expression (high/low) and MM stage as covariates. The stratification factors will be reflected in the STRATA statement. HR and 2-sided 95% CIs will be provided. Covariates with large number of missing data or small number of subjects within a category may be excluded or combined as appropriate.

Supportive subgroup analysis will be performed for the primary endpoint PFS and alternative additional sensitivity and supportive efficacy statistical analyses may be performed if deemed necessary and helpful in understanding the drug effect, which will be specified in the SAP.

8.1.5.5 Interim Analysis

8.1.5.5.1 Progression Free Survival

There is no Interim Analysis for Progression Free Survival.

8.1.5.5.2 Overall Survival

The OS will be analyzed by using a stratified two-sided 3-look group sequential log-rank test with a cumulative two-sided type-I error rate of $\alpha = 0.05$ (one-sided type I error rate

of α = 0.025). A separate α-spending approach will be used for OS. The final OS analysis will be performed when approximately 116 OS events are observed. The interim analyses for OS will be considered at the time of the PFS analysis and when approximately 75% of the total 116 OS events are observed (87 OS events).

8.1.5.6 Multiplicity Adjustments

Statistical tests for the secondary endpoints will be implemented in the testing strategy to maintain family-wise two-sided type I error rate at 0.05. Each of these tests will be performed at an overall two-sided significance level of 0.05. Statistical testing of the secondary endpoints will be performed only if the primary efficacy analysis of PFS is significant.

The testing order and details of testing procedures will be provided in the SAP.

8.1.6 Safety Assessments

The safety of venetoclax plus Bd and placebo plus Bd will be assessed by evaluating study treatment exposure, adverse events, serious adverse events, deaths, and changes in laboratory determinations and vital sign parameters.

8.1.7 Statistical Analyses of Safety

8.1.7.1 Duration of Study Treatment

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

8.1.7.2 Adverse Events

Analyses of adverse events will include only "treatment-emergent" events, i.e., those that have an onset on or after the day of the study treatment. Analyses will not include those that have an onset greater than 30 days after the last dose of the study drug.

Treatment-emergent adverse events will be coded and summarized by system organ class and preferred term according to the Medical Dictionary for Regulatory Activities (MedDRA) adverse event coding dictionary. The percentage of subjects experiencing an adverse event at a given severity, NCI CTCAE version 4.03 toxicity grade and relationship to study treatment will be provided.

8.1.7.3 Serious Adverse Events

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

8.1.7.4 Deaths

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

8.1.7.5 Longitudinal Analyses of Laboratory and Vital Signs Data

Changes from baseline may be summarized for each scheduled post-baseline visit and for the Treatment Completion Visit for hemoglobin, platelet, neutrophil, absolute leukocyte count, creatinine, and calcium, and vital sign parameters. If more than one measurement exists for a subject on a particular day, an arithmetic average will be calculated. This average will be considered to be that subject's measurement for that day. Post-baseline measurements more than 30 days after the last dose of randomized study drug will not be included. Subjects that do not have a baseline measurement or do not have any post-baseline measurements will not be included.

8.1.7.6 Analyses of Laboratory Data Using NCI CTCAE

Where applicable, laboratory values will be categorized according to the NCI CTCAE version 4.03 grades, and shifts from baseline grade to maximum and final post-baseline grades will be assessed. The baseline and final grades will be defined respectively as the

grade of the last measurement collected prior to the first dose of any component of study treatment, and as the grade of the last post-baseline measurement collected no more than 30 days after the last dose of study drug. If multiple values are available for a post baseline measurement, then the value with the highest NCI CTCAE grade will be used in the assessment of shift.

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

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

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

8.1.7.8 Pharmacokinetics

Plasma concentrations of venetoclax and bortezomib (and dexamethasone, JAPAN subjects only) will be tabulated for each subject by visit.

An analysis of venetoclax plasma concentrations may be performed using a nonlinear mixed effect population PK modeling approach. The results from the population PK analysis may not be reported in the clinical study report. Additional analyses may be performed if useful in the interpretation of the data.

8.2 Determination of Sample Size

In order to calculate the required number of PFS events, median PFS of placebo plus Bd and venetoclax plus Bd are assumed to be 9 months and 16.25 months, respectively (HR = 0.554, under the assumption of proportionality). Log-rank test with two-sided

type I error rate of $\alpha = 0.05$ (one-sided type I error rate of $\alpha = 0.025$) and power of $1 - \beta = 90\%$ is used for sample size calculations.

Under the assumptions above and using a 2:1 randomization ratio to the two arms (venetoclax plus Bd versus placebo plus Bd) a total of 136 PFS events per IRC assessment are required. To observe 136 PFS events per IRC assessment, approximately 280 subjects will be randomized.

With accrual assumed as in Table 17, and the assumed overall dropout rate of 16%, the accrual of 280 subjects will take approximately 15 months and 136 PFS events per IRC assessment are expected to be reached after approximately 26 months.

The accrual and the blinded PFS rate will be assessed during the conduct of the trial to determine if the sample size should be adjusted to ensure timely achievement of the required 136 PFS events per IRC assessment.

Table 17. Accrual Information

Accrual Information		
Period No.	**Starting at Time (Months)**	**Accrual Rate (Number of Subjects/Month)**
1	0	0.5
2	2	5
3	4	19
4	7	39
5	12	10

In order to calculate the required number of OS events, median OS of placebo plus Bd and venetoclax plus Bd are assumed to be 24 months and 40 months, respectively (HR = 0.6, under the assumption of proportionality). The study design includes 2 pre-specified interim analyses for the secondary endpoint OS. The final OS analysis will be performed when approximately 116 OS events are observed. The first OS interim analysis will be at the time of PFS analysis. The second OS interim analysis will be based on approximately 75% of the total 116 OS events (87 OS events). Two-sided log-rank test with a

cumulative two-sided type I error rate of $\alpha = 0.05$ (one-sided type I error rate of $\alpha = 0.025$) is used for the 3-look group sequential plan. Group sequential plan using Lan and DeMets[43] α-spending approach with O'Brien-Fleming type boundaries will be applied for the OS efficacy analyses.

Approximately 58 OS events are expected at the time of PFS analysis.

Power calculations for a range of different effect sizes are presented in Table 18.

Table 18. Power Calculation

PFS Analysis (Primary Endpoint)		OS Analysis (Secondary Endpoint)	
HR	**Power (%)**	**HR**	**Power (%)**
0.5	95.6	0.5	93.7
0.55	90.0	0.55	85.2
0.6	79.3	0.6	72.8
0.65	64.8	0.65	58.1

The sample size calculation was performed using the software EAST version 6.4.

9.0 Ethics

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

Good Clinical Practice (GCP) requires that the clinical protocol, any protocol amendments, the Investigator's Brochure, the informed consent and all other forms of subject information related to the study (e.g., advertisements used to recruit subjects) and any other necessary documents be reviewed by an IEC/IRB. The IEC/IRB will review the ethical, scientific and medical appropriateness of the study before it is conducted. IEC/IRB approval of the protocol, informed consent and subject information and/or advertising, as relevant, will be obtained prior to the authorization of drug shipment to a study site.

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

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

9.2 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, ICH GCP guidelines, applicable regulations and guidelines governing clinical study conduct and ethical principles that have their origin in the Declaration of Helsinki. Responsibilities of the clinical Investigator are specified in Appendix A.

In the event a significant disaster/crisis (e.g., epidemic/pandemic, natural disaster, conflict/combat) occurs leading to difficulties in performing protocol-specified procedures, AbbVie will engage with study site personnel in efforts to ensure the safety of subjects, maintain protocol compliance, and minimize risks to the integrity of the study while trying to best manage subject continuity of care. This may include alternative methods for assessments (e.g., phone contacts or virtual site visits), alternative locations for data collection (e.g., use of a local laboratory instead of a central lab), and shipping investigational product and/or supplies direct to subjects to ensure continuity of treatment where allowed. COVID-19 pandemic-related acceptable protocol modifications are detailed throughout the protocol. In all cases, these alternative measures must be allowed by local regulations and permitted by IRB/IEC. Investigators should notify AbbVie if any urgent safety measures are taken to protect the subjects against any immediate hazard.

9.3 Subject Information and Consent

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

Information regarding incentives 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.

In the event a subject withdraws consent to participate from the study, stored biomarker samples will continue to be used for research and analysis. In the event that a subject would like to withdraw consent for research using these samples, the subject may request that their samples be withdrawn. Once AbbVie receives the request, remaining biomarker samples will be destroyed. If the subject changes his/her consent, and the samples have already been tested, those results will still remain as part of the overall research data.

An informed consent, approved by an IRB/IEC, must be voluntarily signed and dated before samples are collected for **optional exploratory research**. The nature of the testing should be explained and the subject given an opportunity to ask questions. The informed consent must be signed before the samples are collected and any testing is performed. If the subject does not consent to provide samples for the **optional exploratory research**, it will not impact their participation in the study.

In the event a subject withdraws from the main study, **optional exploratory research** samples will continue to be stored and analyzed unless the subject specifically withdraws

consent for the **optional samples**. If consent is withdrawn for the **optional sampling**, the subject must inform their study doctor, and once AbbVie is informed, the **optional samples** will be destroyed. However, if the subject withdraws his/her consent and the samples have already been tested, those results will still remain as part of the overall research data.

9.3.1 Informed Consent Form and Explanatory Material

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

9.3.2 Revision of the Consent Form and Explanatory Material

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

10.0 Source Documents and Case Report Form Completion

10.1 Source Documents

Source documents are defined as original documents, data, and records. These may include hospital records, clinical and office charts, laboratory data/information, pharmacy dispensing and other records, recorded data from automated instruments, microfiches, photographic negatives, microfilm or magnetic media, and/or x-rays. Data collected

during this study must be recorded on the appropriate source document. 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).

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

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

10.2 Case Report Forms

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

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

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

Medidata will provide access to the EDC system for the duration of the trial through a password-protected method of internet access. Such access will be removed from Investigator sites at the end of the site's participation in the study. Data from the EDC system will be archived on appropriate data media (CD-ROM, etc.) and provided to the Investigator at that time as a durable record of the site's eCRF data. It will be possible for the Investigator to make paper printouts from that media.

Patient-reported data must be completed for each subject enrolled in this study. These data are being collected with an Electronic Patient Reported Outcome (ePRO) system called Trialmax, provided by the technology vendor Signant Health of Plymouth Meeting, PA, USA. The ePRO system is in compliance with Title 21 CFR Part 11. The documentation related to the system validation of the ePRO system is available through the vendor, Signant Health, while the user acceptance testing of the study specific PRO design will be conducted and maintained at AbbVie.

The subject will be entering the data on an electronic device; the data will be uploaded to a server. The data on the server will be considered source, and maintained and managed by Signant Health.

Internet access to the ePRO data will be provided by Signant Health for the duration of the study. This access will be available for the duration of the study to the site investigator, as well as delegated personnel. Such access will be removed from

investigator sites following the receipt of the study archive. Data from the ePRO system will be archived on appropriate data media (CD-ROM, etc.) and provided to the investigator at that time as a durable record of the site's ePRO data. It will be possible for the investigator to make paper print-outs from that media.

The ePRO data will be collected electronically via a tablet device into which the patient will directly enter the required pieces of information. The electronic device will be programmed to allow data entry for only the visits specified in the protocol and will not allow for patients to complete more than one of the same assessments at any one visit. All data entered on the device will be immediately stored to the device itself and automatically uploaded to a central server administrated by Signant Health. The Investigator and delegated staff will be able to access all uploaded patient entered data via a password protected website, up until the generation, receipt and confirmation of the study archive.

11.0 Data Quality Assurance

AbbVie will ensure that the clinical trial is conducted with a quality management system that will define quality tolerance limits in order to ensure human subject protection and reliability of study results. Data will be generated, documented, and reported in compliance with the protocol, ICH GCP, and applicable regulatory requirements.

Prior to enrolling any subject in the study, a study training visit will be held with AbbVie personnel, the Investigator(s), and the study coordinators/project manager(s). This meeting will include a detailed discussion and review of the protocol and essential documents, performance of study procedures, case report form completion and specimen collection methods.

The AbbVie monitor will monitor the study site throughout the study. Source document review will be made against entries on the case report forms and a quality assurance check will be performed to ensure that the Investigator is complying with the protocol and

regulations. In addition, after the case report forms are retrieved, a review of the data will be conducted by a physician or representative at AbbVie.

All data hand-entered in the database will be verified at AbbVie. Any discrepancies will be reviewed against the hard-copy case report form and corrected on-line. After completion of the entry process, computer logic and manual checks will be created to identify such items as inconsistent study dates. Any necessary corrections will be made to the database via the appropriate change form/electronic CRF.

Routine hematology, serum chemistry and serology, and urinalysis tests will be conducted using a certified clinical laboratory. Laboratory reference ranges will be obtained prior to the initiation of the study and must be entered into Medidata RAVE EDC and updated as necessary throughout the course of the study. A review of all laboratory results will be conducted by the AbbVie monitor, the Investigator and other appropriate personnel from AbbVie.

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

12.0 Use of Information

All information concerning venetoclax processes, basic scientific data, or formulation information, supplied by AbbVie and not previously published is considered confidential information.

The information developed during the conduct of this clinical study is also considered confidential and will be used by AbbVie in connection with the development of venetoclax. This information may be disclosed as deemed necessary by AbbVie to other clinical Investigators, other pharmaceutical companies, and to governmental agencies. To allow for the use of the information derived from this clinical study and to ensure complete and thorough analysis, the Investigator is obligated to provide AbbVie with complete test results and all data developed in this study and to provide direct access to

source data/documents for study-related monitoring, audits, IEC/IRB review, and regulatory inspection.

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

The Investigator will maintain a confidential subject identification code list of all subjects enrolled in the study, including each subject's name, subject number, address, phone number and emergency contact information. This list will be maintained at the study site with other study records under adequate security and restricted access, and will not be retrieved by AbbVie.

Any research that may be done using research samples from this study will be experimental in nature and the results will not be suitable for clinical decision making or subject management. Hence, the subject will not be informed of individual results, should analyses be performed, nor will anyone not directly involved in this research. Correspondingly, researchers will have no access to subject identifiers. Individual results will not be reported to anyone not directly involved in this research other than for regulatory purposes. Data from research may be provided to investigators, used in scientific publications, or presented at medical conventions. Research information will be published or presented only in a way that does not identify any individual subject.

13.0 Completion of the Study

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

The Investigator (Director of the Site in Japan) must retain any records related to the study according to local requirements. If the Investigator (Director of the Site in Japan) is not able to retain the records, he/she must notify AbbVie to arrange alternative archiving options.

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

At the time the number of OS events required for the final OS analysis is reached, the end of study is defined as the date of the last subject's last Safety Follow-Up Visit.

14.0 Investigator's Agreement

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

Protocol Title:	A Phase 3, Multicenter, Randomized, Double Blind, Study of Bortezomib and Dexamethasone in Combination with Either Venetoclax or Placebo in Subjects with Relapsed or Refractory Multiple Myeloma Who are Sensitive or Naïve to Proteasome Inhibitors
Protocol Date:	16 December 2020

Signature of Principal Investigator _____ Date _____

Name of Principal Investigator (printed or typed) _____

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Appendix A. Responsibilities of the Clinical Investigator

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

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

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

Appendix B. List of Protocol Signatories

Name	Title	Functional Area
[redacted]	Director	Statistics
[redacted]	Study Project Manager I	Clinical
[redacted]	Study Management Associate III	Clinical
[redacted]	Executive Medical Director, Hematology	Clinical
[redacted]	Medical Director	Clinical
[redacted]	Director	Clinical Pharmacology
[redacted]	Principal Bioanalytical Investigator	Bioanalysis

Appendix C. Revised International Myeloma Working Group Diagnostic Criteria for Multiple Myeloma

Definition of Multiple Myeloma

Clonal bone marrow plasma cells ≥ 10% or biopsy-proven bony or extramedullary plasmacytoma* and any one or more of the following myeloma defining events:

Myeloma defining events:

1. Evidence of end organ damage that can be attributed to the underlying plasma cell proliferative disorder, specifically:
   - Hypocalcaemia: serum calcium > 0.25 mmol/L (> 1 mg/dL) higher than the upper limit of normal or > 2.75 mmol/L (>11 mg/dL)
   - Renal insufficiency: creatinine clearance† < 40 mL per minute or serum creatinine > 177 μmol/L (> 2 mg/dL)
   - Anemia: haemoglobin value of > 20 g/L below the lower limit of normal, or a haemoglobin value < 100 g/L
   - Bone lesions: one or more osteolytic lesions on skeletal radiography, CT, or PET-CT‡
2. Any one or more of the following biomarkers of malignancy:
   - Clonal bone marrow plasma cell percentage* ≥ 60%
   - Involved:uninvolved serum free light chain ratio§ ≥ 100
   - > 1 focal lesions¶ on MRI studies

PET-CT = 1^8F-fluorodeoxyglucose PET with CT

* Clonality should be established by showing κ/λ-light-chain restriction on flow cytometry, immunohistochemistry, or immunofluorescence. Bone marrow plasma cell percentage should preferably be estimated from a core biopsy specimen; in case of a disparity between the aspirate and core biopsy, the highest value should be used.

† Measured or estimated by validated equations.

‡ If bone marrow has less than 10% clonal plasma cells, more than one bone lesion is required to distinguish from solitary plasmacytoma with minimal marrow involvement.

§ These values are based on the serum Freelite assay (The Binding Site Group, Birmingham, UK). The involved free light chain must be ≥ 100 mg/L.

¶ Each focal lesion must be 5 mm or more in size.

Appendix D. Schedule of Assessments – Screening

Screening Event ↓	Screening	Comments
ELIGIBILITY ASSESSMENTS		Unless otherwise specified, screening procedures should be done within 21 days prior to randomization.
Informed Consent	X	Prior to any screening procedures.
Inclusion/Exclusion Criteria	X	
Medical/Oncology History	X	
SAFETY ASSESSMENTS		
Concomitant Medications and Adverse Event Assessments	X	Medications (prescription or over-the-counter, including vitamins and herbal supplements) will be documented beginning with the Screening Visit and continuing until 30 days following the last dose of study treatment. Serious and non-serious adverse events occurring after the study-specific informed consent is signed but prior to the initial dose of venetoclax/placebo, bortezomib or dexamethasone will be collected only if they are considered by the Investigator to be causally related to the study-required procedures.
Physical Examination	X	Full physical examination done at screening, including height and weight.
Vital Signs	X	
ECOG Performance Status	X	
12-Lead ECG	X	
Arterial blood gas analysis or percutaneous oxygen saturation	X	**JAPAN and FRANCE ONLY**
Chest CT or X-ray	X	**FRANCE ONLY**

Screening Event ↓	Screening	Comments
SAFETY LABORATORY ASSESSMENTS		Labs may be performed within 21 days prior to randomization unless otherwise noted. Historical panels may be used if done within 21 days prior to randomization. Additional labs may be performed as clinically necessary. Refer to Section 5.3.1.1.1 for details on specific testing required for each panel.
Pregnancy Test	X	Serum pregnancy test within 21 days prior to randomization for women of childbearing potential. Will be completed per certified local laboratory.
Serum Chemistry	X	Will be completed per certified local laboratory.
Amylase, Lipase	X	After screening, repeat if clinically indicated. Will be completed per certified central laboratory.
Hematology	X	Must include complete blood count (CBC), differential, and platelets. **Must be done within 2 weeks prior to randomization.** Will be completed per certified local laboratory.
Reticulocytes	X	Will be completed per certified local laboratory.
Coagulation Panel	X	Will be completed per certified central laboratory.
CRP	X	Will be completed per certified central laboratory.
sβ2M	X	Will be completed per certified central laboratory.
Urinalysis	X	Will be completed per certified central laboratory.
Hepatitis serology	X	Will be completed per certified central laboratory.
DISEASE ASSESSMENTS		
Serum Protein Immunofixation	X	Will be completed per certified central laboratory.
Serum Protein Electrophoresis	X	Will be completed per certified central laboratory.
Serum Quantitative Immunoglobulins	X	Will be completed per certified central laboratory.
Serum Free Light Chains	X	Will be completed per certified central laboratory.

Screening Event ↓	Screening	Comments
Corrected Serum Calcium	X	Will be completed based on values obtained from certified local laboratory.
Urine Protein Immunofixation	X	24-hour urine collection. Will be completed per certified central laboratory.
Urine Protein Electrophoresis	X	24-hour urine collection. Will be completed per certified central laboratory.
Skeletal Survey	X	Skeletal survey consists of lateral radiograph of skull, anteroposterior and lateral views of spine, and antero-posterior views of pelvis, ribs, femora, tibiae, fibulae, humeri, ulnae and radii. Historical results obtained within 30 days prior to randomization may be used at Screening provided that the images meet the requirements in the Image Acquisition Guidelines. Use of conventional or low dose CT scan, or MRI bone survey is acceptable.
Chest CT	X	**JAPAN ONLY**
Plasmacytoma Evaluation	X	CT, PET/CT or MRI (same method should be used throughout study) should be performed in all subjects with a history of plasmacytomas or if clinically indicated at baseline to assess for the presence of extramedullary plasmacytoma.
Bone Marrow Aspirate	X	Samples should be collected for IMWG assessments at the local laboratory and additional samples should be sent for biomarker analysis at the central laboratory. Refer to Appendix H for additional samples.
IHC Bone Marrow Core Biopsy	X	Bone marrow core biopsy (fixed formalin paraffin embedded [FFPE] core) should be collected and used for IMWG assessments per institutional guidelines and analyzed at the local laboratory and additional samples should be sent for biomarker analysis at the central laboratory. Refer to Appendix H for additional samples.
RANDOMIZATION		Once all screening procedures have been performed and eligibility has been confirmed, subject can be randomized. The first dose of study treatment must be administered within 5 days of date of randomization.

Appendix E. Schedule of Assessments – Treatment: Cycles 1 – 8

Cycles 1 – 8 Event ↓ Day →	1	2	4	5	8	9	11	12	Rest Days 13 – 21	Comments
SAFETY ASSESSMENTS										
Medical/Oncology History	X									On Cycle 1 Day 1, any changes observed from screening assessments, prior to dosing, and not considered related to study-required procedures will be recorded in the subject's medical or oncology history, as applicable.
Concomitant Medications and Adverse Event Assessments	X		X		X		X			Any events observed from the signing of the informed consent but prior to the initial dose will be recorded as an adverse event, if considered by the Investigator to be causally related to study-required procedures. At each visit, the subject's condition will be reviewed and any clinically significant changes from baseline will be recorded in the source documents and on the adverse event eCRF. If bortezomib is discontinued, evaluate on Day 1 of each cycle only.
ECOG Performance Status	X									May be done within 72 hours prior to dosing.
Physical Examination	X									If the screening physical examination is performed within 7 days of Cycle 1 Day 1, it is not required to repeat the exam on Cycle 1 Day 1 unless clinically indicated. Targeted physical examination, symptom directed can be used for subsequent cycles and may be done within 72 hours before or after scheduled visit. Weight will need to be collected.
Vital Signs	X		X		X		X			Evaluate prior to lab collection.
12 Lead ECG (FRANCE ONLY)	X									Cycle 5 only

Cycles 1 – 8 Event ↓ Day →	1	2	4	5	8	9	11	12	Rest Days 13 – 21	Comments
SAFETY LABORATORY ASSESSMENTS										Labs may be performed pre-dose, within 72 hours prior to scheduled visits, unless otherwise specified. Additional labs may be performed as clinically necessary. Refer to Section 5.3.1.1.1, Table 3 for details on specific testing required for each panel.
Pregnancy Test	X									Urine pregnancy test performed on Cycle 1 Day 1 prior to starting study treatment for women of childbearing potential. Urine pregnancy tests should be repeated on Day 1 of every cycle and evaluated prior to dosing. Urine tests must have a sensitivity of ≥ 25 IU/L.
Serum Chemistry	X		X		X		X			For Cycle 1, Chemistry should be collected on Days 1, 4, 8 and 11. F Cycles 2 – 8, collect on Days 1 and 11 only. May be done pre-dose within 72 h prior to scheduled visits. Results of these laboratory tests must be evaluated before each study treatment administration. Will be completed per certified local laboratory.
Hematology	X		X		X		X			Must include CBC, differential, platelets; May be done pre-dose with 72 h prior to scheduled visits. Results of these laboratory tests must be evaluated before each study treatment administration. Will be completed per certified local laboratory.
Reticulocytes	X									Complete on Day 1 of each cycle. Will be completed per local laboratory.
Coagulation Panel	X									Complete on Day 1 of each cycle only for subjects taking vitamin K antagonists, or as clinically indicated for all subjects.
DISEASE ASSESSMENTS										Day 1 of each cycle until disease progression. SPEP, serum immunofixation, sQI, sFLC, urine protein immunofixation, and UPEP may be performed up to 1 week prior to the scheduled visit day. See Table 4 for further information.
Serum Protein Immunofixation	X									Collection is also mandatory to confirm sCR, CR, or VGPR. Will be completed per certified central laboratory.
Serum Protein Electrophoresis	X									
Serum Quantitative Immunoglobulins	X									Will be completed per certified central laboratory.

Cycles 1 – 8 Event ↓ Day →	1	2	4	5	8	9	11	12	Rest Days 13 – 21	Comments
Serum Free Light Chains	X									Collect only for subjects with no measurable M-protein in Screening serum or urine, and/or to confirm sCR or CR only. Will be completed per certified central laboratory.
Corrected Serum Calcium	X									Serum calcium and albumin from peripheral blood at Day 1 of each cycle until disease progression, even if subject is on subsequent therapy; if used as a criterion for disease progression, it must be confirmed by a second value.
Urine Protein Immunofixation	X									24-hour collection. Collect at Day 1 of each cycle.
Urine Protein Electrophoresis	X									Must be collected to confirm sCR, CR, or VGPR regardless of whether M-protein was measurable at baseline. Will be completed per certified central laboratory.
Skeletal Survey	If clinically indicated									Same method should be used throughout the study.
Plasmacytoma Evaluation	Preformed during treatment only to confirm response of Minimal Response (MR) or better, or to confirm Progressive Disease, or as clinically indicated									CT, PET/CT or MRI – same method should be used throughout study.
Bone Marrow Aspirate and Biopsy	Mandatory for confirmation of sCR and CR, or if clinically indicated									Bone marrow aspirate is mandatory. Bone marrow biopsy is mandatory if indicated per institutional guidelines, otherwise the marrow core is optional. However, if a patient has a suspected CR and flow cytometry is unavailable, then a bone marrow biopsy is required for immunohistochemistry (IHC). Plasma cell percentage and light chain restriction assessments are required. Samples should be collected for assessment at the local laboratory for IMWG assessments. If available, additional samples should be obtained for biomarker analysis at the central laboratory. Refer to Appendix H for additional samples.
Response per IMWG Criteria	X									

Cycles 1 – 8 Event ↓ Day →	1	2	4	5	8	9	11	12	Rest Days 13 – 21	Comments
PRO ASSESSMENTS										Cycles 1, 3, 5 and 7 only. Cycle 1 Day 1 assessment may be done within 72 hours prior to dosing. It is required that PRO assessments be completed prior to any other clinical assessments and prior to dosing.
BPI-SF	X									
PROMIS Cancer Fatigue SF	X									
EORTC QLQ-C30	X									
EORTC QLQ-MY20	X									
EQ-5D-5L	X									
PHARMACOKINETIC SAMPLES	X						X			Refer to Appendix H for samples required.
BIOMARKER SAMPLES	X									Refer to Appendix H for samples required.
OPTIONAL EXPLORATORY RESEARCH SAMPLE – PHARMACOGENETIC	X									Refer to Appendix H for samples required.
DOSING										Refer to Section 5.5.1 for details.
Study Treatment Dispensation/Collection	X									
Dosing with Venetoclax/Placebo	X	X	X	X	X	X	X	X	X	Venetoclax/placebo to be dosed every day of cycle (no rest days).
Dosing with Bortezomib	X		X		X		X			Dosing window is ± 1 day, but there must be at least 72 hours between doses. If bortezomib is held, clinic visits on Day 4, 8 and 11 visits can be skipped and AEs/ConMeds should be evaluated on Day 1 Only.
Dosing with Dexamethasone	X	X	X	X	X	X	X	X		Dexamethasone should be administered the day of bortezomib dosing and the following day. If bortezomib dosing is held, dexamethasone should be administered as scheduled (unless interrupted due to toxicity).

Appendix F. Schedule of Assessments – Treatment: Cycles 9 and Beyond Through Treatment Completion Visit

Cycles 9 and Beyond Event ↓ Day →	1	2	8	9	15	16	22	23	Rest Days 24 – 35	Treatment Completion Visit	Comments
SAFETY ASSESSMENTS											
Concomitant Medications and Adverse Event Assessments	X		X		X		X			X	At each visit, prior to dosing, the subject's condition will be reviewed and any clinically significant changes from baseline will be recorded in the source documents and on the adverse event eCRF. If bortezomib is discontinued, evaluate on Day 1 of each cycle only.
Vaccination Assessment	X									X	At Day 1 of each cycle, the subject's vaccination changes will be reviewed and any changes from last visit will be recorded in the source documents and on the vaccination page in eCRF. Refer to Section 5.2.4.1 for additional details.
Physical Examination	X									X	Targeted physical examination, symptom directed. May be done within 72 hours before scheduled visit. Weight will need to be collected.
Vital Signs	X		X		X		X			X	Evaluate prior to lab collection.
ECOG Performance Status	X									X	May be done within 72 hours prior to dosing.
Subsequent myeloma therapy										X	
12 Lead ECG	X									X	Cycle 9 and Treatment Completion Visit only. FRANCE only: Cycle 9, 12, 15, every 5 cycles thereafter, and Treatment Completion Visit
SAFETY LABORATORY ASSESSMENTS											Labs may be performed pre-dose, within 72 hours prior to scheduled visits, unless otherwise specified. Additional labs may be performed as clinically necessary. Refer to Section 5.3.1.1.1, Table 3 for details on specific testing required for each panel.

Cycles 9 and Beyond Event ↓ Day →	1	2	8	9	15	16	22	23	Rest Days 24 – 35	Treatment Completion Visit	Comments
Pregnancy Test	X										Evaluate prior to dosing for women of childbearing potential. Urine tests must have a sensitivity of ≥ 25 IU/L.
Serum Chemistry	X									X	May be done pre-dose within 72 h prior to scheduled visits, unless otherwise specified. Results of these laboratory tests must be evaluated before each study treatment administration. Will be completed per certified local laboratory.
Hematology	X		X		X		X			X	Must include CBC, differential, platelets; May be done pre-dose within 72 h prior to scheduled visits, unless otherwise specified. Results of these laboratory tests must be evaluated before each study treatment administration. Will be completed per certified local laboratory.
Reticulocytes	X									X	Complete on Day 1 of each cycle and at TCV. Will be completed per certified local laboratory.
Coagulation Panel	X										Complete on Day 1 of each cycle only for subjects taking vitamin K antagonists, or as clinically indicated for all subjects. Will be completed per certified central laboratory.
SARS-CoV-2 test	If clinically indicated										Only for subjects with signs/symptoms of SARS-CoV-2, or as clinically indicated per Investigator's discretion. To be performed locally.
DISEASE ASSESSMENTS											Day 1 of each cycle until disease progression. SPEP, serum immunofixation, sQI, sFLC, urine protein immunofixation, and UPEP may be performed up to 1 week prior to the scheduled visit day. See Table 4 for further information.
Serum Protein Immunofixation	X									X	Collection is also mandatory to confirm sCR, CR, or VGPR. Will be completed per certified central laboratory.
Serum Protein Electrophoresis	X									X	

Cycles 9 and Beyond Event ↓ Day →	1	2	8	9	15	16	22	23	Rest Days 24 – 35	Treatment Completion Visit	Comments
Serum Quantitative Immunoglobulins	X									X	Will be completed per certified central laboratory.
Serum Free Light Chains	X									X	Collect only for subjects with no measurable M-protein in Screening serum or urine, and/or to confirm sCR or CR only. Will be completed per certified central laboratory.
Corrected Serum Calcium	X									X	Serum calcium and albumin from peripheral blood at Day 1 of each cycle until disease progression, even if subject is on subsequent therapy; if used as a criterion for disease progression, it must be confirmed by a second value.
Urine Protein Immunofixation	X									X	24-hour collection. Collect at Day 1 of each cycle. Must be collected to confirm sCR, CR, or VGPR regardless of whether M-protein was measurable at baseline. Will be completed per certified central laboratory.
Urine Protein Electrophoresis	X									X	
Skeletal Survey	If clinically indicated.										Same method should be used throughout the study.
Plasmacytoma Evaluation	Performed during treatment only to confirm response of Minimal Response (MR) or better, or to confirm Progressive Disease, or as clinically indicated										CT, PET/CT or MRI – same method should be used throughout study.
Bone Marrow Aspirate and Biopsy	Mandatory for confirmation of sCR and CR, if applicable. Optional at time of disease progression, if clinically indicated or as an optional procedure.										Bone marrow aspirate is mandatory and bone marrow biopsy is done if part of the SOC, otherwise is optional. However, if a patient has a CR and flow cytometry is unavailable, then a bone marrow biopsy is required for immunohistochemistry (IHC). Plasma cell percentage and light chain restriction assessments are required. Samples should be collected for assessment at the local laboratory for IMWG assessments and additional samples should be sent for biomarker analysis at the central laboratory. Refer to Appendix H for additional samples.
Response per IMWG Criteria	X									X	

Cycles 9 and Beyond Event ↓ Day →	1	2	8	9	15	16	22	23	Rest Days 24 – 35	Treatment Completion Visit	Comments
PRO ASSESSMENTS											To be done every other cycle only, starting on Cycle 9. It is required that PRO assessments be completed prior to any other clinical assessments and prior to dosing. Once the number of final OS events is reached, PRO assessments will no longer be required.
BPI-SF	X									X	Once the number of final OS events is reached, PRO assessments will no longer be required.
PROMIS Cancer Fatigue SF	X									X	Once the number of final OS events is reached, PRO assessments will no longer be required.
EORTC QLQ-C30	X									X	Once the number of final OS events is reached, PRO assessments will no longer be required.
EORTC QLQ-MY20	X									X	Once the number of final OS events is reached, PRO assessments will no longer be required.
EQ-5D-5L	X									X	Once the number of final OS events is reached, PRO assessments will no longer be required.
BIOMARKER SAMPLES										**X**	Refer to Appendix H for samples required.
DOSING											Refer to Section 5.5.1 for details.
Study Treatment Dispensation/Collection	X										
Dosing with Venetoclax/placebo	X	X	X	X	X	X	X	X	X		Venetoclax/placebo to be dosed every day of cycle (no rest days). Once subjects are unblinded, subjects in Arm 2 (Placebo + Bd) are no longer required to take placebo tablets.

Cycles 9 and Beyond Event ↓ Day →	1	2	8	9	15	16	22	23	Rest Days 24 – 35	Treatment Completion Visit	Comments
Dosing with Bortezomib	X		X		X		X				Dosing window is ± 1 day, but there must be at least 72 hours between doses. If Bortezomib is held, clinic visits on Day 8, 15 and 22 visits can be skipped and AEs/ConMeds should be evaluated on Day 1 Only. Bortezomib dosing frequency may be reduced or discontinued per investigator's decision and institutional guidelines once subjects are unblinded.
Dosing with Dexamethasone	X	X	X	X	X	X	X	X			Dexamethasone should be administered the day of bortezomib dosing and the following day. If bortezomib dosing is held, dexamethasone should be administered as scheduled (unless interrupted due to toxicity). Dexamethasone dosing (frequency and/or dose) may be reduced or discontinued per investigator's decision and institutional guidelines once subjects are unblinded. When unblinding occurs, if subjects from Arm 1 (Venetoclax + Bd) and Arm 2 (Placebo + Bd) are on dexamethasone monotherapy, they must be discontinued from the study treatment and from the study once the Safety Follow-Up Visit is completed.

Appendix G. Schedule of Assessments – Follow-Up

Post-Treatment Event ↓ Visit →	Safety Follow-Up Around 30 Days After Discontinuation of Study Treatment or Before Start of Subsequent Treatment (Whichever Occurs First)	Progression Follow-Up Q4 Weeks (± 1 Week) Following Last Dose of Treatment for Subjects Discontinued for Reasons Other than PD for 1 Year; Q 12 Weeks (± 1 Week) Thereafter	Survival Follow-Up Approximately Q12 Weeks for All Subjects	Comments
SAFETY ASSESSMENTS				
Concomitant Medications and Adverse Event Assessments	X			Refer to Section 5.3.1.1 for details. Data on unresolved and new Adverse Events must continue to be collected up to 30 days post last dose of study treatment even if the subject has started subsequent therapy during that time.
Physical Examination	X			Targeted physical examination, symptom directed. May be done within 72 hours before scheduled visit.
Vital Signs	X			Evaluate prior to lab collection.
Pregnancy Test	X			Women of childbearing potential only. Urine tests must have a sensitivity of ≥ 25 IU/L
Subsequent myeloma therapy, and Response	X	X	X	Once the number of final OS events is reached, progression and survival follow up assessments will no longer be required.

Post-Treatment Event ↓ Visit →	Safety Follow-Up Around 30 Days After Discontinuation of Study Treatment or Before Start of Subsequent Treatment (Whichever Occurs First)	Progression Follow-Up Q4 Weeks (± 1 Week) Following Last Dose of Treatment for Subjects Discontinued for Reasons Other than PD for 1 Year; Q 12 Weeks (± 1 Week) Thereafter	Survival Follow-Up Approximately Q12 Weeks for All Subjects	Comments
Non-Treatment Emergent Death Collection	X	X	X	After the end of the AE reporting period (in this instance 30 days after the final dose of study drug), all deaths, including any relevant clinical information leading to the death, regardless of cause, should be reported through use of the Non-Treatment Emergent Death eCRFs. Once the number of final OS events is reached, Non-Treatment Emergent Death collection will no longer be required. Refer to Section 5.3.1.1.2 for details.
Survival Status	X	X	X	Approximately every 12 weeks (or as requested by sponsor to support data analysis) beginning on the date of progression or discontinuation and continuing either until the endpoint of death, until the subject is lost to follow-up, subject withdraws consent, or until study termination by AbbVie, whichever occurs first. Once the number of final OS events is reached, progression and survival follow up survival status collection will no longer be required. Refer to Section 5.3.1.1.2 for details.

Post-Treatment Event ↓ Visit →	Safety Follow-Up Around 30 Days After Discontinuation of Study Treatment or Before Start of Subsequent Treatment (Whichever Occurs First)	Progression Follow-Up Q4 Weeks (± 1 Week) Following Last Dose of Treatment for Subjects Discontinued for Reasons Other than PD for 1 Year; Q 12 Weeks (± 1 Week) Thereafter	Survival Follow-Up Approximately Q12 Weeks for All Subjects	Comments
DISEASE ASSESSMENTS				Only for subjects who discontinued for any reason other than PD.
Serum Protein Immunofixation		X		Collection is also mandatory to confirm sCR, CR, or VGPR. Will be completed per certified central laboratory. Once the number of final OS events is reached, progression follow up assessments will no longer be required.
Serum Protein Electrophoresis		X		
Serum Quantitative Immunoglobulins		X		Will be completed per certified central laboratory. Once the number of final OS events is reached, progression follow up assessments will no longer be required.
Serum Free Light Chains		X		Collect only for subjects with no measurable monoclonal protein in Screening serum or urine, and/or to confirm sCR or CR only. Will be completed per certified central laboratory. Once the number of final OS events is reached, progression follow up assessments will no longer be required.

Post-Treatment Event ↓ Visit →	Safety Follow-Up Around 30 Days After Discontinuation of Study Treatment or Before Start of Subsequent Treatment (Whichever Occurs First)	Progression Follow-Up Q4 Weeks (± 1 Week) Following Last Dose of Treatment for Subjects Discontinued for Reasons Other than PD for 1 Year; Q 12 Weeks (± 1 Week) Thereafter	Survival Follow-Up Approximately Q12 Weeks for All Subjects	Comments
Corrected Serum Calcium		X		Serum calcium and albumin from peripheral blood at Day 1 of each cycle until disease progression, even if subject is on subsequent therapy; if used as a criterion for disease progression, it must be confirmed by a second value. Once the number of final OS events is reached, progression follow up assessments will no longer be required.
Urine Protein Immunofixation		X		24-hour collection. Collect at Day 1 of each cycle. Must be collected to confirm sCR, CR, or VGPR regardless of whether M-protein was measurable at baseline. Will be completed per certified central laboratory. Once the number of final OS events is reached, progression follow up assessments will no longer be required.
Urine Protein Electrophoresis		X		
Skeletal Survey		X		If clinically indicated. Same method should be used throughout the study. Once the number of final OS events is reached, progression follow up assessments will no longer be required.

Post-Treatment Event ↓ Visit →	Safety Follow-Up Around 30 Days After Discontinuation of Study Treatment or Before Start of Subsequent Treatment (Whichever Occurs First)	Progression Follow-Up Q4 Weeks (± 1 Week) Following Last Dose of Treatment for Subjects Discontinued for Reasons Other than PD for 1 Year; Q 12 Weeks (± 1 Week) Thereafter	Survival Follow-Up Approximately Q12 Weeks for All Subjects	Comments
Plasmacytoma Evaluation		X		Performed only to confirm response of Minimal Response (MR) or better, or to confirm Progressive Disease, or as clinically indicated. CT, PET/CT or MRI – same method should be used throughout study if possible. Once the number of final OS events is reached, progression follow up assessments will no longer be required.
Bone Marrow Aspirate and biopsy		X		Optional at time of disease progression, if clinically indicated or as an optional procedure. Once the number of final OS events is reached, progression follow up assessments will no longer be required.
Response per IMWG Criteria		X		Once the number of final OS events is reached, progression follow up assessments will no longer be required.

Appendix H. Pharmacokinetic, Pharmacogenetic, and Biomarker Collection

Schedule of Pharmacokinetic Blood Collection for Venetoclax/Placebo and Bortezomib (and Dexamethasone, JAPAN Subjects Only)

Collection Times	Cycle 1 Day 1	Cycle 1 Day 11 (Japanese Subjects Enrolled in the run-in Phase Only)	Cycles 2, 4, 6, 8 Day 1	Cycles 2, 4, 6, 8 Day 11
Venetoclax/Placebo	6 hrs post-dose (optional)	--	0 (pre-dose)	--
Bortezomib	30 mins (0.5 hr) post-dose	--	--	0 (pre-dose)
Dexamethasone (Subjects enrolled in Japan only)	0.5 and 6 hour post dose	0 (pre-dose), 0.5, 1, 2, 4, 8 and 24 (Day12, pre-dose) hours post dose	--	--

Notes: All "pre-dose" samples in venetoclax/placebo PK sampling are relative to venetoclax or placebo administration. All "pre-dose" samples in bortezomib PK sampling are relative to bortezomib administration. JAPAN-ONLY: All "pre-dose" samples in dexamethasone PK sampling are relative to dexamethasone administration.

The date and time (to the nearest minute) of each venetoclax or placebo dose taken, and whether or not the venetoclax or placebo dose was taken within 30 minutes after completing breakfast (or first meal of the day), will be recorded on the eCRF for every scheduled venetoclax/placebo PK day and for the 2 days prior to every scheduled venetoclax or placebo PK day.

The date and time (to the nearest minute) of each bortezomib dose taken will be recorded on the eCRF for every scheduled bortezomib PK day and for the 2 doses (i.e., Days 4 and 8) prior to every scheduled bortezomib PK day.

The date and time (to the nearest minute) of each dexamethasone dose taken will be recorded (Japanese subjects only) on the eCRF for the scheduled dexamethasone PK day and for the doses immediately prior to and after the scheduled dexamethasone PK day.

Samples should be drawn on actual day of dosing.

Schedule of Pharmacogenetic and Biomarker Collection

Sample Collections (Sample Type)	Screening	C1D1	C5D1	Confirmation of sCR/CR	Approximately 6 Months Post Confirmation of sCR/CR	Approximately 12 Months Post Confirmation of sCR/CR	Treatment Completion Visit	Comments
OPTIONAL EXPLORATORY RESEARCH SAMPLE – PHARMACOGENETIC		X	X				X	One 4 mL whole blood sample for DNA isolation will be collected at C1D1 (prior to first dose of study treatment), C5D1, and the Treatment Completion Visit from each subject who consents to provide samples for pharmacogenetic analysis.
BIOMARKER SAMPLES								
Serum Markers		X	X				X	3.5 mL
Plasma Markers		X	X				X	12 mL
Bone Marrow Biopsy: IHC	X (Mandatory, unless biopsy is not performed per Institutional guidelines)						X (Optional)	Samples should be assessed for IMWG first, and samples should be sent for biomarker analysis at the central lab. Fresh samples are preferred, however, samples collected within 12 weeks prior to first dose of study treatment that are representative of the subject's current disease, without intervening treatment, will be accepted. Core block or tissue slides are acceptable.

Sample Collections (Sample Type)	Screening	C1D1	C5D1	Confirmation of sCR/CR	Approximately 6 Months Post Confirmation of sCR/CR	Approximately 12 Months Post Confirmation of sCR/CR	Treatment Completion Visit	Comments
Bone Marrow Aspirate								Samples should be assessed for IMWG first, and samples should be sent for biomarker analysis at the central lab. At Screening, fresh samples should be obtained within 21 days prior to first dose of study treatment and when possible, should be obtained after all other eligibility criteria have been met. For subjects who achieve an sCR or CR and continue to have this response, a bone marrow aspirate will be collected for MRD assessment at approximately 6 months and 12 months post-confirmed CR/sCR.
qPCR and MRD	X (6 mL)			X (3 mL – for MRD only)	X (3 mL – for MRD only)	X (3 mL – for MRD only)	X (6 mL – Optional)	
FISH	X (4 mL)						X (4 mL – Optional)	

Appendix I. Sample List of Excluded and Cautionary Medication

Cautionary, Consider Alternative Medications, Additional Guidance Noted:
Strong CYP3A inducers** – avasimibe, carbamazepine, enzalutamine, mitotane, phenytoin, rifampin, St. John's wort
Moderate CYP3A inducers** – bosentan, efavirenz, etravirine, modafinil, nafcillin
Strong CYP3A inhibitors† – boceprevir, clarithromycin, cobicistat, conivaptan, danoprevir/ritonavir, elvitegravir/ritonavir, idelalisib,* indinavir/ritonavir, itraconazole, ketoconazole, mibefradil, lopinavir/ritonavir, nefazodone, nelfinavir, paritaprevir/ritonavir combinations, ritonavir, posaconazole, saquinavir/ritonavir, telaprevir, telithromycin, tipranavir/ritonavir, voriconazole
Moderate CYP3A inhibitors‡ – amprenavir, aprepitant, atazanavir, cimetidine, ciprofloxacin, crizotinib,* cyclosporine,* darunavir/ritonavir, diltiazem,[1] erythromycin, fluconazole, fosamprenavir, imatinib,* isavuconazole, tofisopam, verapamil
Cautionary
Warfarin and coumadin derivatives[2]
P-gp substrates
Aliskiren, ambrisentan, colchicine, dabigatran etexilate, digoxin, everolimus,* fexofenadine, lapatinib,* loperami maraviroc, nilotinib,* ranolazine, saxagliptin, sirolimus,* sitagliptin, talinolol, tolvaptan, topotecan*
BCRP substrates
Methotrexate,* mitoxantrone,* irrinotecan,* lapatinib,* rosuvastatin, sulfasalazine, topoteca
OATP1B1/1B3 substrates
Atrasentan, atorvastatin, ezetimibe, fluvastatin, glyburide, rosuvastatin, simvastatin acid, pitavastatin, pravasta repaglinide, telmisartan, valsartan, olmesartan
P-gp inhibitors
Amiodarone, captopril, carvedilol, dronedarone, felodipine, quercetin, ronalzine, ticagre
BCRP inhibitors
Geftinib,*
Corticosteroids
Cortisone, Hydrocortisone, Methylprednisolone, Prednisolone, Prednisone, Triamcinolone, Betamethasone, Dexamethasone

* These are anticancer agents; contact AbbVie TA MD (refer to Section 6.1.5) before use.

** If subject requires use of these medications, use with caution and contact AbbVie TA MD or designee (refer to Section 6.1.5) for guidance.

† If subject requires use of these medications, use with caution and reduce the venetoclax/placebo dose by 4-fold. Patients should be monitored more closely for signs of toxicities and the dose may need to be further adjusted. After discontinuation of CYP3A inhibitor, wait for 3 days before venetoclax/placebo dose is increased back to the target dose. Once subjects are unblinded, dose adjustment will no longer apply for subjects in Arm 2 (Placebo + Bd).

‡ If subject requires use of these medications, use with caution and reduce the venetoclax/placebo dose by 2-fold. Patients should be monitored more closely for signs of toxicities and the dose may need to be further adjusted. After discontinuation of CYP3A inhibitor, wait for 3 days before venetoclax/placebo dose is increased back to the target dose. Once subjects are unblinded, dose adjustment will no longer apply for subjects in Arm 2 (Placebo + Bd).

1 Moderate CYP3A inhibitor per venetoclax FDA USPI.
2 Closely monitor the international normalized ratio (INR).

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

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

In addition to the medications listed in this table, subjects receiving venetoclax/placebo should not consume grapefruit, grapefruit products, Seville oranges (including marmalade containing Seville oranges) or starfruits.

Appendix J. IMWG Response Criteria for Multiple Myeloma

Response Subcategory	Response Criteria[a]
Stringent complete response (sCR)*	• 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 • Normal FLC (free light chain) ratio and • Absence of clonal cells in bone marrow[b] by immunohistochemistry or immunofluorescence[c] or 2 to 4 color flow cytometry
Complete response (CR)*	• 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 (VGPR)*	• Serum and urine M-component detectable by immunofixation but not on electrophoresis or • ≥ 90% reduction in serum M-component plus urine M component < 100 mg per 24-hr 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 (PR)	• ≥ 50% reduction of serum M-protein and • Reduction in 24-hr urinary M-protein by ≥ 90% or to < 200 mg per 24-hr ○ 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. • ≥ 50% reduction in the size of soft tissue plasmacytomas is also required, if present at baseline.
Minimal response (MR)	• 25% – 49% reduction of serum M-protein and • 50% – 89% reduction in 24-hour urinary M-protein and • 25% – 49% reduction in size of soft tissue plasmacytomas, if present at baseline, and • No increase in size or number of lytic bone lesions (development of compression fracture does not exclude response).
Stable disease (SD)[e]	Not meeting criteria for sCR, CR, VGPR, PR, MR or progressive disease (PD).

a. All response categories require two consecutive assessments made at anytime before the institution of any new therapy; all categories 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.

b. Confirmation with repeat bone marrow biopsy not needed.

c. Presence/absence of clonal cells is based upon the k/λ ratio. An abnormal k/λ ratio by immunohistochemistry, and/or flow cytometry and/or immunofluorescence 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 for this study is defined as meeting at least one of the following three measurements: Serum M-protein ≥ 0.5 g/dL (≥ 5 g/L) or Urine M-protein ≥ 200 mg/24 hr or serum FLC assay with an involved FLC level ≥ 10 mg/dL (≥ 100 mg/L) provided serum FLC ratio 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.

Note: *** Clarification to IMWG criteria for coding CR and VGPR in subjects in whom the only measurable disease is by serum FLC levels:** CR in such subjects is defined as a normal FLC ratio of 0.26 – 1.65 in addition to CR criteria listed above. VGPR in such subjects is defined as a > 90% decrease in the difference between involved and uninvolved free light chain 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 on serum, urine, both, or neither.

Relapse Subcategory	Relapse Criteria

Progressive disease (PD)*	Requires any one or more of the following:
	• Increase of ≥ 25% from lowest response level in any of the following:
	  ○ Serum M-protein[a] absolute increase ≥ 0.5 g/dL, and/or
	  ○ Urine M-protein absolute increase ≥ 200 mg/24-hr, and/or
	  ○ In subjects without measurable serum and urine M-protein levels, the difference between involved and uninvolved FLC levels (the absolute increase must be > 10 mg/dL), and/or
	• Definite development of new bone lesions or soft tissue plasmacytomas, and/or
	• Definite increase in the size of existing bone lesions or soft tissue plasmacytomas
	  ○ A definite increase in size of bone lesions and/or plasmacytomas is defined as ≥ 50% increase from nadir in the sum of the product of the cross-diameters (SPD) of > 1 lesion, or ≥ 50% increase in the longest diameter of a previous lesion > 1 cm in short axis.[45]
	• Development of hypercalcemia (corrected serum calcium > 11.5 mg/dL) that can be attributed solely to the plasma cell proliferative disorder.

Clinical Relapse	Requires any one or more of the following direct indicators of increasing disease and/or end organ dysfunction (CRAB features).[b] • Development of new soft tissue plasmacytomas or bone lesions on skeletal survey, MRI or other imaging, and/or • Definite increase in size of existing plasmacytomas or bone lesions. A definite increase is defined as a 50% (and at least 1 cm) increase as measured serially by the sum of the products of the cross diameters of the measurable lesion, and/or • Hypercalcemia > 11.5 mg/dL (> 2.875 mmol/L), and/or • Decrease in hemoglobin of ≥ 2 g/dL dL (≥ 1.25 mmol/L) or < 10 g/dL, and/or • Rise in serum creatinine by > 2 mg/dL (≥ 177 mmol/L), and/or • Hyperviscosity

a. For progressive disease, serum M-component increases of ≥ 1 g/dL are sufficient to define relapse if starting M-component is ≥ 5 g/dL.

b. For purposes of calculating time to progression and progression-free survival, CR subjects should also be evaluated using criteria listed above for progressive disease.

* The "25% increase" refers to M-protein, FLC, and bone marrow results and does not refer to bone lesions, soft tissue plasmacytomas, or hypercalcemia. The "lowest response value" does not need to be a confirmed value.

Appendix K. 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 mg/dL (475.8 µmol/liter)	N/A
Hyperphosphatemia	Phosphorus > 4.5 mg/dL (1.5 mmol/liter)	N/A
Hyperkalemia	Potassium > 6 mmol/liter	Cardiac dysrhythmia or sudden death probably or definitely caused by hyperkalemia
Hypocalcemia	Corrected calcium < 7.0 mg/dL (1.75 mmol/liter) or ionized calcium < 1.12 mg/dL (0.3 mmol/liter)#	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!	N/A	Increase in the serum creatinine level of 0.3 mg/dL (26.5 µmol/liter) or the presence of oliguria (average urine output of < 0.5 mL/kg/hr over a 6-hour period)

* Laboratory TLS requires two 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 column.

Corrected Serum Calcium = [mg/dL] = Measured serum calcium [mg/dL] + 0.8 × (4 – serum albumin [g/dL]).

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

Note: Laboratory tumor lysis syndrome and at least one clinical complication.

Cross reference: Howard SC 2011[44]

Appendix L. Japan Specific Information

1.0 Clinical Expense and Compensation

1.1 Expenditure of the Clinical Expense

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

1.2 Compensation for Health Impairment and Insurance

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

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

1.3 Pharmacogenetic Testing

Pharmacogenetic testing on samples collected in Japan will be restricted to the subject's response to study treatment in terms of pharmacokinetics, efficacy, tolerability, and safety.

Appendix M. Corticosteroid Conversion Table

Corticosteroid Conversion Table[46-48]	
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