1.0 Title Page

Clinical Study Protocol M13-367

A Phase 1/2 Study Evaluating the Safety and Pharmacokinetics of ABT-199 in Subjects with Relapsed or Refractory Multiple Myeloma

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

AbbVie Investigational Product:	Venetoclax (ABT-199)
Date:	17 February 2021
Development Phase:	1/2
EudraCT:	2012-000589-38
Study Design:	This is an open-label study designed to determine the safety, pharmacokinetics, maximum tolerated dose, and the recommended Phase 2 dose of ABT-199 in subjects with relapsed or refractory multiple myeloma.
Investigator:	Investigator information on file at AbbVie.
Sponsor:	AbbVie* Collaborative Partners Genentech, Inc.
Sponsor/Emergency Contact:	[redacted], **MD** Medical Director, TA Oncology Pharmacyclics Switzerland GmbH An AbbVie Company Mühlentalstrasse 36 CH-8200 Schaffhausen Located in Europe: Phone: [redacted] Emergency 24-hour Number: [redacted] Email: [redacted]

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

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.

1.1 Protocol Amendment: Summary of Changes

Previous Protocol Versions

Protocol	Date
Original	11 April 2012
Administration Change 1	17 October 2012
Amendment 1	16 November 2012
Amendment 2	22 March 2013
Amendment 3	03 March 2014
Amendment 4	01 December 2014
Amendment 5	23 April 2016
Amendment 6	05 October 2017
Amendment 7	11 January 2018
Amendment 8	30 May 2018
Amendment 9	15 March 2019
Amendment 10	24 September 2019
Amendment 11	03 November 2020

The purpose of this amendment is to:

- Update to Section 5.1 Overall Study Design and Plan: Description

  Rationale: *To clarify subjects will continue on treatment until the end of study provided they continue to tolerate Venetoclax, have no evidence of disease progression, and do not meet any criteria for subject discontinuation (Section 5.4.1)*

- Update to Section 13.0 Completion of the Study

  Rationale: *To clarify end of study is the end of study is defined as the date of the last subject's last visit, including Safety Follow Up.*

1.2 Synopsis

AbbVie	**Protocol Number:** M13-367
Name of Study Drug: Venetoclax (ABT-199)	**Phase of Development:** 1/2
Name of Active Ingredient: Not available	**Date of Protocol Synopsis:** 17 February 2021
Protocol Title: A Phase 1/2 Study Evaluating the Safety and Pharmacokinetics of ABT-199 in Subjects with Relapsed or Refractory Multiple Myeloma	
Objectives: Phase 1 Portion (Dose Escalation, Safety Expansion and Venetoclax-Dexamethasone (VenDex) Combination: The primary objectives are to assess the safety profile, characterize pharmacokinetics (PK), determine the dosing schedule, the maximum tolerated dose (MTD), and the recommended Phase 2 dose (RPTD) of venetoclax monotherapy when administered in subjects with relapsed or refractory multiple myeloma (MM). This study will also assess the safety profile and PK of venetoclax in combination with dexamethasone in subjects with t(11;14)-positive MM. The secondary objectives are to evaluate the preliminary efficacy data regarding the effect of venetoclax monotherapy or combined with dexamethasone on objective response rate (ORR), time to response (TTR), time to disease progression (TTP), and duration of response (DOR). Phase 2 Portion (VenDex Expansion): The primary objective of the Phase 2 portion is to further evaluate the ORR and very good partial response or better rate (VGPR+) in subjects with t(11;14)-positive multiple myeloma. The secondary objectives are to monitor safety, progression free survival (PFS), DOR, TTR, TTP, and overall survival (OS) and to evaluate 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]). The tertiary objectives of the Phase 2 portion are to assess 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. The exploratory objectives for both portions are to evaluate pharmacodynamic and predictive biomarkers for association with PK, safety, and efficacy. In addition, minimal residual disease (MRD) will be assessed in the bone marrow by next generation sequencing (NGS).	
Investigators: Multicenter	
Study Sites: Approximately 32 sites.	
Study Population: Relapsed/refractory multiple myeloma subjects.	
Number of Subjects to be Enrolled: Approximately 166 – 186 (86 subjects in the Phase 1 portion and approximately 80 – 100 subjects in the Phase 2 portion)	

Methodology:

This is a Phase 1/2, open-label, multicenter study evaluating the safety and PK profile of venetoclax under a once daily dosing schedule. This study will consist of 2 distinct portions (Phase 1 and Phase 2). The Phase 1 portion includes dose escalation, safety expansion, venetoclax-dexamethasone (VenDex) combination. The dose escalation cohort of the study will evaluate the safety and pharmacokinetic profile of venetoclax in approximately 30 subjects, with the objective of defining dose limiting toxicities (DLTs) and the MTD. The safety expansion cohort will evaluate venetoclax at the MTD defined in the dose escalation portion in approximately 36 additional subjects in order to further define the toxicity profile, test biomarker correlates, and better inform the RPTD determination for subjects with MM. The VenDex combination cohort will evaluate the safety and efficacy of venetoclax at the RPTD in combination with dexamethasone in approximately 20 subjects with t(11;14)-positive MM. The Phase 2 portion is an expansion cohort of the VenDex combination and will further evaluate the efficacy of approximately 80 – 100 additional relapsed or refractory subjects with t(11;14)-positive MM. Investigators and/or qualified site staff will assess the ORR and VGPR+ rate per IMWG criteria.

Survival information (i.e., alive or deceased, and if deceased, the date and cause of death) 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, 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. Subject must request to be withdrawn specifically from survival follow-up.

Diagnosis and Main Criteria for Inclusion/Exclusion:

Main Inclusion:

1. Subject must be ≥ 18 years of age.
2. Subject has an ECOG performance score of ≤ 1.
   - For subjects in the Phase 2 portion: ECOG performance score of ≤ 2.
3. Diagnosis of multiple myeloma which requires treatment and has been previously treated with:
   - For subjects in the Dose Escalation cohort of the study:
     - ≥ 1 prior line of therapy. Induction therapy followed by stem cell transplant and maintenance therapy will be considered as a single line of therapy.
   - For subjects in the Safety Expansion cohort of the study:
     - Have received treatment with a proteasome inhibitor and an immunomodulatory (IMiD®) agent (e.g., thalidomide, lenalidomide, pomalidomide). Induction therapy followed by stem cell transplant and maintenance therapy will be considered as a single line of therapy.
   - For subjects in the Venetoclax-Dexamethasone (VenDex) Combination cohort of the study:
     - Have received treatment with a proteasome inhibitor and an immunomodulatory (IMiD®) agent (e.g., thalidomide, lenalidomide, pomalidomide). Induction therapy followed by stem cell transplant and maintenance therapy will be considered as a single line of therapy, AND
     - Have MM positive for the t(11;14) translocation, as determined by an analytically validated fluorescence in situ hybridization (FISH) assay per the central laboratory testing.

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

Main Inclusion (Continued):

- For subjects in the Phase 2 cohort of the study:
  - Have MM positive for the t(11;14) translocation, as determined by an analytically validated fluorescence in situ hybridization (FISH) assay per central laboratory testing (enrollment with local t(11;14)-positive FISH results will be considered at the discretion of the TA MD).

    AND
  - Subject must have evidence of disease progression on or within 60 days of the last dose of the most recent previous treatment regimen based on the IMWG criteria,

    AND
  - Subject must have previously received at least 2 lines of therapy, including an immunomodulatory drug (lenalidomide or pomalidomide), a proteasome inhibitor (bortezomib, carfilzomib or ixazomib), daratumumab, and glucocorticoids.
    - For United States (US) Subjects: Daratumumab combination regimen **must** be one of the prior lines of therapy (for this study, daratumumab plus corticosteroids will not be considered a combination regimen)
    - For Non-US Subjects: Either daratumumab monotherapy or daratumumab combination therapy is acceptable. Daratumumab monotherapy will be limited to approximately 20 percent of the total number of Phase 2 subjects.

4. Subject must have measurable disease at Screening, defined as any of the following:
   - Serum monoclonal protein ≥ 1.0 g/dL (≥ 10 g/L) by protein electrophoresis,
   - ≥ 200 mg of monoclonal protein in the urine on 24-hour electrophoresis, or
   - Serum immunoglobulin free light chain (FLC) ≥ 10 mg/dL provided serum FLC ratio is abnormal.
5. Subjects with a history of autologous or allogenic stem cell transplantation must have adequate peripheral blood counts independent of any growth factor support, and have recovered from any transplant-related toxicity(s) and be:
   - 100 days post-autologous transplant (prior to first dose of study drug), or
   - ≥ 6 months post-allogenic transplant (prior to first dose of study drug) and not have active graft-versus-host disease (GVHD), i.e., requiring treatment.

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

Main Inclusion (Continued):

6. Subjects must meet the following laboratory parameters, per laboratory reference range, at least once during screening period:
   - ANC ≥ 1000/μL

     Subjects may use growth factor support to achieve ANC eligibility criteria.
   - AST and ALT ≤ 3 × upper limit of normal range (ULN)
   - Calculated creatinine clearance ≥ 30 mL/min using a modified Cockcroft-Gault calculation or a 24-hour urine collection for Creatinine Clearance:

     $$eC_{Cr} = \frac{(140 - \text{Age}) \bullet \text{weight (kg)} \bullet [0.85 \text{ if Female}]}{72 \bullet \text{Serum Creatinine (mg/dL)}}$$

     OR, if serum creatinine is in μmol/L:

     $$eC_{Cr} = \frac{(140 - \text{Age}) \bullet \text{weight (kg)} \bullet [1.23 \text{ if Male, } 1.04 \text{ if Female}]}{\text{Serum Creatinine (μmol/L)}}$$
   - Platelet count ≥ 30,000 mm^3, independent of transfusion for 2 weeks
   - Hemoglobin ≥ 8.0 g/dL, subjects may receive blood transfusion to achieve hemoglobin eligibility criteria per investigator discretion.
   - Total bilirubin ≤ 1.5 × ULN

     Subjects with Gilbert's Syndrome may have bilirubin > 1.5 × ULN.

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

Main Exclusion:

1. Subject exhibits evidence of other clinically significant uncontrolled condition(s), including, but not limited to:
   - Acute infection within 14 days prior to first dose of study drug requiring antibiotic, antifungal, or antiviral therapy
   - Diagnosis of fever and neutropenia within 1 week prior to first dose of study drug.
2. Subject has a cardiovascular disability status of New York Heart Association Class ≥ 3.
3. Subject has a significant history of renal, neurologic, psychiatric, endocrinologic, metabolic, immunologic, cardiovascular or hepatic disease within the last 6 months that, in the opinion of the investigator, would adversely affect his/her participation in the study.
4. Subject has a history of other active malignancies other than multiple myeloma within the past 3 years prior to study entry, with the following exceptions:
   - Adequately treated in situ carcinoma of the cervix uteri;
   - Basal cell carcinoma of the skin or localized squamous cell carcinoma of the skin;
   - Localized prostate cancer Gleason grade 6 or lower AND with stable Prostate Specific Antigen (PSA) levels off treatment
   - Previous malignancy confined and surgically resected (or treated with other modalities) with curative intent.
5. Known Human Immunodeficiency Viral (HIV) infection.
6. Active hepatitis B or C infection based on screening blood testing.
7. Subject is receiving other ongoing anti-myeloma therapy.
8. Subject has received any of the following within 7 days prior to the first dose of study drug:
   - Strong or moderate CYP3A inhibitors, or
   - Strong or moderate CYP3A inducers.

Investigational Products:	Venetoclax (ABT-199): 10 mg, 50 mg, and 100 mg Tablets Dexamethasone (For subjects enrolled to the VenDex combination and Phase 2 cohorts): 4 mg tablets
Non-Investigational Product:	Dexamethasone (For subjects enrolled to the dose escalation and safety expansion cohorts)
Doses:	All subjects will begin dosing with a lead-in period with step-wise dose escalation to the designated cohort dose during the dose escalation and safety expansion portions. Subjects in the first cohort will begin the lead-in period with a starting dose of 50 mg and will step up in increments anticipated to be at least 50 mg to a designated cohort dose level of 300 mg. Based on additional clinical data from the enrolled subjects, the starting dose for the lead-in period may be further reduced to less than 50 mg. In the first dose-escalation cohort, the first dose for the second subject will not be administered until at least 1 week after the first dose of the first subject. Staggered enrollment may continue for subsequent cohorts. In subsequent cohorts, modifications in the lead-in period may occur based on tolerability. Increases or decreases in the lead-in period starting dose and/or changes in the dosing increments may be implemented. For example, the starting dose of 50 mg in subsequent cohorts may be lowered; dose escalation may then occur in smaller increments. The lead-in period may be eliminated if toxicities such as clinically significant metabolic abnormalities of tumor lysis syndrome (TLS) are not observed. A lower starting dose and/or modifications to the lead-in regimen may be implemented for individual subject(s) at particularly high risk for TLS. The venetoclax designated cohort dose will begin at 300 mg/day and escalate to the MTD with a minimum of 3 subjects at each dose level. Designated cohort dose escalation or de-escalation decisions to the next designated cohort dose will be made after subjects have completed the lead-in period (if applicable) plus one cycle (21 days) at the designated cohort dose. Escalation of designated cohort dose will occur in increments of 100 mg unless data indicate smaller increments are required. De-escalation will occur in increments of 50 mg unless data indicate other increments are required. Decisions will be informed by subject tolerability and safety data. During dose escalation and safety expansion portions, upon assessment of progressive disease, investigators may add dexamethasone dosed orally starting at 40 mg using label guidelines. Dexamethasone will be dosed on Days 1, 8, and 15 of each 21-day cycle.

Doses (Continued):	During the VenDex combination and Phase 2 cohorts, a lead-in period with step wise dose escalation will not be implemented. Subjects will take venetoclax RPTD of 800 mg daily (QD) in combination with dexamethasone. Dexamethasone (40 mg) will be dosed orally (PO) on Days 1, 8, and 15 of each 21-day cycle. All subjects who are ≥ 75 years old may start dexamethasone at a 20 mg dose.
Mode of Administration:	Oral (PO)

Duration of Treatment: Anticipated duration is 10 months.

Criteria for Evaluation:

Efficacy Assessment: Phase 1 Portion subjects will be evaluated for preliminary efficacy using the International Uniform Response Criteria for Multiple Myeloma (IMWG, 2011); Phase 2 Portion subjects will be evaluated for efficacy using IMWG 2016 response criteria.

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 Assessment: Intensive pharmacokinetic samples will be collected for venetoclax in the dose escalation cohort. Sparse pharmacokinetic samples will be collected for venetoclax in the dose escalation, safety expansion, VenDex combination and Phase 2 cohorts. For the intensive pharmacokinetic days, values for the pharmacokinetic parameters of venetoclax, including the maximum observed plasma concentration (C_{max}), the time to C_{max} (peak time, T_{max}) and the area under the plasma concentration-time curve (AUC) over a 24-hour dose interval (AUC_{0-24}) will be determined using noncompartmental methods. Additional parameters may be calculated if useful in the interpretation of the data.

Biomarkers: Biospecimens (blood, 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 (IgH translocations, amplifications, or deletions), and MRD. 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. Results may or may not be included in the clinical study report.

Safety Assessment: Adverse event monitoring, vital signs, physical examination, 12-lead ECG, multiple gated acquisition scan (MUGA)/2D echocardiogram, and laboratory assessments. Guidelines for the management for TLS are provided.

Statistical Methods: 3+3 design (for dose escalation purposes)

Efficacy: The following efficacy endpoints will be assessed: ORR, VGPR+, PFS, DOR, TTR, TTP, and OS.

Pharmacokinetic: An analysis will be performed on PK variables for single and multiple doses to simultaneously explore for demographic variables that explain some of the variability in pharmacokinetics and to address questions of dose proportionality and linear kinetics. Additional analyses, e.g., time to reach steady state, will be performed if useful and appropriate.

Safety: A safety analysis will be performed for all subjects participating in the study unless otherwise indicated. For the study as a whole, adverse events will be evaluated and summarized. Laboratory test results and vital signs will be explored for trends and summarized as appropriate.

1.3 List of Abbreviations and Definition of Terms

Abbreviations

ALT	Alanine aminotransferase
AML	Acute Myeloid Leukemia
ANC	Absolute Neutrophil Count
aPTT	Activated Partial Thromboplastin Time
AST	Aspartate aminotransferase
BPI-SF	Brief Pain Inventory – Short Form
BUN	Blood Urea Nitrogen
C	Cycle
CFR	Code of Federal Regulations
CHF	Congestive Heart Failure
CR	Complete Response
COVID-19	Coronavirus Disease-2019
CSF	Colony Stimulating Factors
CTCAE	Common Terminology Criteria for Adverse Events
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
DLBCL	Diffuse Large B-Cell Lymphoma
DLT	Dose Limiting Toxicity
DNA	Deoxyribonucleic Acid
DOR	Duration of Response
DTP	Direct-to-patient
EBMT	European Society for Blood and Marrow Transplantation
EBV	Epstein Barr Virus
EC	Ethics Committee
ECG	Electrocardiogram

ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EDTA	Edetic Acid (Ethylenediaminetetraacetic Acid)
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	Fluorescence In Situ Hybridization
FL	Follicular Lymphoma
FLC	Free Light Chain
GCP	Good Clinical Practice
GVHD	Graft-Versus-Host Disease
HAV-IgM	Hepatitis A Virus Immunoglobulin M
HBsAg	Hepatitis B Surface Antigen
HCV Ab	Hepatitis C Virus Antibody
HDPE	High Density Polyethylene
HIV	Human Immunodeficiency Virus
Hr	Hour
HRQoL	Heath-related Quality of Life
HSV	Herpes Simplex Virus
IBW	Ideal Body Weight
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IF	Immunofixation
Ig	Immunoglobulin
IHC	Immunohistochemistry
IMiD®	Immunomodulatory Thalidomide Derivative Compound
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
IUD	Intrauterine Device
IV	Intravenous
Kg	Kilogram

LDH	Lactate Dehydrogenase
MCHC	Mean Corpuscular Hemoglobin Concentration
MCL	Mantle Cell Lymphoma
MCV	Mean Corpuscular Volume
MedDRA	Medical Dictionary for Regulatory Activities
µg	Microgram
Mg	Milligram
Min	Minute
mL	Milliliter
MM	Multiple Myeloma
MPV	Mean Platelet Volume
MR	Minimal Response
MRD	Minimal Residual Disease
MTD	Maximum Tolerated Dose
MUGA	Multiple Gated Acquisition Scan
NCI	National Cancer Institute
NGS	Next Generation Sequencing
ORR	Objective Response Rate
OS	Overall Survival
PD	Progressive Disease
PFS	Progression-Free Survival
PG	Pharmacogenetic
PK	Pharmacokinetic
PR	Partial Response
PRO	Patient Reported Outcomes
PROMIS	Patient Reported Outcomes Measurement Information System
PT	Prothrombin Time
QD	Once Daily
QoL	Quality of Life
QTc	QT Interval Corrected for Heart Rate
QTcB	QT Interval Corrected for Heart Rate by Bazett's Formula
RBC	Red Blood Cell
RNA	Ribonucleic Acid
RS	Richter's Syndrome

SAE	Serious Adverse Event
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
sβ2M	Serum β2 microglobulin
sCR	Stringent Complete Response
SCT	Stem Cell Transplant
SD	Stable Disease
sFLC	Serum Free Light Chains
SPD	Sum of the Product of the Diameters
SPEP	Serum Protein Electrophoresis
sQI	Serum Quantitative Immunoglobulins
SST	Serum Separator Tube
TA MD	Therapeutic Area Medical Director
TLS	Tumor Lysis Syndrome
TTP	Time to Disease Progression
TTR	Time to Response
ULN	Upper Limit of Normal Range
UPEP	Urine Protein Electrophoresis
US	United States
VenDex	Venetoclax and Dexamethasone
VGPR	Very Good Partial Response
VGPR+	Very Good Partial Response or better
VZV	Varicella Zoster Virus
WBC	White Blood Cell
WOCBP	Women Of Childbearing Potential

Pharmacokinetic and Statistical Abbreviations

AUC	Area Under the Plasma Concentration-Time Curve
AUC_t	Area Under the Plasma Concentration-Time Curve from Time Zero to Time of Last Measurable Concentration
AUC_∞	Area Under the Plasma Concentration-Time Curve from Time Zero to Infinity
β	Beta
C_{max}	Maximum Observed Plasma Concentration
T_{max}	Time to Maximum Observed Plasma Concentration

2.0 Table of Contents

List of Tables

List of Figures

List of Appendices

3.0 Introduction

3.1 Multiple Myeloma (MM)

Multiple myeloma is an incurable malignancy arising from post germinal center, terminally differentiated plasma cells, characterized by an excess of monotypic plasma cells in the bone marrow, resulting in elevated levels of monoclonal immunoglobulins (Ig) in the serum and/or urine.[1] Common clinical sequelae include lytic bone lesions, fractures, myelosuppression, and renal failure. In the United States of America, the estimated annual diagnosed incidence is 16,000, with approximately 50,000 prevalent cases. In Europe, the estimated annual diagnosed incidence is 21,611 with approximately 54,536 prevalent cases.[2] Multiple myeloma accounts for 10% of all hematologic malignancies and 1% of all malignancies. Advances in high-dose chemotherapy and stem cell transplantation have improved overall survival and event-free disease periods in patients with MM, but relapses are inevitable.[3,4] New therapeutic agents, such as bortezomib and thalidomide analogues (IMiD®), have shown promising clinical benefit in patients with relapsed or refractory disease. Current treatments include combination chemotherapy with regimens using melphalan (Alkeran®), bortezomib (Velcade®), thalidomide (Thalomid®), and lenalidomide (Revlimid®) with and without corticosteroids. Younger patients are consolidated with high-dose therapy (ablative chemotherapy or radiation) with autologous stem cell transplantation. In addition, newer agents with encouraging single agent activity are currently in clinical trials for the relapsed/refractory population. Treatment of subjects with carlfilzomib, a new generation proteasome inhibitor, has resulted in a response rate of about 25% in subjects who received a prior IMiD® and Velcade®.[5] Pomalidomide, a new generation immunomodulatory drug, in combination with dexamethasone resulted in a similar response rate in MM subjects refractory to both an IMiD® and Velcade®.[6] Despite these therapeutic advances, MM remains essentially incurable and is associated with high morbidity and mortality.[7]

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-x_S, Bad, Bik, Bim, and Hrk) members of the Bcl-2 family. Anti-apoptotic Bcl-2 family members are localized in the mitochondrial outer membrane, nuclear membrane, or the endoplasmic reticulum, while most of the pro-apoptotic members are in the cytosol or localized to the cytoskeleton. Normally, Bax and Bak are sequestered by the anti-apoptotic proteins Bcl-2, Bcl-x_L, and/or Mcl-1 and prevented from translocating to mitochondria. However, various damaging stimuli can result in their liberation and translocation to the mitochondrial outer membrane, leading to an increase in mitochondrial permeability, the release of cytochrome c, and activation of caspase 9 through its binding to Apaf-1. This in turn leads to activation of effector caspases like caspase 3 and cellular apoptosis. 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. Dysregulation of apoptotic pathways in these cells, often via Bcl-2 overexpression, is thought to play a major role in the development and progression of multiple myeloma. Antagonizing Bcl-2 function to induce apoptosis is thus a compelling therapeutic approach in multiple myeloma.

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.

3.3 Pharmacology, Preclinical Data and Initial Clinical Data

ABT-199 (Venetoclax) Activity and Preclinical Pharmacokinetic Profile

ABT-199 (Venetoclax) is a novel, orally bioavailable small molecule inhibitor of Bcl-2 (K_i < 0.10 nM) with much lower affinity for Bcl-xL and Bcl-w (> 480-fold and > 2,000-fold lower affinity, respectively). In vitro, venetocalx has demonstrated broad

cell killing activity against hematopoietic tumor cell lines including B-cell follicular lymphomas (FL), mantle cell lymphomas (MCL), diffuse large B-cell lymphomas (DLBCL), acute myeloid leukemias (AML), and multiple myelomas (MM). Venetoclax was especially potent against FL and DLBCL cell lines expressing high levels of Bcl-2 due to the t(14;18) translocation. The sensitivity of MM cell lines correlated most closely with their Bcl-2/Mcl-1 mRNA expression ratio, with the most sensitive cell lines expressing high levels of Bcl-2 relative to Mcl-1, a known resistance factor for Bcl-2 inhibitors. Multiple myloma cell lines bearing the t(11;14) translocation were particularly sensitive to venetoclax (6 of 8 cell lines with an 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).[8]

The pharmacokinetic behavior of venetoclax was evaluated in multiple animal species. In mouse, rat, monkey and dog the pharmacodynamic profile was characterized by low plasma clearance and low volumes of distribution. Half-lives ranged from 2.2 hours in monkey to 12 hours in dog. Food had a marked effect on the oral bioavailability in dogs.

Venetoclax has high protein binding to human, rat, dog, and monkey plasma proteins (> 99.9%). In rats, venetoclax was widely distributed into liver, kidneys, spleen, heart, lungs, small intestine, and white fat, but was poorly distributed in testes, brain, muscle, and bone. Metabolism was the major route of elimination with biliary excretion of the parent drug playing the secondary role in rats. Venetoclax showed moderate metabolic stability in vitro hepatic systems across species tested, except for low to moderate stability in dog hepatocytes.

In vitro, venetoclax was metabolized by CYP3A4; it was not a potent inhibitor of CYP3A4, CYP1A2, CYP2B6, CYP2C19, or CYP2D6 (IC50 > 30 μM); it did not induce CYP3A4 or CYP1A2 at concentrations up to 10 μM. Venetoclax is a substrate for P-gp and BCRP. Studies in Oatp1a/b cluster KO mice indicated that venetoclax may be an OATP substrate. Active uptake of venetoclax or M27 was not observed in cells overexpressing OATP1B1, OATP1B3 or OCT1. Venetoclax is a P-gp, BCRP and OATP1B1 inhibitor in vitro.

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.[29]

Venetoclax Preclinical Toxicology

Venetoclax has been assessed in repeated-dose general toxicology studies, and in genetic, developmental/reproductive, and safety pharmacology studies.

Repeated-dose oral toxicity studies with venetoclax were conducted in mice and dogs. GLP-compliant definitive toxicity studies consisted of IND-enabling studies in mice and dogs with 4 weeks of dosing followed by a 4-week (dose-free) recovery period; a 2-week toxicity study in dogs that focused on lymphocyte recovery over an extended (18-week) recovery period; and chronic toxicity studies in mice (6 months) and dogs (9 months). No recovery periods were included in the chronic toxicity studies. The maximum venetoclax plasma exposures (mean $AUC_{0\text{-}24\ h}$) achieved in the 4-week studies were 92 µg•hr/mL (at 600 mg/kg/day) in mice and 572 µg•hr/mL (at 150 mg/kg/day) in dogs. In the chronic toxicity studies, AUCs reached 34.1 µh•h/mL (at 300 mg/kg/day) in mice and 139 µh•h/mL (at 20 mg/kg/day) in dogs.

The primary toxicities associated with venetoclax administration included effects on the hematologic system (decreased lymphocytes and erythrocytes) in mice and dogs; the male dog reproductive system (testicular germ cell depletion); and embryofetal toxicity in mice.

In mice and dogs, venetoclax produced robust decreases in lymphocytes in the peripheral blood (of up to 75% in mice and up to 81% in dogs) and in lymphoid tissues. In dogs, the recovery of lymphocyte counts (total lymphocytes, CD4+ and CD8+ T cells and mature B cells) was prolonged, requiring up to 18 weeks after completion of 2 weeks of dosing. B cells were the most sensitive lymphocyte subtype based on the magnitude of decrease and/or the length of time required for recovery. Decreases of lymphocytes in lymphoid tissues were reversible in mice and reversible to partially reversible in dogs.

venetoclax-related decreases in lymphocytes in blood and lymphoid tissues are considered pharmacologically-mediated and non-adverse.[9]

Venetoclax effects on red blood cell mass parameters principally consisted dose-related decreases of hematocrit and hemoglobin in mice and dogs; these effects were adverse only at the highest dosages in the 4-week mouse and dog studies and were reversible. Effects on the white and red cell counts are readily monitored in clinical trial subjects.

No effects of venetoclax have been identified in female reproductive tissues in mice or dogs in general toxicology studies. However, in dogs venetoclax produced adverse, non-reversible, non-dose related microscopic findings of testicular germ cell depletion at all dosages tested; however, there were no testicular effects in mice. The testicular effecs may be related to venetoclax pharmacology, as one or more members of the Bcl-2 family of proteins play a role in spermatogenesis.[10-12] The translatability of the testicular findings in dogs to humans is unknown. In view of the potential treatment benefits of venetoclax, this finding is anticipated not to impact the treatment of subjects with relapsed or refractory multiple myeloma.

Venetoclax resulted in increased postimplantation loss and decreased fetal body weights in the mouse embryofetal development study 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, and there were no other effects on development or fertility.

Venetoclax produced loss of hair pigmentation in dogs (reversibility has not been assessed). Evidence from Bcl-2 knockout mouse (Bcl-2 -/-) studies indicates that hair hypopigmentation is consistent with the pharmacological effect of Bcl-2 functional loss, and occurs due to loss of hair follicle melanocytes dependent on Bcl-2 for survival.[13] A dedicated physical exam of the skin and extensive ophthalmic exams determined that pigmentation of the skin and in the eye (particularly, the iris and fundus) of the dog appeared unaffected.

Other effects of venetoclax included single cell necrosis in various epithelial tissues in dogs (i.e., gallbladder, stomach, exocrine pancreas, and epididymides) that was of minimal magnitude and produced no loss of mucosal integrity; and increased pigment in Kupffer cells or macrophages in the liver and gallbladder of dogs. None of the effects were considered to be adverse, and all were reversible.

Dogs at the high dose of 150 mg/kg/day in the 4-week study had clinical signs of swelling of the skin on the ears, head (cranial area), and forepaws and/or hindpaws. Most but not all animals (8 of 10 dogs) were affected. The clinical signs were mild to moderate in severity, transient and sporadic in occurrence, and were absent during the recovery period. The swelling reactions were observed after the first dose in 3 dogs, and therefore not consistent with drug-induced immediate (IgE-mediated, Type I) hypersensitivity; however, other immune-mediated mechanisms could be involved. Although the basis for the swelling reactions was not established, there were no signs of anaphylaxis. Clinical signs of swelling were not observed at the lower dosages of venetoclax evaluated in chronic toxicity studies in mice or dogs. Any occurrences of swelling reactions in subjects can be monitored and treated.

There was no evidence of in vitro or in vivo genetic toxicity of venetoclax.

Venetoclax was tested in a battery of safety pharmacology assays, and produced no effects in the CNS/neurobehavioral or respiratory studies in mice at oral doses up to and including the highest dose of 600 mg/kg. No effects on corrected QT interval (QTc) were observed up to a maximum plasma concentration of 46 µg/mL in dogs. 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 µg/mL). In the anesthetized dog at higher plasma concentrations, venetoclax produced mild reductions in myocardial contractility (–6% to –13%) and cardiac output (–11% to –19%) at plasma concentrations of ≥ 16 µg/mL and ≥ 32 µg/mL, respectively. These concentrations are greater than the plasma concentration of venetoclax in oncology subjects (e.g., 2.18 µg/mL at the 400 mg dose).

On the basis of nonclinical safety pharmacology and toxicology evaluations of venetoclax, and on the basis of nonclinical and human studies of related antiapoptotic Bcl-2 family protein inhibitors, potential mechanism-based toxicities may include lymphopenia and neutropenia,[14] signs of tumor lysis, reduction in red cell mass, decreased spermatogenesis, skin swelling and hair hypopigmentation. The potential for development of hair color change in humans is unknown. No adverse events of changes in hair color, skin pigmentation, or eye color have been reported in the venetoclax clinical studies to date. Although no effects of venetoclax on female reproductive tissues have been observed in general repeat-dose toxicology studies, embryofetal toxicity studies in animals have identified a fetal toxicity risk.

Thrombocytopenia has not been observed in toxicology studies in mice and dogs. These findings are consistent with venetoclax as a Bcl-2 specific (Bcl-xL sparing) inhibitor. Consequently, thrombocytopenia is not expected to be a dose limiting toxicity (DLT) clinically.

In vitro studies have shown that venetoclax is metabolized primarily by CYP3A4; thus, coadministration of venetoclax with drugs that inhibit CYP3A4 (such as ketoconazole) is predicted to cause a significant increase in the exposure of venetoclax and will be undertaken with dose modifications as outlined in Section 5.2.4.4.

A detailed discussion of the preclinical toxicology, metabolism, and pharmacology can be found in the Investigator's Brochure.[15-17,29]

Venetoclax Clinical Data

Venetoclax is being investigated in Phase 1 to Phase 3 clinical oncology studies conducted as monotherapy or in combination with a variety of compounds for the treatment of hematologic malignancies including MM, chronic lymphocytic leukemia (CLL), small lymphocytic leukemia (SLL), NHL, acute myeloid leukemia (AML), and myelodysplastic syndrome (MDS). Data are available from drug-drug interaction studies

of venetoclax and ketoconazole, rifampin, and warfarin digoxin, ritonavir, and azythromycin.

As of 28 November 2018, on the basis of open-label and unblinded data available in the clinical databases for company-sponsored studies with unblinded data in the venetoclax oncology development program, a total of 2543 adult subjects (1313 CLL/SLL, 361 AML, 218 MM, 570 NHL, and 59 MDS, 20 ALL, 1 rhabdomyocarcoma, and 1 Evans tumor) in the pooled analysis dataset across all monotherapy and combination therapy oncology studies in the venetoclax development program have been exposed to at least 1 dose of venetoclax. An additional 20 pediatric subjects (< 18 years of age; 5 ALL, 10 AML, 3 neuroblastoma, 2 other solid tumors) have been exposed to at least 1 dose of venetoclax.

Overall for MM, when treated with venetoclax as a single agent or in combination with other therapies, most subjects experience at least 1 adverse event. Overall 78% of subjects experience ≥ grade 3 adverse events, and the most common events were cytopenias. Forty-four percent (44%) of subjects experienced SAEs. Findings from the analysis based on the FAIRs were consistent with the findings from the analysis based on the subject incidence rates. All of the adverse events reported in the current MM studies are consistent with underlying disease or concomitant medical conditions, as well as other combination agents used to treat MM patients. Neutropenia and infections reported in subjects with MM treated with venetoclax are consistent with the expected safety profile of venetoclax.

A detailed discussion of the preclinical toxicology, metabolism, and pharmacology of venetoclax can be found in the Investigator's Brochure.[15-17,29]

The BELLINI study, a global, 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, was unblinded as per protocol for the final analysis of the primary efficacy endpoint. As of the data cutoff date of 26 November 2018, 194 patients were

randomized to the venetoclax arm, and 97 to the placebo arm (2:1 randomization). The BELLINI study met its primary endpoint of progression-free survival (22.4 versus 11.5 months, HR 0.63, 95% CI: 0.44 – 0.90) and showed statistically significant improvements in ORR (82% vs 68%) and VGPR or better (59% vs 36%) in the venetoclax arm compared to the control arm. However, there were 51 deaths in the safety analysis set, 40 (20.7%) in the venetoclax arm and 11 (11.5%) in the placebo arm (the median OS has not been reached in either arm). The imbalance was predominantly seen in the treatment-emergent deaths, which are those occurring on therapy or within 30 days after the last dose of therapy. Among the 14 treatment-emergent deaths reported, 13 (6.7%) were in the venetoclax arm and 1 (1.0%) in placebo arm. Of the 13 treatment-emergent deaths on the venetoclax arm, 8 were attributed by investigator to an event of infection, more than half of them also in the setting of refractory or progressive disease. Although the majority of infection-related deaths occurred within 180 days of starting study treatment, some have occurred later, even after a year or more on treatment. A higher rate of Grade 3 or 4 neutropenia was seen in the venetoclax arm compared to placebo, but an association of infection-related deaths with neutropenia has not been established at this point. Among the 37 non-treatment emergent deaths (those occurring more than 30 days after the last dose of study treatment), 27 (14.0%) were in the venetoclax arm (6 of them attributed to infection, 3.1%), and 10 (10.4%) in the placebo arm (2 of them attributed to infection, 2.1%). After the data cutoff of 26 November 2018, additional deaths were reported in the BELLINI trial. As of 01 March 2019, there were 65 deaths in the safety analysis set, 48 (24.7%) in Venetoclax arm and 17 (17.5%) in the placebo arm.

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.

Venetoclax and Dexamethasone Combination

Preclinical data support studying venetoclax in relapsed or refractory MM subjects, in particular, those with a Bcl-2 profile (high Bcl-2/low Mcl-1) which is more frequently

observed in MM bearing the t(11;14) translocation.[8] Noteworthy, recent published data also demonstrate that dexamethasone highly sensitizes multiple myeloma cell lines and primary samples to venetoclax by increasing Bim and Bcl-2 expression. Dexamethasone appears to shift Bim binding towards Bcl-2 instead of Mcl-1 resulting in increased sensitivity to venetoclax, even in cell lines with prior resistance to Bcl-2 inhibition.[18] The addition of dexamethasone to venetoclax could be clinically beneficial for subjects with multiple myeloma expressing higher levels of resistance factors such as Mcl-1.

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.

3.4 Benefits and Risks

Based on data available, there is observed anti-tumor activity in hematological malignancies (such as CLL, NHL, AML and MM) subjects receiving venetoclax. In addition, the safety profile is acceptable in treating advanced cancer patients. Ongoing monitoring for safety will continue as outlined in the Risk Assessment. Therefore, the overall risk benefit profile supports further investigation of venetoclax in cancer patients.

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

Since the antitumorigenic effects of venetoclax and dexamethasone on myeloma cells are via distinctive mechanisms of action, the combination of these 2 drugs is anticipated to result in an enhanced therapeutic effect that could potentially benefit patients with MM. The goal of the Phase 2 portion of the study is to determine the efficacy and safety profile of venetoclax and dexamethasone combination therapy in patients with t(11;14)-positive MM.

Following the analysis of the BELLINI study (see Section 3.3) guidance for dose interruption/reduction following a Grade ≥ 3 or serious infection in subjects receiving venetoclax have been implemented (Section 6.1.8.3 and Section 6.1.8.4)

The safety profile of venetoclax as a monotherapy or in combination with dexamethasone in patients with R/R MM has been favorable and 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, thrombocytopenia, anemia, and gastrointestinal adverse events. The safety and efficacy data to date of venetoclax in combination with dexamethasone from the Phase 1 portion of the study supports further evaluation of this combination in subjects with R/R MM.

For further details on venetoclax, please see findings from completed studies including safety data in the most current venetoclax Investigator Brochure[29] and the dexamethasone package insert.

Based on the BELLINI data referenced above, the FDA placed Study M13-367 on partial clinical hold on 14 March 2019. A total of 117 subjects have been enrolled (Phase 1: 86; Phase 2: 31) to Study M13-367. No new subjects will be enrolled into the Study M13-367. Subjects who are currently receiving venetoclax monotherapy or venetoclax and dexamethasone in combination will be allowed to continue study treatment per protocol if the investigator believes the subject is continuing to receive clinical benefit. For subjects who choose to continue study treatment, study procedures have been modified as described in Table 6 and throughout protocol. Additionally, pneumococcal and influenza vaccinations requirements applicable for subjects on study treatment have been implemented, as well as recommendations for subjects in follow up (please refer to Section 5.2.4.1).

Considering the coronavirus (COVID-19) pandemic, the benefit and risk to subjects participating in this study has been re-evaluated. Subjects receiving venetoclax 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 R/R multiple myeloma, no change to the benefit/risk balance for subjects in this study is expected.

3.5 Differences Statement

One Phase 1 clinical trial investigating the safety, pharmacokinetics, maximum tolerated dose, and recommended Phase 2 dose (RPTD) of venetoclax monotherapy in subjects with relapsed or refractory chronic lymphocytic leukemia and non-Hodgkin's lymphoma is underway. This is the first Phase 1 protocol of venetoclax monotherapy in subjects with relapsed or refractory multiple myeloma. In addition, one Phase 1 clinical trial investigating the safety, pharmacokinetics, maximum tolerated dose, and RPTD of venetoclax in combination with bortezomib and dexamethasone as standard therapy in subjects with relapsed or refractory multiple myeloma is underway.

4.0 Study Objectives

Phase 1 Portion (Dose Escalation, Safety Expansion and Venetoclax-Dexamethasone Combination):

The primary objectives are to assess the safety profile, characterize pharmacokinetics (PK), determine the dosing schedule, the maximum tolerated dose (MTD), and the recommended Phase 2 dose (RPTD) of venetoclax monotherapy when administered in subjects with relapsed or refractory multiple myeloma. This study will also assess the safety profile and PK of venetoclax in combination with dexamethasone in subjects with t(11;14)-positive multiple myeloma. The secondary objectives are to evaluate the preliminary efficacy data regarding the effect of venetoclax monotherapy or combined with dexamethasone on overall response rate (ORR), time to response (TTR), time to disease progression (TTP), and duration of response (DOR).

The Phase 2 Portion (Venetoclax-Dexamethasone Expansion):

The primary objective of the Phase 2 portion is to further evaluate the ORR and very good partial response or better rate (VGPR+) in subjects with t(11;14)-positive multiple myeloma, with the secondary objectives to monitor safety and evaluate progression-free survival (PFS), DOR, TTR, TTP, and overall survival (OS) and to evaluate 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]). The tertiary objectives of the Phase 2 portion are to assess 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).

The exploratory objectives for all study portions are to evaluate pharmacodynamic and predictive biomarkers for association with PK, safety, and efficacy. In addition, minimal residual disease (MRD) will be assessed in the bone marrow by next generation sequencing (NGS).

5.0 Investigational Plan

5.1 Overall Study Design and Plan: Description

This is a Phase 1/2, open-label, multicenter study evaluating the safety and PK of venetoclax when administered in male and female subjects with relapsed or refractory MM. The study is designed to enroll approximately 166 – 186 subjects. Subjects in this study will be enrolled at approximately 32 research sites globally. This study is sponsored by AbbVie in collaboration with Roche/Genentech.

This study will consist of 2 distinct portions (Phase 1 and Phase 2). The Phase 1 portion includes dose escalation, safety expansion, and VenDex combination cohorts. The

first cohort of the study will evaluate the safety and pharmacokinetics profile of venetoclax, to be administered in approximately 30 subjects following a dose escalation scheme, with the objective of defining the dose limiting toxicity (DLT) and the MTD.

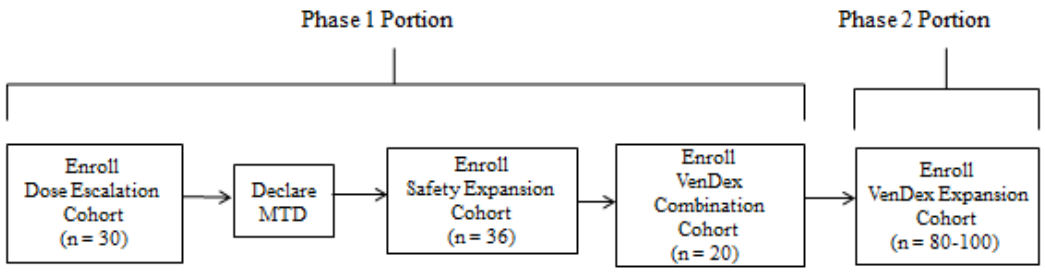
The second cohort of the study is a safety expansion cohort that will further evaluate venetoclax safety at the MTD (or RPTD) and explore Bcl-2 family expression profile in approximately 36 subjects.

The third cohort of the study is a (VenDex) combination cohort that will evaluate venetoclax safety and efficacy at the RPTD in combination with dexamethasone in approximately 20 subjects with t(11;14)-positive MM.

The Phase 2 portion of the study is an expansion of the combination cohort that will further evaluate ORR and VGPR+ of venetoclax and dexamethasone in approximately 80 –100 relapsed or refractory subjects with t(11;14)-positive MM. Disease assessment for each post-baseline IMWG assessment will be performed by the investigator.

The overall study design is shown in Figure 1.

Figure 1. Overall Study Design



Dosing Schedule During Dose Escalation Portion

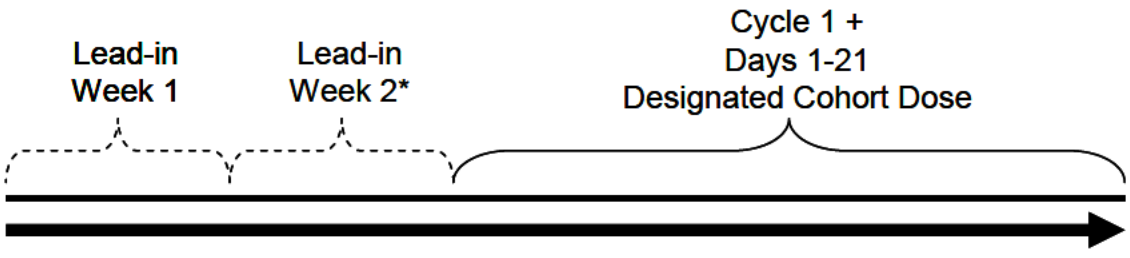
During the first two cohorts of the study (dose escalation and safety expansion), to mitigate the risk for TLS, a lead-in period will be employed to evaluate a step-wise dose escalation.

During the VenDex combination cohort and Phase 2 portion, a lead-in period will not be employed.

For subjects enrolled to the dose escalation and safety expansion cohorts, upon completion of the lead-in period, subjects will receive their designated cohort dose of venetoclax. Upon assessment of progressive disease and discussion with AbbVie Therapeutic Area Medical Director (TA MD), the investigator may add dexamethasone treatment starting at 40 mg orally (PO) on Days 1, 8, and 15 of each 21-day cycle per the dexamethasone prescribing information. All subjects who are ≥ 75 years old may start dexamethasone at a 20 mg dose.

A dosing schedule for Lead-in, Cycle 1 and all subsequent cycles is depicted in Figure 2 for the dose escalation cohort. A cycle is defined as 21 days.

Figure 2. Dosing Schedule for Lead-In to Designated Cohort Dose: Dose Escalation Cohorts



* Lead-in Week 1 and Week 2 are required for Cohort 1 but may be removed based on safety data collected for subsequent cohort(s).

Subjects in the first cohort will begin the lead-in period with a starting dose of 50 mg and will step up in weekly increments anticipated to be at least 50 mg to the designated cohort

dose level of 300 mg. Subjects will continue to receive the same starting dose of Venetoclax once daily for 1 week starting on Lead-in Day 1. If, after approximately 1 week, subjects have absence or resolution of metabolic abnormalities comprising TLS and do not experience a DLT (refer to Section 6.1.8.1), the dose level will be subsequently increased in increments anticipated to be at least 50 mg per week until the designated cohort dose level is achieved. The decision to escalate will be made by AbbVie following discussion between the investigator and the AbbVie TA MD.

In the first dose escalation cohort, the Lead-in Day 1 dose for the second subject will not be administered until at least 1 week following the Lead-in Day 1 dose of the first subject. Staggered enrollment may continue for subsequent cohorts if decided by AbbVie, following discussion between the investigators and the AbbVie TA MD.

Each dose of venetoclax will be taken orally with approximately 240 mL of water within 30 minutes after the completion of a low-fat breakfast.

On days that pre-dose PK sampling is required, venetoclax dosing will occur in the clinic to facilitate PK sampling following the completion of a low-fat breakfast. For subjects in the Dose Escalation cohorts, dosing will occur in the clinic to facilitate PK sampling following the completion of a **standard** low-fat breakfast on the intensive PK day, Cycle 2 Day 1.

Dose Modification and Escalation Guidelines

In subsequent cohorts, modifications in the lead-in period may occur based on tolerability. Increases or decreases in the lead-in period starting dose and/or changes in the dosing increments may be implemented. For example, the starting dose of 50 mg in subsequent cohorts may be lowered; dose escalation may then occur in smaller increments. The lead-in period may be eliminated if clinically significant metabolic abnormalities of TLS are not observed. Decisions to modify the lead-in period will be made by AbbVie following discussion between the investigators and AbbVie TA MD. Lead-in doses to the designated cohort doses for Cohorts 1 to 3 are depicted in Table 1.

Table 1. Lead-In Doses to Designated Cohort Doses

Cohort	Starting Dose* (mg) (Lead-in Week 1)	Step 2 (mg) * (Lead-in Week 2)	Designated Cohort Dose (mg)
1	50	100	300
2	100**	300	600
3	300**	600	900
4	400**	800	1200

* Starting dose and/or Step 2 may be removed in cohorts subsequent to Cohort 1 if no metabolic abnormalities of TLS are observed in the prior cohort.

** Higher starting dose would only occur if metabolic abnormalities of TLS are not observed at lower doses.

A lower starting dose and/or modifications to the lead-in regimen may be implemented for individual subject(s) at particularly high risk for TLS (refer to Management of Tumor Lysis Syndrome, Section 6.1.8.4). The decision to modify the lead-in period dosing regimen for an individual subject will be made by AbbVie following discussion between the investigator and AbbVie TA MD and communicated to the IRB/EC, as appropriate.

Designated cohort dose escalation or de-escalation decisions to the next designated cohort dose will be made after subjects have completed the lead-in period plus one cycle (21 days) at the designated cohort dose. Escalation of designated cohort dose will occur in multiples of 100 mg but may occur in other increments as determined by available data. De-escalation will occur in increments of 50 mg unless data indicate other increments are required. Decisions will be informed by subject tolerability and safety data. Escalation or de-escalation of the designated cohort dose will be determined by AbbVie following discussion between the investigators and AbbVie TA MD.

A minimum of 3 subjects will be enrolled per cohort. Additional subjects may be enrolled at a current dose level at the discretion of the AbbVie medical monitor. Dose escalation decisions may be made following the completion of the lead-in period (if applicable) plus one cycle (21 days) of dosing at the designated cohort dose for the subjects in the intended cohort (e.g., first three evaluable). Available data from all subjects receiving study drug will be considered in dose escalation decisions. Adverse events occurring after this defined period and PK assessment may also be considered in dose escalation decisions.

If continuous dosing is not feasible, a lower dose or alternative dosing schedules may be employed. Alternative doses and schedules will be determined after discussions between the investigators and the AbbVie TA MD, based on factors such as pharmacokinetic data, recovery periods for observed DLTs and toxicity data.

Escalation of venetoclax to the next designated cohort dose level will proceed if all assigned subjects in the intended cohort (e.g., first three evaluable) complete the lead-in period plus one cycle (21 days) at the designated cohort dose without experiencing a DLT (refer to Section 6.1.8.1). If one (1) subject within any dose level experiences a DLT, up to 6 subjects will be enrolled at that dose level. Additional subjects may be enrolled at the current dose level at the discretion of the AbbVie TA MD. If < 33% of the subjects enrolled at a dose level experience a DLT, then escalation of the designated cohort dose may continue. If ≥ 33% of the subjects enrolled at a dose level experience a DLT, dose escalation will stop and the previous lead-in period and designated cohort dosing regimen will be considered the MTD or dose de-escalation of the designated cohort dose, and/or a modified lead-in period may be explored if MTD is not declared.

Dose escalation guidelines are summarized in Table 2.

Table 2. Dose Escalation Guidelines

Number of Subjects with DLT	Dose Escalation
0 of 3	Begin enrollment in the next dose level
1 of 3	Enroll 6 subjects in current dose level
1 of 6 or n < 33%	Begin enrollment in the next dose level
≥ 2 of 6 or n ≥ 33%	Previous dose determined as the MTD or dose de-escalation

Note: If a DLT of TLS occurs during the lead-in period, it will affect dosing decisions in the lead-in period. (Refer to Section 6.1.8.1, Definition – Dose Limiting Toxicity).

If dose de-escalation or modification of the lead-in period occur and < 33% of subjects enrolled experience a DLT at the reduced designated cohort dose and/or the modified lead-in period regimen, this dosing regimen will be declared the MTD. If ≥ 33% of the subjects enrolled at the reduced designated cohort dose and/or the modified lead-in period

regimen still experience a DLT, dose de-escalation of the designated cohort dose and/or modified lead-in period regimen will continue to be explored.

The MTD will be defined as the highest designated cohort dose level (and corresponding lead-in period regimen, if applicable) at which < 33% of the subjects enrolled experience a DLT.

Transition from Dose Escalation to Safety Expansion Portion

Once the MTD is determined, enrollment into the dose escalation portion of the study will end. The dose level for the safety expansion portion will be communicated to all participating investigators prior to the start of enrollment. Subjects from the dose escalation portion of the study are not eligible for enrollment in the safety expansion portion of the study.

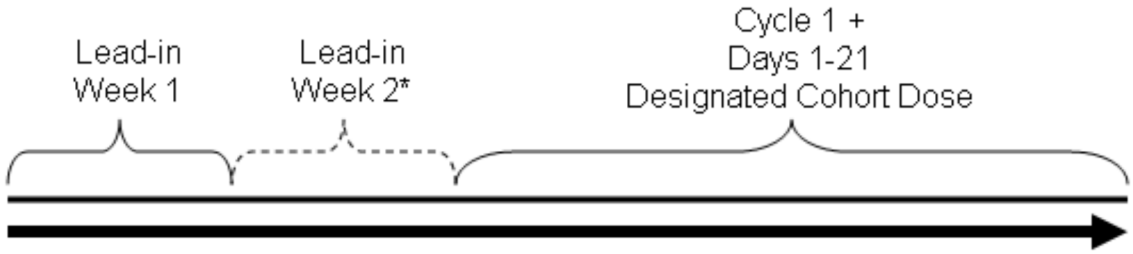
Safety Expansion Cohort

Once the MTD is declared, a cohort of approximately 36 additional subjects with relapsed or refractory MM will be enrolled at the MTD, or RPTD, in order to further define the toxicity profile and better inform the RPTD determination for subjects with MM. It is expected, based on a prevalence rate of about 40%, that approximately 14 of 36 subjects will overexpress Bcl-2 and have low Bcl-x_L.

To mitigate the risk for TLS observed, subjects will receive TLS prophylaxis prior to and during treatment (refer to Management of Tumor Lysis Syndrome, Section 6.1.8.4). TLS prophylaxis and subject management guidelines may be modified or removed based on results from the dose escalation portion.

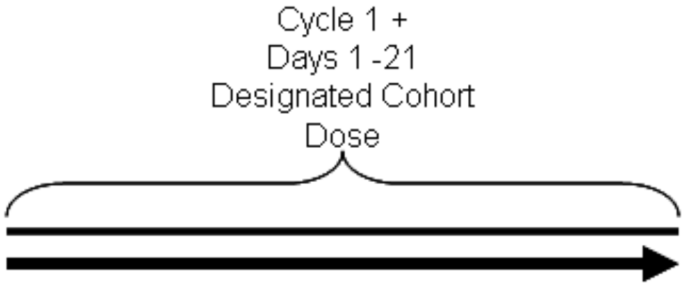
The dosing schedule for the safety expansion cohort, if a lead-in period is required, is depicted in Figure 3. The dosing schedule for the safety expansion portion, if a lead-in period is not required, is depicted in Figure 4.

Figure 3. Safety Expansion Cohort Dosing, if a Lead-in Period is Required



* Week 2 of the Lead-in dosing may be applicable based on safety data.

Figure 4. Safety Expansion Cohort Dosing, if a Lead-in Period is Not Required



If, during the safety expansion cohort of the study, toxicities are observed during the lead-in period (if applicable) plus one cycle (21 days) at the designated cohort dose at a frequency higher than the definition of MTD (> 33%), a lower dose or alternative dosing schedules may be examined. The alternative dose and schedule will be determined by AbbVie after discussion between the investigators and the AbbVie TA MD.

During the dose escalation and safety expansion cohorts, upon assessment of progressive disease and discussion with AbbVie TA MD, the investigator may add dexamethasone treatment starting at 40 mg (PO) orally on Days 1, 8, and 15 of each 21-day cycle per the dexamethasone prescribing information. All subjects who are ≥ 75 years old may start dexamethasone at a 20 mg dose.

Intrasubject Dose Escalation

During the dose escalation cohort, in order to maximize the collection of information at relevant doses and to minimize the exposure of individuals to suboptimal doses, subjects may progressively escalate their current dose to the highest cleared venetoclax dose level or any dose below. Individuals will need to complete at least 2 cycles at their designated cohort dose (or current dose) level prior to any escalation as determined by investigator and the AbbVie TA MD.

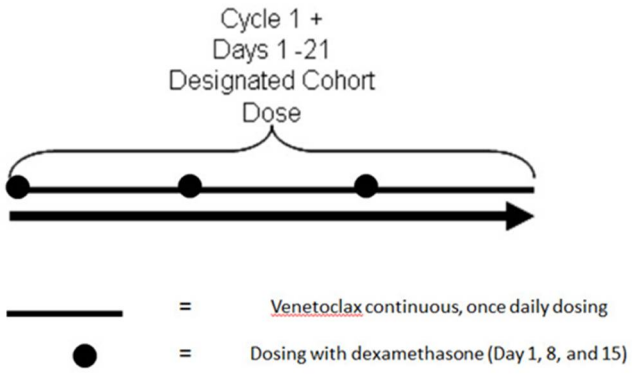
TLS prophylaxis and management will be implemented at each dose escalation. For subjects who dose escalate. TLS prophylaxis and management will be discussed between the AbbVie TA MD and investigator. Refer to Section 6.1.8.4 Management of Tumor Lysis Syndrome for additional information.

Venetoclax-Dexamethasone Combination Cohort

The combination cohort will explore the safety and efficacy of venetoclax in combination with dexamethasone in approximately 20 subjects with t(11;14)-positive MM. Subjects will receive venetoclax daily (Day1 – 21) at the RPTD with dexamethasone (40 mg PO) on Days 1, 8, and 15 of each 21-day cycle, per the dexamethasone prescribing information. All subjects who are ≥ 75 years old may start dexamethasone at a 20 mg dose.

During the VenDex combination cohort, a lead-in period will not be employed. The dosing schedule for the VenDex combination portion is depicted in Figure 5.

Figure 5. VenDex Combination Cohort Dosing Schedule, Without Lead-In Period



Phase 2 Portion:

The Phase 2 cohort will further explore the efficacy of venetoclax in combination with dexamethasone in approximately 80 – 100 relapsed or refractory subjects with t(11;14)-positive MM. Subjects will receive venetoclax daily (Day 1 – 21) with dexamethasone orally Day 1, 8, and 15 per the prescribing information.

Subjects enrolled in the VenDex combination and Phase 2 cohorts may discontinue dexamethasone due to toxicity or intolerability, and may continue receiving venetoclax once daily as monotherapy. Subjects will continue study treatment until the end of the study provided they continue to tolerate venetoclax, have no evidence of disease progression, and do not meet any criteria for subject discontinuation (Section 5.4.1).

Option to Continue Venetoclax Treatment

All subjects will continue receiving study drug until the end of study provided they continue to tolerate venetoclax, have no evidence of disease progression and do not meet any of the criteria for subject discontinuation (Section 5.4.1).

5.2 Selection of Study Population

Subjects will undergo screening procedures within approximately 21 days prior to initial study drug administration, with the exception of the skeletal survey which must be completed within approximately 30 days prior to planned study drug administration. Adult male and female subjects who meet the inclusion criteria and who do not meet any of the exclusion criteria will be eligible for enrollment into the study.

5.2.1 Inclusion Criteria

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

1. Subject must be ≥ 18 years of age.
2. Subject has an ECOG performance score of ≤ 1.
   - For subjects in the Phase 2 portion: ECOG performance score of ≤ 2
3. Diagnosis of multiple myeloma that requires treatment and has been previously treated with:
   - For subjects in the Dose Escalation cohort of the study:
     - ≥ 1 prior line of therapy. Induction therapy followed by stem cell transplant and maintenance therapy will be considered as a single line of therapy.
   - For subjects in the Safety Expansion cohort of the study:
     - Have received treatment with a proteasome inhibitor and an immunomodulatory (IMiD®) agent (e.g., thalidomide, lenalidomide, pomalidomide). Induction therapy followed by stem cell transplant and maintenance therapy will be considered as a single line of therapy.
   - For subjects in the VenDex Combination cohort:
     - Have received treatment with a proteasome inhibitor and an immunomodulatory (IMiD®) agent (e.g., thalidomide, lenalidomide, pomalidomide), AND

- Have MM positive for t(11;14) translocation as determined by an analytically validated fluorescence in-situ hybridization (FISH) assay per the central laboratory testing

- For subjects in the Phase 2 cohort:
  - Have MM positive for the t(11;14) translocation, as determined by an analytically validated fluorescence in situ hybridization (FISH) assay per the central laboratory testing (enrollment with local t(11;14)-positive FISH results only will be considered at the discretion of the TA MD)

    AND
  - Subject must have evidence of disease progression on or within 60 days of the last dose of the most recent previous treatment regimen based on the IMWG criteria, AND
  - Subject must have previously received at least 2 lines of therapy, including an immunomodulatory drug (lenalidomide or pomalidomide), a proteasome inhibitor (bortezomib, carfilzomib or ixazomib), daratumumab, and glucocorticoids.
    - For US subjects: Daratumumab combination regimen **must** be one of the prior lines of therapy (for this study, daratumumab plus corticosteroids will not be considered a combination regimen)
    - For Non-US Subjects: Either daratumumab monotherapy or combination therapy is acceptable. Daratumumab monotherapy will be limited to approximately 20 percent of the total number of Phase 2 subjects.

4. Subject must have had measurable disease at Screening, defined as any of the following:
   - Serum monoclonal protein ≥ 1.0 g/dL (≥ 10 g/L) by protein electrophoresis, or
   - ≥ 200 mg of monoclonal protein in the urine on 24-hour electrophoresis, or
   - Serum immunoglobulin free light chain (FLC) ≥ 10 mg/dL provided serum FLC ratio is abnormal.

5. Subjects with a history of autologous or allogenic stem cell transplantation must have adequate peripheral blood counts independent of any growth factor support, and have recovered from any transplant related toxicity(s) and be:
   - > 100 days post-autologous transplant (prior to first dose of study drug), or
   - ≥ 6 months post-allogenic transplant (prior to first dose of study drug) and not have active graft-versus-host disease (GVHD), i.e., requiring treatment.
6. Subjects must meet the following laboratory parameters, per laboratory reference range, at least once during the screening period:
   - Absolute neutrophil count (ANC) ≥ 1000/µL,

     Subjects may use growth factor support to achieve ANC eligibility criteria.
   - AST and ALT ≤ 3 × upper limit of normal range (ULN),
   - Calculated creatinine clearance ≥ 30 mL/min using a modified Cockcroft-Gault calculation or a 24-hour urine collection for Creatinine Clearance:

$$eC_{Cr} = \frac{(140 - \text{Age}) \bullet \text{weight (kg)} \bullet [0.85 \text{ if Female}]}{72 \bullet \text{Serum Creatinine (mg/dL)}}$$

     OR, if serum creatinine is in µmol/L:

$$eC_{Cr} = \frac{(140 - \text{Age}) \bullet \text{weight (kg)} \bullet [1.23 \text{ if Male, } 1.04 \text{ if Female}]}{\text{Serum Creatinine (µmol/L)}}$$

   - Platelet count ≥ 30,000 mm^3, independent of transfusion for 2 weeks
   - Hemoglobin ≥ 8.0 g/dL, subjects may receive blood transfusion to achieve hemoglobin eligibility criteria per investigator discretion.
   - Total bilirubin ≤ 1.5 × ULN

     Subjects with Gilbert's Syndrome may have bilirubin > 1.5 × ULN.
7. If female, subject must be:
   - Postmenopausal defined as:
     - Age > 55 years with no menses for 12 or more months without an alternative medical cause.

- Age ≤ 55 years with no menses for 12 or more months without an alternative medical cause AND an FSH level > 40 IU/L.

OR

- Permanently surgical sterile (bilateral oophorectomy, bilateral salpingestomy, or hysterectomy).

OR

- A Women of Childbearing Potential (WOCP) practicing at least one protocol specified method of birth control (Section 5.2.5) starting at Cycle 1 Day 1 (or earlier) through at least 30 days after last dose of study drug.

8. Females of childbearing potential (must have negative results for pregnancy test performed:
   - At Screening, on a serum sample obtained within 21 days prior to the first study drug administration, and
   - Prior to dosing, on a urine sample obtained on the first day of study drug dosing, if it has been > 7 days since obtaining the serum pregnancy test results.
   - Females of non-childbearing potential (either postmenopausal or permanently surgically sterile as defined above) at Screening do not require pregnancy testing.
9. This criterion has been removed.
10. 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.

Rationale for Inclusion Criteria

(1 – 4) To select the subject population

(5, 6) For the safety of the subjects

(7 – 9) The impact of venetoclax on pregnancy is unknown

(10) In accordance with harmonized Good Clinical Practice (GCP)

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 exhibits evidence of other clinically significant uncontrolled condition(s), including, but not limited to:
   - Acute infection within 14 days prior to first dose of study drug requiring antibiotic, antifungal, or antiviral therapy
   - Diagnosis of fever and neutropenia within 1 week prior to first dose of study drug.
2. Subject has a cardiovascular disability status of New York Heart Association Class ≥ 3.
3. Subject has a significant history of renal, neurologic, psychiatric, endocrinologic, metabolic, immunologic, cardiovascular or hepatic disease within the last 6 months that, in the opinion of the investigator, would adversely affect his/her participation in the study.
4. Subject has a history of other active malignancies other than multiple myeloma within the past 3 years prior to study entry, with the following exceptions:
   - Adequately treated in situ carcinoma of the cervix uteri,
   - Basal cell carcinoma of the skin or localized squamous cell carcinoma of the skin,
   - Localized prostate cancer Gleason grade 6 or lower AND with stable Prostate Specific Antigen (PSA) levels off treatment
   - Previous malignancy confined and surgically resected (or treated with other modalities) with curative intent.
5. Known Human Immunodeficiency Viral (HIV) infection
6. Active hepatitis B or C infection based on screening blood testing.

7. Subject is receiving other ongoing anti-myeloma therapy.
8. Subject has received any of the following within 7 days prior to the first dose of study drug:
   - Strong or moderate CYP3A inhibitors, or
   - Strong or moderate CYP3A inducers.
9. Subject has received any of the following within 14 days prior to the first dose of study drug or has not recovered to less than a Grade 2 clinically significant adverse effect(s)/toxicity(s) of the previous therapy: any anti-myeloma therapy including chemotherapy, radiotherapy, or investigational therapy, including targeted small molecule agents.
10. This criterion has been removed.
11. Subject has received prior treatment with a BCL-2 family inhibitor.
12. This criterion has been removed.
13. Subject is pregnant, parturient, or breastfeeding; deprived of freedom by judicial or administrative decision; hospitalized and unable to provide consent, or otherwise unable to provide consent.
14. Subject has consumed grapefruit, grapefruit products, Seville oranges (including marmalade containing Seville oranges) or star fruit within 3 days prior to the first dose of study drug.
15. Subject has received immunization with live vaccine within 60 days of dosing.
16. Recent corticosteroid therapy at a cumulative dose equivalent to > 140 mg of prednisone or a single dose equivalent to ≥ 40 mg of dexamethasone within 2 weeks prior to the first dose of study drug.

Rationale for Exclusion Criteria

(1 – 2, 4, 7) To select the appropriate subject population

(3, 5, 6, 8 – 11, 14, 15, 16) For the safety of the subjects

(13) The impact of venetoclax on pregnancy is unknown

5.2.3 Determination of the Number of Prior Lines of Therapy and Refractoriness to Prior Therapies

A line of therapy consists of at least:

- 1 complete cycle of a single agent; or
- A regimen consisting of combination of several drugs; or
- A planned sequential therapy of various regimens.[20]

A treatment is considered a new line of therapy if any of the following 3 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.
- Stem Cell Transplant (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 or allogeneic) 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.

Definition of Refractory Myeloma to a Prior Therapy

In this study, a subject will be considered refractory to a prior line of therapy if any of the following criteria are met:

- Subject has not achieved at least a minimum response, as defined per European Society for Blood and Marrow Transplantation (EBMT) or IMWG response criteria, while on that primary or salvage therapy.
- Subject has progressive disease while on that primary or salvage therapy, or within 60 days of last dose of the therapy.

5.2.4 Prior and Concomitant Therapy

If a subject reports taking any over-the-counter or prescription medications, vitamins and/or herbal supplements or if administration of any medication becomes necessary from 3 weeks prior to study drug administration until 30 days following the last dose of study drug, the name of the medication, dosage information including dose, route and frequency, date(s) of administration including start and end dates, and reason for use must be recorded on the appropriate electronic case report form (eCRF). The AbbVie TA MD identified in Section 7.0 should be contacted if there are any questions regarding concomitant or prior therapy(ies).

Information regarding potential drug interactions with venetoclax can be located in the most current Venetoclax Investigator's Brochure.

5.2.4.1 Pretreatment Guidance

Anti-infective Prophylaxis

It is recommended that subjects should receive anti-infective prophylaxis (e.g., amoxicillin/clavulanic acid, levofloxacin, or equivalent per institutional guidelines) at least during the first 90 days of study, when Grade 4 neutropenia develops (ANC < 500 cells/uL) and continued until the neutropenia improves to Grade 3 or better (ANC > 500 cells/uL), and upon disease progression for at least 30 days, unless contraindicated

per investigator discretion. Furthermore, it is recommended that subjects deemed at high risk of infection receive immunoglobulin replacement therapy (i.e., IVIG) per institutional guidelines or at the Investigator's discretion. Pneumocystis prophylaxis is allowed per institutional guidelines or at the Investigator's discretion.

- The use of antibiotics that are moderate or strong CYP3A4 inhibitors (Section 5.2.4.3 and Appendix C) should be avoided or used with caution and with the appropriate venetoclax dose modification (Table 4) as per protocol.

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 in the appropriate eCRF.

COVID-19 Pandemic-Related Acceptable Protocol Modifications:

A delay in pneumococcal and/or influenza vaccination may take place per PI discretion if the subject tests positive for SARS-CoV-2 until such time that the subject has clinically recovered from COVID-19 or per institutional guidelines. In all other cases pneumococcal and/or Influenza vaccinations should continue as scheduled per protocol.

Tumor Lysis Syndrome Prophylaxis

There is a potential for TLS in subjects affected by hematologic malignancies. Refer to Section 6.1.8.4, Management of Tumor Lysis Syndrome for required TLS prophylaxis.

5.2.4.2 Allowed Treatments

The following concomitant medications **are allowed** during study treatment. Please refer to Table 3 for a list of excluded and cautionary 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 drug.
- 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.[21,40]
- 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, refer to Appendix I, Corticosteroid Conversion Table.
- 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 7.0), 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, cautionary and allowed medications/food are summarized in Table 3.

Table 3. Excluded and Cautionary Medications/Food

Excluded Food (From 3 Days Prior to Study Administration Until Last Day of Treatment)
• Grapefruit and grapefruit products • Seville Oranges (including marmalade containing Seville oranges) • Starfruit
Excluded Medications
• Any systemic anti-myeloma therapies other than dexamethasone and venetoclax while on study treatment. • Biologic agents (e.g., monoclonal antibodies) for anti-neoplastic intent. • Immunization with live vaccines.
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 50% for moderate inhibitors and 75% 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. Please Section 5.2.4.4 for additional details. 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 6.1.6) for guidance.
Cautionary
• Warfarin* • P-gp substrates • BCRP substrates • OATP1B1/1B3 substrates • P-gp inhibitors • BCRP inhibitors • High Dose Corticoidsteroids^

* Closely monitor the international normalized ratio (INR).

^ Refer to Appendix I for additional guidance.

A sample list of excluded medications and cautionary medications that fall into the categories within Section 5.2.4 can be found in Appendix C. 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.

If the investigator determines that such a medication is medically necessary, the investigator will notify the AbbVie TA MD and discuss the investigator's use of these medications and the investigator's plans to medically monitor the potential study subject under consideration.

5.2.4.4 Dose Modifications for Moderate and Strong CYP3A Inhibitors Used with Venetoclax

Use of venetoclax with moderate or strong CYP3A inhibitors should be avoided and the investigator should consider alternative medications. If the administration of a moderate or strong CYP3A is necessary based on the investigator's clinical judgment, then venetoclax dose should be reduced during the period it is co-administered with a moderate or strong CYP3A inhibitors. Dose reductions for venetoclax dose levels used with moderate and strong CYP3A inhibitors are provided on Table 4. Subjects should be monitored more closely for signs of toxicities and the dose may need to be further reduced. Guidelines in Table 18, Table 19 and Table 20 should also be followed for venetoclax-toxicity related dose reductions when moderate or strong CYP3A inhibitors are concomitantly administered. After discontinuation of CYP3A inhibitor, wait for 3 days before venetoclax dose is increased back to previous dose level.

Table 4. Dose Modifications for Venetoclax: Moderate and Strong CYP3A Inhibitor Use

Dose with No Moderate or Strong CYP3A Inhibitor	With Moderate CYP3A Inhibitor	With Strong CYP3A Inhibitor
1200 mg QD	600 mg QD	300 mg QD
800 or 900 mg QD	400 mg QD	200 mg QD
600 mg QD	300 mg QD	100 mg QD
400 mg QD	200 mg QD	100 mg QD
300 mg QD	100 mg QD	Interrupt venetoclax temporarily
200 mg QD	100 mg QD	Interrupt venetoclax temporarily
100 mg QD	Interrupt venetoclax temporarily	Interrupt venetoclax temporarily

5.2.5 Contraception Recommendations

While participating in this research study, female subjects should not become pregnant or breastfeed.

If female, subject must be either postmenopausal or permanently surgically sterile (refer to inclusion criteria for definitions of both) OR a Women of Childbearing Potential (WOCB), practicing at least one of the following highly effective methods of birth control, on Day 1 (or earlier) through at least 30 days.

- Combined (estrogen and progestogen containing) hormonal contraception (oral, intravaginal, transdermal) associated with the inhibition of ovulation, initiated at least 1 month prior to first dose of study drug. Also, barrier method must be used during this study from initial study drug administration to 30 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 1 month prior to first dose of study drug. Also, barrier method must be used during this study from initial study drug administration to 30 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 1 month before study participation.
- Bilateral tubal occlusion via hysteroscopy (i.e., Essure), provided a hysterosalpingogram confirms success of the procedure at least 1 month before study participation.
- Vasectomized partner(s), provided the vasectomized partner verbally confirms receipt of medical assessment of the surgical success, and is the sole sexual partner of the WOCBP trial participant.
- Intrauterine device (IUD).
- Intrauterine hormone-releasing system (IUS).
- True abstinence: Refraining from heterosexual intercourse when this is in line with the preferred and usual lifestyle of the subject [periodic abstinence

(e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable].

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

5.3.1 Efficacy and Safety Measurements Assessed and Flow Chart

Table 5. Study Activities for Phase 1 Portion: Screening Through Cycle 3 Day 1

Event↓ Day→	Screening[a]	Lead-in (if applicable) Not applicable for VenDex Combination Cohort			Cycle 1				Cycle 2			Cycle 3
		1	2	8^	1	2	3	8, 15	1	2	8, 15	1
Informed Consent	X											
Medical/Oncology History	X	X			X							
Concomitant Medications, Vaccinations and Adverse Experiences	X	X	X	X	X	X	X	X	X	X	X	X
Physical Examination	X (+ height)	X*		SD*	X*			SD*	X*		SD*	X*
Vital Signs[b]	X	X[b]	0 hr	X[b]	X[b]	0 hr		X‡	X‡		X‡	X*
ECOG Performance status	X	X*		X*	X*				X*			X*
Cardiac Assessments (ECG and MUGA)[c]	X											
Pregnancy Test*	Serum	Urine[d]*			Urine[d]*							
Chemistry[e]	X	0 hr‡	0 hr	0 hr‡	0 hr‡	0 hr		X‡	X‡		X‡	X*
Hematology[e]	X	0 hr‡	0 hr	0 hr‡	0 hr‡	0 hr		X‡	X‡		X‡	X*
Coagulation and Urinalysis	X	X*			X*				X*			X*
Viral Serologies	X											
Viral Polymerase Chain Reaction	X											
Lymphocyte Enumeration	X				X*							X*
Assessments for IMWG Response Criteria[f]	X											X*

Table 5. Study Activities for Phase 1 Portion: Screening Through Cycle 3 Day 1 (Continued)

Event↓ Day→	Screening[a]	Lead-in (if applicable) Not applicable for VenDex Combination Cohort			Cycle 1				Cycle 2			Cycle 3
		1	2	8^	1	2	3	8, 15	1	2	8, 15	1
Skeletal Survey[g]	X[a,g]											
Plasmacytoma Evaluation	X											X*
Bone Marrow Aspirate and Biopsy[h]	X											
PK/Biomarker/Exploratory Research Sample Collections[i]	X[a,i]	X	X	X	X	X			X	X		X
TLS Prophylaxis[j]		X		X	X							
Subject Diary and Study Drug Dispensation/Collection		X		X	X				X			X
Clinical Disease Progression Assessment									X			X

0 hr = pre-dose within 4 hours prior to dosing; ‡ = within 24 hours prior to the scheduled visit; * = within 72 hours before or after scheduled visit; SD = Symptom-Directed; ^= Lead-in Day 15 procedures, if implemented, are the same as Lead-in Day 8. Unless otherwise specified, study visits may occur within 4 days from anticipated date for operational or logistical purposes

Table 5. Study Activities for Phase 1 Portion: Cycle 4 Day 1 Through Follow-up (Continued)

Event↓ Day→	Cycle 4 and Every Cycle[k] 1	Cycle 5 1	Cycle 7 1	Cycle 9 and Every 4th Cycle[k] 1	Intrasubject Dose Escalation[j]	Confirmation of Response[k]	Final Visit[k]	Safety Follow-up[k]
Informed Consent								
Medical/Oncology History								
Concomitant Medications, Vaccinations and Adverse Experiences	X	X	X	X		X	X	X
Physical Examination	X*	X*	X*	X*			X*	X*
Vital Signs[b]	X*	X*	X*	X*	X[b]		X*	X*
ECOG Performance status	X*	X*	X*	X*			X*	X*
Cardiac Assessments (ECG and MUGA)[c]							X*	
Urine Pregnancy Test*	X*	X*	X*	X*			X*	X*
Chemistry[e]	X*	X*	X*	X*	X	X*	X*	X
Hematology[e]	X*	X*	X*	X*	X		X*	X*
Coagulation and Urinalysis	X*	X*	X*	X*			X*	X*
Viral Serologies[l]	X*							
Viral Polymerase Chain Reaction								
Lymphocyte Enumeration		X*		X*			X*	
Assessments for IMWG Response Criteria[f]		X*		X*		X*	X*	
Skeletal Survey[g]								
Plasmacytoma Evaluation		X*		X*		X*	X*	
Bone Marrow Aspirate and Biopsy[h]		X				X	X*	

Table 5. Study Activities for Phase 1 Portion: Cycle 4 Day 1 Through Follow-up (Continued)

Event↓ Day→	Cycle 4 and Every Cycle[k] 1	Cycle 5 1	Cycle 7 1	Cycle 9 and Every 4th Cycle[k] 1	Intrasubject Dose Escalation[j] 1	Confirmation of Response[k] 1	Final Visit[k] 1	Safety Follow-up[k] 1
PK/Biomarker/Exploratory Research Sample Collections[i]		X	X	X	X	CR, sCR only	X	
TLS Prophylaxis[j]					X			
Subject Diary and Study Drug Dispensation/Collection	X	X	X	X			X	
Clinical Disease Progression Assessment	X	X	X	X			X	

0 hr = pre-dose within 4 hours prior to dosing; ‡ = within 24 hours prior to the scheduled visit; * = within 72 hours before or after scheduled visit; CR = Complete Response; sCR = Stringent Complete Response; SD = Symptom-Directed; ^= Lead-in Day 15 procedures, if implemented, are the same as Lead-in Day 8. Unless otherwise specified, study visits may occur within 4 days from anticipated date for operational or logistical purposes

a. Screening procedures must be performed within approximately 21 days of first dose of study drug, except for skeletal survey which must be performed within approximately 3 months prior to first dose.

b. Vital signs are to be evaluated prior to each laboratory collection for TLS prophylaxis and management.

c. 2D Echo allowed if multiple gated acquisition (MUGA) scan cannot be obtained; however, MUGA is preferred.

d. Urine pregnancy testing must be completed prior to first dose of study drug (Lead-in Day 1 or Cycle 1 Day 1) for women of childbearing potential if it has been > 7 days since Screening serum pregnancy test result.

e. Hematology and chemistry labs:

- Will be performed per the requirements of Section 6.1.8.4, Management of Tumor Lysis Syndrome.
- Lead-in Day 1 through Cycle 1 Day 3 and Intra-subject Dose Escalation testing must be performed ±20 minutes of the indicated timepoint except for zero-hour labs (0 hr) must be performed within 4 hours prior to dosing, unless otherwise indicated. All labs should be performed immediately and assessed by the investigator real time to ensure appropriate subject management.

Table 5. Study Activities for Phase 1 Portion: Cycle 4 Day 1 Through Follow-up (Continued)

- Cycle 1 Day 8 through Cycle 2 testing may be performed predose within 24 hours prior to the scheduled visit.
- Cycle 3 Day 1 through end of study labs may be performed predose within 72 hours before or after the scheduled visit.
- Refer to Table 12 for listing of specific tests required and for handling procedure that must be followed to avoid ex vivo uric acid degradation in the presence of rasburicase. Reticulocyte counts only required at Screening, Lead-in Day 1 (if applicable), Day 1 of each Cycle and Final Visit. Serum β2 microglobulin (sβ2M) and C-reactive Protein (CRP) are only required at Screening. Amylase and lipase are only required at Screening, Cycle 3 Day 1, and Final Visit/Time of Relapse. Cholesterol and triglycerides are only required at Screening and Final Visit.
- Additional hematology and chemistry labs may be performed as clinically necessary.

f. Refer to Table 14, Assessments for IMWG Response Criteria for details on timing and requirements for specific procedures. IMWG labs may be completed up to 1 week prior to the scheduled assessment day, in order to allow time for the labs to be resulted prior the actual assessment visit.

g. Skeletal survey consists of lateral radiograph of skull, antero-posterior and lateral views of spine, antero-posterior views of pelvis, ribs, femora, tibiae, fibulae, humeri, ulnae, and radii. Skeletal survey is not required to assess response unless clinically indicated. Results obtained within approximately 3 months prior to planned first dose (Lead-in Day 1 or Cycle 1 Day 1) may be used at Screening.

h. Bone Marrow Biopsy/Aspirate:

- Due to differences in bone marrow core biopsy collection methodology between the sites in the US and France, the core biopsy collection will be considered an optional procedure for subjects enrolled in France for the dose escalation phase but mandatory at Screening in the safety expansion and VenDex combination cohorts. Samples should be split for biomarkers whenever possible.
- Screening samples: When possible, fresh samples should be obtained within 21 days prior to the first dose of study drug and should be obtained after all other eligibility criteria have been met.
- Timing of Cycle 5 Day 1 sample may be requested earlier if a CR or sCR is suspected.
- sCR or CR confirmatory bone marrow aspirate must include immunophenotyping. A bone marrow biopsy is mandatory in the circumstance that an aspirate sample is not available (e.g., due to a dry tap).

i. Refer to Table 8, Pharmacokinetic Sampling and Table 9, Biomarker and Exploratory Research Sampling, for details of specific collections.

j. TLS prophylaxis may be initiated in all subjects starting 72 hours prior to the first dose of venetoclax and prior to each dose escalation per the guidelines in Section 6.1.8.4. For subjects who intrasubject dose escalate, TLS prophylaxis and management will be discussed between AbbVie TA MD and investigator. Refer to Section 5.1 Intrasubject Dose Escalation.

k. Allowed modifications to study activities due to COVID-19 are described under the individual study procedures in Section 5.3.1.1.

l. SARS-CoV-2 test (preferred molecular testing e.g., PCR) if clinically indicated per Investigator's discretion (done locally).

Table 6. Study Activities for Phase 2 Portion: Screening Through Cycle 10+

Cycle length = 21 days	Scrn	Cycle 1			Cycle 2		Cycles 3 – 9	Cycles 10+[a]	
Study Day:		1	8	15	1	15	1	1	**Comments – Day 1 (After Cycle 1) Visits May Occur Within 4 Days for Logistical or Operational Reasons**
Informed Consent	✓								Prior to any study related activities
Medical/oncology history	✓								Update medical history before first dose of study drug if necessary.
Physical examination (including weight)	✓				✓		✓	✓	Exam is **optional** on Cycle 1 Day 1 if the Screening exam was conducted within previous 7 days. Targeted, symptom directed physical examination can be performed for subsequent cycles and may be done within 72 hours before scheduled visit.
Vital signs	✓	✓	✓	✓	✓	✓	✓	✓	
Concomitant medications, Vaccinations and AE assessments	✓	✓	✓	✓	✓	✓	✓	✓	Monitor continuously until 30 days after last dose of study drug.
ECOG performance status	✓	✓			✓		✓	✓	May be done ≤ 3 days before the scheduled visit.
12-lead ECG	✓								
Serum pregnancy test	✓								Only for women of childbearing potential.
Urine pregnancy test		✓			✓		✓	✓	Only for women of childbearing potential.
Serum chemistry	✓	✓			✓		✓	✓	**Optional** on Cycle 1, Day 1 if Screening collection was within previous 3 days. May be done ≤ 3 days before the scheduled visit
Hematology	✓	✓	✓	✓	✓	✓	✓	✓	**Optional** on Cycle 1 Day 1 if Screening collection was within previous 3 days. May be done ≤ 3 days before the scheduled visit
Coagulation panel	✓				✓		✓	✓	Screening collection required, thereafter only collect Day 1 of every cycle for subjects taking vitamin K antagonists, or as clinically indicated.
Viral Serology	✓							If clinically indicated	SARS-CoV-2 test (preferred molecular testing e.g., PCR) at any timepoint if clinically indicated per Investigator's discretion (done locally)
Amylase, lipase	✓	As clinically indicated							

Table 6. Study Activities for Phase 2 Portion: Screening Through Cycle 10+ (Continued)

Cycle length = 21 days	Scrn	Cycle 1			Cycle 2		Cycles 3 – 9	Cycles 10+[a]	
Study Day:		1	8	15	1	15	1	1	**Comments – Day 1 (After Cycle 1) Visits May Occur Within 4 Days for Logistical or Operational Reasons**
Serum protein immunofixation*	✓	✓			✓		✓	✓	Disease assessment samples to be collected per Table 15. Collect baseline disease assessment labs if screening labs are > 7 days prior to Cycle 1 Day 1. * These samples should be collected at every response assessment and also at the time of suspected CR or disease progression (clinical or biochemical) ** For IgA or IgD myeloma, preferred for disease assessments *** Collect serially only for subjects without measureable M-protein in Screening serum or urine; collect for all subjects at the time of suspected CR or disease progression (clinical or biochemical)
Serum protein electrophoresis*	✓	✓			✓		✓	✓	
Serum quantitative immunoglobulins**	✓	✓			✓		✓	✓	
Serum free light chains***	✓	✓			✓		✓	✓	
Serum β2 microglobulin (sβ2M)	✓								
Urine protein immunofixation*	✓	✓			✓		✓	✓	
Urine protein electrophoresis*	✓	✓			✓		✓	✓	
Skeletal survey	✓	As clinically indicated							Historical results obtained ≤ 30 days before first dose may be used at Screening. The same radiological method as used at Screening should be used throughout the study.
Plasmacytoma evaluation	✓				✓		✓	✓	If plasmacytoma is palpable on physical exam, then this should be documented every cycle. Subjects with history of plasmacytoma only evaluable by radiologic assessment should have CT, PETCT (CT component), or MRI performed every 3 months. Otherwise, as clinically indicated
Bone marrow aspirate (including MRD)	✓	Complete to confirm sCR or CR; Also complete at 6 and 12 months post-confirmation of CR for patients who maintained this response							Screening FISH result per central laboratory testing required to meet eligibility criteria (enrollment with local t(ll;14)-positive FISH results only will be considered at the discretion of the TA MD). Samples should be collected per Table 10.
Bone marrow core biopsy	✓	To confirm sCR and CR							A bone marrow biopsy should be collected unless not recommended per institutional guidelines. However, a bone marrow biopsy is mandatory in the circumstance that an aspirate sample is not available.
IMWG response assessment					✓		✓	✓	Response assessment must be based on central lab results. Refer to Section 5.3.3.2.

Table 6. Study Activities for Phase 2 Portion: Screening Through Cycle 10+ (Continued)

Cycle length = 21 days	Scrn	Cycle 1			Cycle 2		Cycles 3 – 9	Cycles 10+[a]	
Study Day:		1	8	15	1	15	1	1	**Comments – Day 1 (After Cycle 1) Visits May Occur Within 4 Days for Logistical or Operational Reasons**
PRO ASSESSMENTS									Cycles 1, 3, 5, 7 and every odd (9, 11, 13 etc., cycle) 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		✓					✓	✓[b]	
PROMIS Cancer Fatigue SF		✓					✓	✓[b]	
EORTC QLQ-C30		✓					✓	✓[b]	
EORTC QLQ-MY20		✓					✓	✓[b]	
EQ-5D-5L		✓					✓	✓[b]	
PHARMACOKINETICS, PHARMACODYNAMICS, AND PHARMACOGENOMICS									
Pharmacokinetic assessments					✓		✓		Samples to be collected per Table 8
Biomarker samples (peripheral blood)	✓	✓			✓		✓	✓	Refer to Table 10 for additional sampling details. (Collections occur at Screening, on Day 1 of Cycles 1 – 5, and at confirmation of sCR/CR.)
TREATMENT									
Venetoclax		Given orally daily, starting on Day 1 of Cycle 1							
Dexamethasone		Given orally Day 1, 8, 15							
Subject Diary Dispensation/Collection		✓			✓		✓	✓	

a. Allowed modifications due to COVID-19 are described under the individual study procedures in Section 5.3.1.1.

b. No additional PRO assesments following implementation of Protocol Amendment 10.

Table 7. Final Visit and Follow-Up Activities for Phase 2 Portion

	Final Visit[a]	Safety Follow-Up[a]	Follow-Up[a]	Comments **Safety follow-up** will occur approximately 30 days after discontinuation of study drug or before start of subsequent treatment, whichever occurs first
LABS & EXAMS				
Physical examination (including weight)	✓	✓		Targeted, symptom directed physical examination can be performed for subsequent cycles and may be done within 72 hours before scheduled visit.
Vital signs	✓	✓		
Concomitant medications, Vaccinations and AE assessments	✓	✓		Monitor continuously until 30 days after last dose of study drug.
Vaccinations			✓	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.
ECOG performance status	✓		✓	May be done ≤ 3 days before the scheduled visit. Collect at Final Visit and 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
12-lead ECG	✓			
Urine pregnancy test	✓	✓		Only for women of childbearing potential.
Serum chemistry	✓	✓		May be done ≤ 3 days before the scheduled visit.
Hematology	✓	✓		May be done ≤ 3 days before the scheduled visit.
Amylase, lipase	As clinically indicated			
Progressive Disease 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
Overall Survival Assessment and Post Study Multiple Myeloma Treatment			✓	Every 12 weeks (± 2 weeks) until death, or for 24 months after the last subject's first dose whichever occurs first
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, including any relevant clinical information leading to the death, regardless of cause, should be reported through use of the Non-Treatment Emergent Death eCRFs. Refer to Section 5.3.1.1 for details.

Table 7. Final Visit and Follow-Up Activities for Phase 2 Portion (Continued)

	Final Visit[a]	Safety Follow-Up[a]	Follow-Up[a]	Comments **Safety follow-up** will occur approximately 30 days after discontinuation of study drug or before start of subsequent treatment, whichever occurs first
DISEASE ASSESSMENTS				
Serum protein immunofixation*	✓		✓	During follow-up, collect only for subjects who discontinue for reasons other than progression, until PD. *These samples should be collected at every response assessment and also at the time of suspected CR or disease progression (clinical or biochemical) **For IgA or IgD myeloma, preferred for disease assessments. ***Collect serially only for subjects without measureable M-protein in Screening serum or urine; collect for all subjects at the time of suspected CR or disease progression (clinical or biochemical).
Serum protein electrophoresis*	✓		✓	
Serum quantitative immunoglobulins**	✓		✓	
Serum free light chains***	✓		✓	
Urine protein immunofixation*	✓		✓	
Urine protein electrophoresis*	✓		✓	
Skeletal survey	If clinically indicated			The same radiological method as used at Screening should be used throughout the study.
Plasmacytoma evaluation	✓		✓	If plasmacytoma is palpable on physical exam, then this should be documented every cycle. Subjects with plasmacytoma only evaluable radiologic assessment should have CT or MRI or PET CT (CT component) performed every 3 months.
Bone marrow aspirate	✓ (Optional)			Samples should be collected per Table 10
Bone marrow core biopsy	✓ (Optional)			Samples to be collected per Table 10
IMWG response assessment	✓		✓	During follow-up, collect only for subjects who discontinue for reasons other than progression, until PD.
TREATMENT				
Subject Diary Collection	✓			
Record subsequent myeloma therapy	✓	✓	✓	
PHARMACOKINETICS, PHARMACODYNAMICS, AND PHARMACOGENOMICS				
Biomarker samples (peripheral blood)	✓			Refer to Table 10 for additional sampling details

a. Allowed modifications due to COVID-19 are described under the individual study procedures in Section 5.3.1.1.

Table 8. Schedule of Pharmacokinetic Blood Collection for Venetoclax

Collection Times	Not applicable for VenDex Combination Cohort		Cycle 1 Day 1	Cycle 2 Day 1	Cycle 2 Day 2	Cycles 3, 5, 7, 9 Day 1	Intrasubject Dose Escalation**
	Lead-in Day 1*	Lead-in Day 8*					
Dose Escalation Cohort	8† hr post-dose	8† hr post-dose	8† hr post-dose	0 (pre-dose), 2, 4, 6, 8 hrs post-dose	24 hours post Cycle 2 Day 1 dose (pre-dose of Cycle 2 Day 2)	0 (pre-dose)	8† hr post-dose (optional) and at the next scheduled study visit 0 hr (pre-dose)
Safety Expansion Cohort	8† hr post-dose	8† hr post-dose	8† hr post-dose	0 (pre-dose)	N/A	0 (pre-dose)	8† hr post-dose (optional) and at the next scheduled study visit 0 hr (pre-dose)
VenDex Combination Cohort	N/A	N/A	8† hr post dose	0 (pre-dose)	N/A	0 (pre-dose)	N/A
Phase 2 Cohort	N/A	N/A	N/A	0 (pre-dose)	N/A	0 (pre-dose) Cycles 3, 5, and 7 only	N/A

* = applicable when a Lead-in period is implemented. ** = This is only for subjects who are escalating above their designated cohort dose (or current dose) to a higher dose level during dose escalation portion. Refer to Section 5.1 Intra-Subject Dose Escalation. An 8 hour post-dose collection may be performed on the day of the escalation, if possible. At the next scheduled study visit, a sample will be collected at 0 hour (pre-dose).

N/A = No PK samples will be collected. † = The 8 hour post-dose PK sample may be collected up to 1 hour earlier, if necessary to facilitate sample processing.

Table 8. Schedule of Pharmacokinetic Blood Collection for Venetoclax (Continued)

Notes:

- All "pre-dose" samples are relative to venetoclax administration.
- Subjects will take a low-fat breakfast prior to all study drug administration. Dose Escalation subjects will take a standard low-fat breakfast prior to study drug administration on intensive PK sample collection day Cycle 2 Day 1.
- The date and time (to the nearest minute) of each study drug dose taken and whether or not the dose was taken within 30 minutes after completing breakfast will be recorded on the eCRF for every scheduled PK day and for the 2 days prior to every scheduled PK day:
- If a dose escalation is planned for an individual subject after clearing the designated cohort dose, dosing time and breakfast completion will be recorded for the 2 days prior to the escalation. Subjects may only escalate beyond their assigned designated cohort dose (or current dose) on Day 1 of a cycle with prior approval of the AbbVie TA MD.

Table 9. Biomarker and Exploratory Research Sampling – Phase 1 Portion

Sample Collections (Sample Type)	Sample Type	Screening (Preferred) OR Prior to First Dose	Lead-In Day 2[a]	Cycle 1 Days 1 and 2	Cycle 3 Day 1	Cycle 5 Day 1	Cycle 9 and every 4th Cycle Day 1[e]	Confirmation of CR, sCR[e]	Time of Relapse (Preferred) OR Final Visit[e]
Pharmacogenetics *Optional sample, additional consent required*	Blood	4 mL							
Serum Markers (pre-dose)	Blood	5 mL	3.5 mL	3.5 mL	3.5 mL	3.5 mL	3.5 mL[f]		3.5 mL
Plasma Markers (pre-dose)	Blood	6 mL			3 mL	3 mL	3 mL[f]		3 mL
Minimal Residual Disease (MRD) Assessment	Aspirate	1 mL				3 mL		3 mL	
Cytogenetics/FISH	Aspirate	3 mL[b]				2 mL[b,d]			2 mL[b]
Bcl-2 Family Member Analysis	Aspirate	8 mL[b]				4 mL[b,d]			4 mL[b]
In Vitro Sensitivity of MM Cells *Optional samples, France only*	Aspirate	3 mL[b]							
BH3 Profiling *Optional samples, US only*	Aspirate	1 mL[b]							1 mL[b]
Bcl-2 family member Protein Analysis *Optional samples: France (dose escalation – all time points; safety expansion/venetoclax-dexamethasone combination – C5D1 and relapse/Final Visit)*	FFPE core biopsy[b,c]	FFPE core[b,c]				FFPE core[b,c,d]			FFPE core[b,c]

sCR = Stringent Complete Response; CR = Complete Response; FFPE = Formalin-fixed paraffin-embedded

Table 9. Biomarker and Exploratory Research Sampling – Phase 1 Portion (Continued)

a. Lead-in Day 2 (if applicable) sample only to be collected if subject is being seen for laboratory monitoring and sample collection is feasible. Not applicable for subjects who enroll to the venetoclax-dexamethasone combination portion.

b. Bone marrow aspirate and core samples should be split from samples obtained for IMWG criteria assessment whenever possible.

c. Due to differences in bone marrow core biopsy collection methodology between the sites in the US and France, the core biopsy collection will be considered an optional procedure for subjects enrolled in France for the dose escalation phase but mandatory at Screening in the safety expansion and venetoclax-dexamethasone portion.

d. If the Cycle 5 Day 1 bone marrow aspirate and biopsy are completed early based on observed response data (e.g., sCR or CR is suspected), those samples should not be split for use in biomarker testing and a second aspirate and biopsy should not be collected at the Cycle 5 Day 1 time point.

e. Allowed modifications due to COVID-19 are described under the individual study procedures in Section 5.3.1.1.

f. No additional collections following implementation of Protocol Amendment 12.

Table 10. Biomarker and Exploratory Research Sampling – Phase 2 Portion

Sample Collections (Sample Type)	Screening	C1D1	Cycles 2 – 5 Day 1	Confirmation of sCR/CR[a]	6 Months Post-Confirmation of sCR/CR[a]	12 Months Post-Confirmation of sCR/CR[a]	Final Visit[a]
PERIPHERAL BLOOD SAMPLES	Samples should be collected pre-dose.						
Pharmacogenetics *(Optional sample)*		X					
Immuno-phenotyping (US only)		4 mL	4 mL				4 mL[b]
Immuno-sequencing (US only)		4 mL	4 mL				4 mL
Serum Markers		3.5 mL	3.5 mL	3.5 mL			3.5 mL
Plasma Markers		3 mL	3 mL	3 mL			3 mL
BONE MARROW CORE BIOPSY SAMPLES	When possible, samples should be assessed for IWMG first, and split for biomarker analysis. Fresh samples are preferred, however, samples collected within 12 weeks prior to first dose of study drug that are representative of the subject's current disease, without intervening treatment will be accepted. Core block or tissue slides are acceptable.						
Bcl-2 family member Protein Analysis	X						X (Optional)

Table 10. Biomarker and Exploratory Research Sampling – Phase 2 Portion (Continued)

Sample Collections (Sample Type)	Screening	C1D1	Cycles 2 – 5 Day 1	Confirmation of sCR/CR[a]	6 Months Post-Confirmation of sCR/CR[a]	12 Months Post-Confirmation of sCR/CR[a]	Final Visit[a]
BONE MARROW ASPIRATE SAMPLES	Samples should be assessed for IWMG first, and split for biomarker analysis. At Screening, fresh samples should be obtained within 21 days prior to first dose of study drug and when possible, should be obtained after all other eligibility criteria have been met.						
Minimal Residual Disease (MRD) Assessment	3 mL			3 mL	3 mL	3 mL	
Bcl-2 Family Member Analysis	12 mL						12 mL (Optional)
Cytogenetics/FISH	3 mL						3 mL (Optional)[b]
Translational Research	3 mL						3 mL (Optional)[b]

a. Allowed modifications due to COVID-19 are described under the individual study procedures in Section 5.3.1.1.

b. No additional collections following implementation of Protocol Amendment 11.

5.3.1.1 Study Procedures

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

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. General COVID-19 study execution guidance and COVID-19 pandemic-related acceptable protocol modifications are provided in the following sections of the protocol if visits cannot be conducted onsite due to travel restrictions or other pandemic-related reasons:

- Section 3.4 Benefits and Risks
- Section 5.2.4.1 – Pretreatment Requirements Pneumococcal and Influenza Vaccination
- Section 5.3.1 Efficacy and Safety Measurements Assessed and Flow Chart
- Section 5.3.1.1 Study Procedures
  - Informed Consent
  - Concomitant Medications and Adverse Experiences
  - Physical Examination
  - Vital Signs
  - ECOG
  - Cardiac Assessments
  - Clinical Laboratory Tests
  - Skeletal Survey
  - Plasmacytoma Evaluation
  - IMWG Testings
  - Subject Diaries
  - Progression of Disease

  - Biomarker testings
  - Virology -SARS-CoV-2 test (preferred molecular testing e.g., PCR)
- Section 5.4.1 Discontinuation of Individual Subjects
- Section 5.5.1 Treatments
- Section 5.5.6 Treatment Compliance
- Section 6.1.6 Adverse Event Reporting
- Section 7.0 Protocol Deviation
- Section 9.2 Ethical Conduct of the Study
- Section 11.0 Data Quality Assurance

Screening procedures must be performed within approximately 21 days prior to study drug administration. Skeletal survey results obtained within < 30 days prior to planned first dose of study drug may be used for Screening.

For subjects enrolled to the VenDex combination and Phase 2 cohorts, a lead-in period will not be employed.

Informed Consent

Signed informed consent will be obtained from the subject 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.

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 following will be collected during the Screening Visit and updated prior to first dose of study drug (Lead-in Day 1 or Cycle 1 Day 1):

- Complete medical history, including documentation of any clinically significant medical condition
- History of tobacco and alcohol use
- Detailed oncology history, including:
  - Histology
  - Date of cancer diagnosis
  - Stage/Grade
  - Any surgical procedures
  - Prior treatments administered (including dates, type of modality, response to treatment and reason for treatment discontinuation)
  - Refractory or relapsed status must be assessed and documented per the definitions in Section 5.2.3
- Detailed prior and concomitant medication usage including dates of usage and dosing information for all medications and supplements taken

On the first day of dosing (Lead-in Day 1 or Cycle 1 Day 1) any additional medical history that is observed after signing of the informed consent but prior to initial venetoclax admininistration and considered not related to study required procedures will be recorded in the subject's medical history.

Concomitant Medications and Adverse Experiences

Medication (prescription or over-the-counter, including vitamins and herbal supplements) will be recorded beginning with the Screening Visit and continuing until 30 days following the last dose of study drug.

On the first day of dosing (Lead-in Day 1 or Cycle 1 Day 1), any serious adverse events observed from the time of signing the informed consent but prior to initial venetoclax

administration will be reported, if considered by the Investigator to be causally related to study-required procedures. At each visit, including the Final Visit and the 30-day Safety Follow-up Visit, the subject's medical history will be reviewed and any changes from baseline will be recorded on the adverse event eCRF.

COVID-19 Pandemic-Related Acceptable Protocol Modifications

Due to the COVID-19 pandemic, concomitant medication and AE assessments 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 6.1.6.

Physical Examination

A physical examination (including weight) will be performed according to Table 5, Table 6, and Table 7 as applicable.

Physical examinations may be performed within 72 hours before or after the scheduled visit day.

A symptom-directed physical examination will be performed when necessary.

Any clinically significant physical examination changes after dosing will be recorded as adverse events.

COVID-19 Pandemic-Related Acceptable Protocol Modifications:

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, physical exam (including body weight) may be performed by another licensed practitioner.

Vital Signs

Body temperature (oral or tympanic), blood pressure, and pulse will be measured after the subject has been sitting at least 3 minutes according to Table 5, Table 6, and Table 7 as applicable.

Vital signs may be performed within 72 hours before or after the visit day, unless otherwise specified.

COVID-19 Pandemic-Related Acceptable Protocol Modifications:

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, vital signs (including body weight) may be collected by the subject or caregiver as needed.

ECOG Performance Status

The ECOG[22] performance status will be assessed according to Table 5, Table 6, and Table 7 as applicable.

ECOG performance status may be performed within 72 hours before or after the visit day.

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 Modifications:

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 (Phase 2 Portion Only)

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 Table 6 and Table 7 throughout the trial. Subjects may complete all baseline PRO assessments within 72 hours prior to the first dose of venetoclax. It is required that PRO assessments be completed prior to any other clinical assessments and prior to dosing for subsequent cycle visits. With the implementation of Protocol Amendment 10 PRO Assessments will no longer be collected.

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.[32] 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.[33] 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.[34] 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.[35] 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.[36] 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.[37,38] 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.[39] 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 11. 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

Cardiac Assessments

Cardiac assessments will include 12-lead electrocardiogram and multiple gated acquisition scan (MUGA, preferred) or 2D echocardiogram according to Table 5, Table 6, and Table 7, as applicable. Data from the cardiac assessments will be entered into EDC eCRF within 5 days of report availability.

12-Lead Electrocardiogram

A 12-lead resting ECG will be obtained according to Table 5, Table 6, and Table 7 as applicable.

An appropriately qualified physician at the study site (local reader) will read all ECGs. The local reading of the ECG will be used by the investigator for subject safety assessments, including adverse event determination and management, dose escalation, and

termination of subjects from the study. The local reader will write on the ECG tracing global interpretation as either:

- normal ECG
- abnormal ECG - not clinically significant
- abnormal ECG - clinically significant
- unable to evaluate

The reader will then sign and date the ECG. Any reports that are abnormal clinically significant will be faxed to the Oncology Safety Management Team via the contact information provided in Section 6.1.6 within 5 business days. The corrected QT interval measurement (Bazett QTcB) will be documented in the eCRF only if the local reader selects the "prolonged QT" box for an abnormal ECG. Correction by the Bazett formula (QTcB) is suggested for logistical reasons and for consistency across sites; however, correction by other methods may be acceptable based on consultation with AbbVie TA MD. 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 Modifications

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.

Multiple Gated Acquisition Scan (MUGA)

A MUGA scan will be performed according to Table 5, as applicable.

If a MUGA scan cannot be performed, a 2D echocardiogram with doppler may be performed. Subjects may have either a MUGA or echocardiogram performed; however, MUGA is the preferred method and it is preferred that the same method of assessment (MUGA or 2D echocardiogram) is used throughout the study for a given subject. A MUGA scan (or 2D echocardiogram) is not required for the Phase 2 portion.

A qualified physician will sign and date the MUGA/echocardiogram reports and determine if any findings outside normal physiological variation are clinically significant (in consultation with a cardiologist, if necessary). If any findings outside normal physiological variation are clinically significant, this will be documented on the appropriate eCRF and the report will be faxed to the AbbVie Oncology Safety Management Team via the contact information in Section 6.1.6 within 5 days of obtaining the report, unless otherwise noted. If necessary, AbbVie may request that copies of other MUGA/echocardiogram reports be sent in for further analysis by AbbVie.

The original MUGA/echocardiogram report with physician assessment will be retained in the subject's records at the study site. Repeat MUGAs/echocardiograms will be performed whenever clinically necessary.

COVID-19 Pandemic-Related Acceptable Protocol Modifications

MUGA or 2D ECHO (if MUGA scan cannot be done) may be done at other centers providing modality/technique is equivalent.

Clinical Laboratory Tests

Local laboratories will be utilized to process and provide results for all clinical laboratory tests except IMWG assessments, viral PCR, and viral serologies, which will be performed at a central laboratory. For the Phase 1 portion, IMWG assessment samples may also be collected and sent to the local laboratory at Screening. **Phase 2 subjects must have all IMWG assessment samples collected and sent to the central laboratory.** Viral PCR and/or viral serologies may be performed locally if approved by AbbVie.

Screening labs must be completed within 21 days prior to the subject's first dose of venetoclax.

Lead-in Day 1, if applicable, or Cycle 1 Day 1 through Cycle 1 Day 2 testing must be performed ±20 minutes of the indicated timepoint except for 0 hr pre-dose labs which must be performed within 4 hours prior to dosing, unless otherwise indicated. All labs for

Lead-in Day 1, if applicable, or Cycle 1 Day 1 through Cycle 1 Day 2 should be performed immediately and assessed by the investigator real-time.

Cycle 1 Day 8 through Cycle 2 labs must be completed within 72 hours prior to the subject's scheduled visit.

All laboratory testing starting with Cycle 3 may be performed within ±72 hours of the scheduled visit day unless otherwise specified.

Local laboratory results should be entered into the eCRF as directed. Laboratory normal ranges for local laboratories will be provided to the AbbVie Clinical Team as requested.

All local laboratory measurements will be entered into the eCRF **within 5 days** of report availability, unless the report reflects a Grade 3 or 4 test result in which case the results will be entered immediately into the eCRF **within 24 hours** of report availability.

Pregnancy Test

For female subjects of childbearing potential, pregnancy testing will be performed according to Table 5, Table 6, and Table 7 as applicable.

Female subjects considered not of childbearing potential must meet any of the following criteria:

- Postmenopausal, age > 55 years with no menses for 12 or more months without an alternative medical cause.
- Postmenopausal, age ≤ 55 years with no menses for 12 or more months without an alternative medical cause AND an FSH level > 40 IU/L.
- Permanently surgically sterile (bilateral oophorectomy, bilateral salpingectomy, or hysterectomy).
- Females who have not experienced menarche (at least one menstrual period).

Chemistry and Hematology

Chemistry and hematology testing are to be performed within the specified windows according to Table 5, Table 6, and Table 7 as applicable.

If subject is taking rasburicase, the special sample handling procedure outlined in Table 12 and Table 13 must be followed to avoid ex vivo uric acid degradation in the presence of rasburicase.

If laboratory abnormalities consistent with TLS are observed, see Appendix G. Recommendations for Initial Management of Electrolyte Imbalances and Prevention of Tumor Lysis Syndrome (TLS) in Multiple Myeloma Subjects for procedures to follow.

Phase 1 Portion: Reticulocyte count only required at Screening, Lead-in Day 1, Day 1 of each Cycle and Final Visit. Serum β2 microglobulin (sβ2), C-reactive protein (CRP) are only required at Screening. Cholesterol and triglycerides are only required at Screening and Final Visit. Amylase and lipase are only required at Screening, Cycle 3 Day 1 and Final Visit.

Phase 2 Portion: Reticulocyte count, CRP, cholesterol and triglycerides are not required. Serum β2 microglobulin (sβ2), amylase and lipase are only required at Screening and as clinically indicated.

Chemistry tests should be performed under fasting conditions, if possible.

Coagulation

PT/aPTT samples will be performed according to Table 5, Table 6, and Table 7 as applicable.

Urinalysis

Urinalysis will be performed according to Table 5.

Viral Serologies

Samples will be collected to identify hepatitis A (HAV-IgM), hepatitis B (HBsAg, anti-HBs, total anti-HBc, IgM anti-HBc), hepatitis C (HCV) antibody or RNA, cytomegalovirus* (IgM and IgG), varicella zoster* virus (IgM and IgG), herpes simplex* virus (HSV 1 IgG, HSV 2 IgG), and Epstein-Barr* virus (IgM and IgG), at the following time points:

- Screening or prior to the first dose of study drug (Lead-in Day 1 or Cycle 1 Day 1)
- As needed throughout study

* These samples will not be collected for subjects screening or enrolled to the VenDex combination and Phase 2 cohorts of the study.

Viral serology samples are to be collected and sent to the central laboratory for testing. If prior agreement is reached between the investigative site and AbbVie, the viral serology testing may be performed locally.

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.

Viral Polymerase Chain Reaction

Polymerase chain reaction (PCR) samples will be collected to identify herpes simplex* virus (HSV) Type 1 and 2 DNA*, Cytomegalovirus DNA*, Epstein-Barr virus DNA*, Herpesvirus 6 DNA (HHV-6)*, Herpesvirus 7 DNA (HHV-7)*, Herpesvirus 8 DNA (HHV-8)*, Adenovirus DNA*, Enterovirus RNA*, BK* and JC virus DNA*, and Parvovirus B19 DNA* at the following time points:

- Screening
- As needed throughout the study

* These samples will not be collected for subjects screening and enrolled to the VenDex combination and Phase 2 cohorts of the study.

Viral polymerase chain reaction (PCR) samples are to be collected and sent to the central laboratory for archiving and will only be analyzed if needed due to manifestations of possible infections during the treatment period. If prior agreement is reached between the investigative site and AbbVie, the viral PCR sample may be stored and tested (if necessary) locally.

SARS-CoV-2 testing (molecular testing e.g., PCR) to be done at any timepoint if clinically indicated, per Investigator's decision. Testing will be performed locally.

Lymphocyte Enumeration

Lymphocyte enumeration to identify B- and T-cell lymphocyte subpopulations will be performed according to Table 5.

B- and T-cell lymphocyte subpopulations:

- T-cells (CD3)
- B-cells (CD19)
- Natural killer (CD16 + CD56)
- Helper T-cells (CD4)
- T-suppressor or T-cytotoxic cells (CD8)
- Other lymphocyte studies

Lymphocyte enumerations may be performed within 72 hours of the scheduled visit.

Lymphocyte enumeration will not be collected for Phase 2 cohort subjects.

Assessments for IMWG Response Criteria

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

applicable), skeletal survey, and bone marrow aspirate and biopsy, will be utilized for disease assessment. Subjects will be evaluated against the International Myeloma Working Group (IMWG)[23-25,30] criteria for disease response.

Disease assessments will be performed and submitted to the **central laboratory** for reporting according to Table 5, Table 6, and Table 7 as applicable. Phase 2 subjects **must** have all IMWG response assessments based on the central laboratory results.

Response criteria definitions are outlined in Appendix E.

All response categories (i.e., sCR, CR, VGPR, PR, MR, and PD) require 2 consecutive assessments for confirmation made at any time before declaring response/PD and the institution of any new therapy **(no minimum interval between the 2 consecutive assessments is required, and the assessments can be done the same day). However, to confirm response or PD, 2 discrete samples are required and testing cannot be based upon the splitting of a single sample.** Only one bone marrow assessment is required. All response categories sCR, CR, VGPR, PR, MR, and SD also require no known evidence of progressive or new bone lesions if radiographic studies were performed. Radiographic studies are not required to satisfy these response requirements, unless plasmacytoma is present at baseline. Any soft tissue plasmacytoma documented at baseline must undergo serial monitoring as per Table 5, Table 6, and Table 7.

The following laboratory tests are required for the assessment of disease response and may be performed up to 1 week prior to the scheduled assessment visit day.

Serum Protein Immunofixation, Serum Protein Electrophoresis (SPEP)

Blood samples for serum protein immunofixation and SPEP testing will be collected for all subjects according to Table 14 and Table 15 as applicable.

Serum Quantitative Immunoglobulins (sQI)

Blood samples for sQI testing will be collected for all subjects according to Table 14 and Table 15 as applicable.

Serum Free Light Chains (sFLC)

Blood samples for serum free light chain testing will be collected for all subjects according to Table 14 and Table 15 as applicable.

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

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

24-hr urine samples for urine protein immunofixation and UPEP testing will be collected for all subjects according to Table 14 and Table 15 as applicable.

COVID-19 Pandemic-Related Acceptable Protocol Modifications

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

Skeletal Survey

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

COVID-19 Pandemic-Related Acceptable Protocol Modifications

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 via physical examination or radiography (if clinically indicated) should be completed according to Table 5, Table 6, and Table 7 as applicable:

Plasmacytoma evaluations may be performed within 72 hours before or after the visit day. The frequency of plasmacytoma evaluation by radiography may be altered per discussion between the investigator and AbbVie TA MD.

COVID-19 Pandemic-Related Acceptable Protocol Modifications

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 according to Table 5, Table 6, Table 7, Table 9 and Table 10, as applicable.

Due to differences in bone marrow core biopsy collection procedures between the sites in the US and France, the core biopsy collection will be considered an optional procedure for subjects enrolled in France during the dose escalation portion. During the safety expansion and VenDex combination, the core biopsy collection is required for all sites (US and France). During the Phase 2 cohort, the core biopsy will be collected per Section 5.3.1.5.

All aspirate collections are required. 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, plasma cell % and kappa (κ)/lambda (λ) for clonality) performed by a local laboratory as well as for shipment of a portion to AbbVie (or designee) for the biomarker analyses (refer to Section 5.3.6). Samples should be assessed for IMWG first and then split for biomarker analysis.

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

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

A bone marrow aspirate collection is mandatory at screening and to confirm sCR/CR. At screening, fresh samples should be obtained within 21 days of first dose of study, and, when possible, should be obtained after all other eligibility criteria have been met. For Phase 2, a bone marrow aspirate is optional at time of study drug discontinuation or disease progression.

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

biopsies are optional to confirm sCR, CR, or at the time of treatment completion or disease progression.

Table 12. Clinical Laboratory Tests – Phase 1 Portion

Hematology	**Chemistry**[a]	**Urinalysis**
Hematocrit Hemoglobin Red blood cell (RBC) count White blood cell (WBC) count Neutrophils Lymphocytes Monocytes Basophils Eosinophils Platelet count (estimate not acceptable) Mean platelet volume (MPV) Mean corpuscular hemoglobin (MCH) Mean corpuscular volume (MCV) Mean corpuscular hemoglobin concentration (MCHC) Reticulocyte count (Screening, Lead-in Day 1 (if applicable), Day 1 of each Cycle and Final Visit only)	Blood urea nitrogen (BUN) Creatinine Total bilirubin Serum glutamic-pyruvic transaminase (SGPT/ALT) Serum glutamic-oxaloacetic transaminase (SGOT/AST) Alkaline phosphatase Sodium Potassium Calcium Inorganic phosphorus Uric acid[b] Cholesterol (Screening and Final Visit only) Total protein Glucose Triglycerides (Screening and Final Visit only) Albumin Lactate dehydrogenase (LDH) Magnesium Chloride Bicarbonate Amylase (Screening, Cycle 3 Day 1 and Final Visit only) Lipase (Screening, Cycle 3 Day 1 and Final Visit only) Serum β2 microglobulin (sβ2M) (Screening only) C-reactive protein (CRP) (Screening only)	Specific gravity Ketones pH Protein Blood Glucose Microscopic examination (as indicated)
Coagulation		**Testing for Response Assessment**
Prothrombin time (PT) Activated partial thromboplastin time (aPTT)		Serum protein immunofixation Serum protein electrophoresis (SPEP) Serum quantitative immunoglobulins (sQI) Serum free light chains (sFLC) Urine protein immunofixation (24-hr urine) Urine protein electrophoresis (UPEP) (24-hr urine)
		Lymphocyte Enumeration
		T-cells (CD3) B-cells (CD19) Natural killer (CD16 + CD56) Helper T-cells (CD4) T-suppressor or T-cytotoxic cells (CD8) Other lymphocyte studies

Table 12. Clinical Laboratory Tests – Phase 1 Portion (Continued)

Viral PCR[c]		Viral Serologies
Herpes simplex virus (HSV), Type 1 and 2 DNA Cytomegalovirus DNA Epstein-Barr virus DNA Herpesvirus 6 (HHV-6) DNA Herpesvirus 7 (HHV-7) DNA Herpesvirus 8 (HHV-8) DNA Adenovirus DNA Enterovirus RNA BK and JC virus DNA Parvovirus B19 DNA SARS-CoV-2[d] testing (at local lab)		Hepatitis A (HAV-IgM) Hepatitis B (HBsAg, anti-HBs, total anti-HBc, IgM anti-HBc) Hepatitis C (HCV antibody or RNA) Cytomegalovirus[c] (IgM, IgG) Varicella zoster virus[c] (IgM, IgG) Herpes simplex virus[c] (HSV 1 IgG, HSV 2 IgG) Epstein-Barr virus[c] (IgM, IgG) SARS-CoV-2 serology testing[d] (PCR preferred) at local lab

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

b. At room temperature, rasburicase causes enzymatic degradation of the uric acid in blood/plasma/serum samples potentially resulting in spuriously low plasma uric acid assay readings. The following special sample handling procedure must be followed to avoid ex vivo uric acid degradation if the subject has taken rasburicase.

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.

c. Tests are not required for subjects enrolled to the VenDex combination cohort of the study.

d. SARS-CoV-2 testing performed at local lab for all Phase 1 and 2 subjects on study treatment, as clinically indicated per Investigator's discretion.

Table 13. Clinical Laboratory Tests – Phase 2 Portion

Hematology – Local Lab	**Chemistry[a] – Local Lab**	**Testing for Response Assessment – Central Lab**
Hemoglobin Red blood cell (RBC) count White blood cell (WBC) count Neutrophils Lymphocytes Monocytes Basophils Eosinophils Platelet count (estimate not acceptable)	Blood urea nitrogen (BUN) Creatinine Total bilirubin Serum glutamic-pyruvic transaminase (SGPT/ALT) Serum glutamic-oxaloacetic transaminase (SGOT/AST) Alkaline phosphatase Sodium Potassium Calcium Inorganic phosphorus Uric acid[b] Total protein Glucose Albumin Lactate dehydrogenase (LDH) Magnesium Chloride Amylase (Screening, and as clinically indicated) Lipase (Screening, and as clinically indicated) Serum β2 microglobulin (sβ2M) (Screening only)	Serum protein immunofixation Serum protein electrophoresis (SPEP) Serum quantitative immunoglobulins (sQI) Serum free light chains (sFLC) Urine protein immunofixation (24-hr urine) Urine protein electrophoresis (UPEP) (24-hr urine)
Coagulation – Local Lab		**Viral Serologies –**
Prothrombin time (PT) Activated partial thromboplastin time (aPTT)		**Central Lab:** Hepatitis B (HBsAg, anti-HBs, total anti-HBc, IgM anti-HBc) Hepatitis C (HCV antibody or RNA) **Local Lab:** SARS-CoV-2 serology testing (PCR preferred)
		Viral PCR – Local Lab
		SARS-CoV-2[c] testing

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

b. At room temperature, rasburicase causes enzymatic degradation of the uric acid in blood/plasma/serum samples potentially resulting in spuriously low plasma uric acid assay readings. The following special sample handling procedure must be followed to avoid ex vivo uric acid degradation if the subject has taken rasburicase.

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.

c. SARS-CoV-2 testing performed at local lab for all Phase 1 and 2 subjects on study treatment, as clinically indicated per Investigator's discretion.

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

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

- The investigator will follow the out-of-range value to a satisfactory clinical resolution.

A laboratory test value that requires a subject to be discontinued from the study, necessitates therapeutic medical intervention, meets protocol specific criteria (see Section 6.1.8 regarding toxicity management), and/or the investigator considers clinically significant will be recorded as an adverse event.

COVID-19 Pandemic-Related Acceptable Protocol Modifications

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

Table 14. Assessments for IMWG Response Criteria (Phase 1 Portion)

	Screening	Cycle 3 Day 1	Cycle 5 Day 1	Cycle 9 Day 1 and every 4th Cycle	To Confirm sCR, CR or VGPR	Final Visit
Serum protein immunofixation	X	S	S	S	X	S
Serum protein electrophoresis	X	S	S	S	X	S
Serum quantitative immunoglobulins	X	S	S	S		S
Serum free light chains	X	O	O	O	X – sCR only	O
Urine protein immunofixation	X	U	U	U	X	U
Urine protein electrophoresis	X	U	U	U	X	U
Skeletal Survey	X					
Plasmacytoma Evaluation	X	X	X	X	X – sCR or CR only	X
Bone Marrow Aspirate and Biopsy*	X		X		X± – sCR or CR only	X

sCR = Stringent complete response; CR = Complete response; VGPR = Very good partial response

S = Collect only for subjects with monoclonal protein in Screening serum.

U = Collect only for subjects with monoclonal protein in Screening urine.

X = Collect for all subjects.

O = Collect for subjects without monoclonal protein in Screening serum or urine.

* Due to differences in bone marrow core biopsy collection procedures between the sites in the US and France, the core biopsy collection will be considered an optional procedure for subjects enrolled in France during the dose escalation portion. During the safety expansion and venetoclax-dexamethasone combination, the core biopsy collection is required for all sites (US and France).

± A bone marrow core biopsy collection is not required to confirm sCR or CR, unless it is performed at Cycle 5, Day 1 (or earlier based on observed response data). However, a bone marrow biopsy is mandatory in the circumstance that an aspirate sample is not available (e.g., due to a dry tap).

Note: IMWG labs may be collected up to 1 week prior to scheduled assessment visit.

Cross reference: Durie 2007,[24] Rajkumar 2011[25]

Table 15. Assessments for IMWG Response Criteria (Phase 2 Portion)

	Screening	Cycle 1 Day 1[a]	Day 1 of Each Subsequent Cycle	To Confirm sCR or CR	At Suspected PD	Final Visit or Follow-Up
Serum protein electrophoresis	X	X	X	X	X	X
Serum protein immunofixation	X	X	X	X	X	X
Serum quantitative immunoglobulins[d]	X	X	X	X	X	X
Serum free light chains	X	O	O	X	X	O
Urine protein immunofixation	X	X	X	X	X	X
Urine protein electrophoresis	X	X	X	X	X	X
Skeletal survey	X	As clinically indicated				
Plasmacytoma evaluation	If clinically indicated	If plasmacytoma is palpable on physical exam, then this should be documented every cycle. Subjects with history of plasmacytoma only evaluable radiologic assessment should have CT or MRI or PET-CT (CT component) performed every 3 months. Otherwise, as clinically indicated.				
Bone marrow aspirate and biopsy[c]	X			X	X[b]	X[b]

CR = Complete Response; sCR = Stringent Complete 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. Collection of bone marrow sample at PD or Final Visit is optional.

c. Bone marrow biopsy should be collected, unless not recommended per Institutional guidelines. A core biopsy is not required to confirm sCR or CR, only an aspirate is required. A core biopsy is mandatory in the circumstance that an aspirate sample is not available (e.g., due to a dry tap).

d. For IgA or IgD Myeloma, serum Immunoglobulins are preferred for disease assessments.

Cross reference: Kumar 2016[30]

COVID-19 Pandemic-Related Acceptable Protocol Modifications

If travel restrictions or other changes in local regulations in light of the COVID-19 pandemic prevent the subject from 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, Serum quantitative immunoglobulins). 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. For Phase 1 subjects local IMWG assessments are allowable per protocol prior to the COVID-19 Pandemic.

TLS Prophylaxis

TLS prophylaxis will be initiated in all subjects starting 72 hours prior to the first dose of venetoclax, prior to each dose escalation of venetoclax, and prior to the first dose of venetoclax with dexamethasone, per the guidelines in Section 6.1.8.4.

Subject Diaries

Subject diaries will be provided at Lead-in Day 1 (if applicable), weekly throughout Lead-in period (if applicable), Cycle 1 Day 1, and Day 1 of each cycle thereafter.

Subjects will be instructed to record the date and time each dose of study drug is taken (indicating if any doses of study drug are missed) and time of breakfast completion. The date and time (to the nearest minute) of each study drug taken and whether or not the dose was taken within 30 minutes after completing breakfast will be recorded on the eCRF on the scheduled PK days and for 2 days prior to every scheduled PK day.

Subjects will also be instructed to record adverse events and concomitant medications in the subject diaries.

Subject diaries should be reviewed at each study visit. Subject diaries will be collected from subjects weekly throughout the Lead-in period (if applicable) and on Day 1 of every cycle. The diaries are to be returned to the site, reviewed by study staff at visits where study drug is dispensed to the subject, and appropriately filed with the subject's source documents for this study.

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. AEs, 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.

Clinical Disease Progression Assessment

Subjects will be assessed for clinical disease progression according to Table 5, Table 6, Table 7 as applicable. Two consecutive laboratory assessments for confirmation of PD made at any time before the start of new therapy are required 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), 2 consecutive assessments from 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.

The following assessments are not sufficient to determine PD:

- Rising serum FLC if disease is measurable in the serum, urine, or both.
  - Serum FLC can be used to determine PD according to the IMWG criteria only for subjects without measurable serum and urine M-protein.
- Clinical relapse based on indicators that are not part of the IMWG criteria for PD (e.g., decrease in hemoglobin, hypercalcemia, increase in serum creatinine, hyperviscosity), and relapse from CR should not be considered PD.
- General worsening of the subject's condition. If a subject's condition has deteriorated to a point that remaining on protocol therapy is not an option, every effort should be made to document PD by at least one of the following

assessments prior to the initiation of new therapy: SPEP, UPEP, bone marrow biopsy, plasmacytoma evaluation, or skeletal survey.

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

Dexamethasone Dosing for PD Subjects During Dose Escalation and Safety Expansion Portions

Subjects enrolled to dose escalation and safety expansion cohorts of the study, upon assessment of progressive disease per IMWG criteria and discussion with AbbVie TA MD, the investigator may add dexamethasone treatment starting at 40 mg orally on Days 1, 8, and 15 of each 21-day cycle per the dexamethasone prescribing information. All subjects who are ≥ 75 years old may start dexamethasone at a 20 mg dose.

Progressive Disease Assessment

Phase 2 cohort subjects that discontinue the study treatment for reasons other than PD, even after receiving 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.

COVID-19 Pandemic-Related Acceptable Protocol Modifications

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 Table 7. This discussion shall be documented in the source notes.

Overall Survival Assessments

For the Phase 2 portion, after study treatment and at the time of disease progression, subjects will be followed for overall survival. Survival information (i.e., the date, cause of death and any relevant clinical information leading to death) and post-study myeloma therapy (i.e., transplantation, regimens, dates of initiation and completion, etc) will be collected every 12 weeks (± 2 weeks) (or as needed to allow for more frequent data collection) until death, or for 24 months after the last subject's first dose whichever occurs first. Survival information may be obtained via telephone calls and/or clinical visits starting at the time of disease progression or after Final Visit. All Phase 2 subjects will be followed for survival information unless the subject requests to be withdrawn specifically from this study survival follow-up; this request must be documented in the subject's medical record and signed by the Investigator. In such instances, sites may enter confirmation of death using source documentation from publicly available records such as death certificates or funeral notices.

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

Non-Treatment Emergent Death Collection

After the end of the AE reporting period (i.e., 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.

Assignment of Subject Numbers

Subjects will be assigned unique consecutive subject numbers at Screening via IRT, as described in Section 5.5.3. The results of all screening evaluations must be within clinically acceptable limits, upon review by the investigator, before a subject can be

administered study drug. Subjects will not be enrolled in the study if laboratory or other screening results are unacceptable.

5.3.1.2 Confinement

Subjects will not be confined during this study but, may be hospitalized for TLS prophylaxis treatment and observation.

5.3.1.3 Meals and Dietary Requirements

Subjects will self-administer venetoclax orally with approximately 240 mL of water within 30 minutes after the completion of a low-fat breakfast once daily. Dose Escalation portion subjects will consume a **standard** low-fat breakfast prior to study drug administration on intensive PK sample collection day Cycle 2 Day 1; a sample of a standard low-fat meal description is provided in Appendix D. All subjects may not consume the following:

- Grapefruit or grapefruit products, Seville oranges (including marmalade containing Seville oranges) or star fruit within the 3-day period prior to the first study drug administration and until the last day of treatment is completed due to possible CYP3A mediated metabolic interaction.

Meal information (e.g., whether or not the dose was taken within 30 minutes after completing breakfast or whether grapefruit products were consumed within the past 3 days) will be recorded.

5.3.1.4 Collection and Handling of Biomarker and Exploratory Research Samples

Blood, serum, plasma, bone marrow aspirate and bone marrow core biopsy tissue will be collected per Table 9 and Table 10. 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 will be discussed in the Biomarker and Exploratory 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. The procedure for obtaining and documenting informed consent is discussed in Section 9.3.

5.3.1.5 Samples for Mandatory Biomarker Analysis

A summary table of biomarker sample collections for the Dose Escalation, Safety Expansion, and VenDex Combination Cohorts is found in Table 9. A summary table of biomarker sample collections for the Phase 2 portion is found in Table 10.

Blood Collection for Serum Markers

Blood will be collected by venipuncture into an appropriately labeled serum separator tube (SST) according to Table 9 and Table 10 as applicable.

Blood Collection for Plasma Markers

Blood will be collected by venipuncture into an appropriately labeled K_2EDTA tube according to Table 9 and Table 10 as applicable.

Bone Marrow Aspirate Collection

A sufficient bone marrow aspirate must be collected for clinical assessment as well as for biomarker analyses (performed by central/referral laboratory). Priority of the aspirate sample split for biomarker analysis is as follows:

1. Cytogenetics/FISH

2. Translational Research (Phase 2 portion only)
3. Bcl-2 Family Member Analysis
4. Minimal Residual Disease (MRD) Assessment
5. In vitro Sensitivity Assay for MM Cells (France only, optional collection), 3 mL at Screening only/BH3 Profiling (US only, optional collection), 1 mL at Screening and time of relapse (Phase 1 Portion only)

Cytogenetics/Fluorescence In Situ Hybridization (FISH)

Bone marrow aspirate samples will be collected according to Table 9 and Table 10 as applicable.

MRD

Bone marrow aspirate samples will be collected according to Table 9 and Table 10 as applicable.

Bcl-2 Family Member Analysis

Bone marrow aspirate samples will be collected according to Table 9 and Table 10 as applicable.

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

Bcl-2 Family Member Protein Analysis

A bone marrow core biopsy sample will be collected according to Table 9 and Table 10 as applicable. One of the following forms of pre-therapy tumor tissue (newly collected tissue or archived tissue) will be collected at Screening to enable biomarker assessments as outlined in the study objectives:

- **Fresh tumor tissue:** Fresh BMC biopsies performed during screening are preferred unless not recommended per Institution guidelines. Tissue should be fixed, decalcified, and embedded in paraffin according to institutional

procedures. While sending FFPE blocks is preferred, slides prepared by the local pathology laboratory are acceptable and should be prepared as described in the study-specific laboratory manual. In addition, a pathology report, with 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 and within 12 weeks prior to first dose of study drug. While sending FFPE blocks is preferred, slides prepared by the local pathology laboratory are acceptable and should be prepared and stored as described in the study-specific laboratory manual. In addition, a pathology report, with all the subject identifying information redacted, should be submitted along with the tissue sample.

Due to differences in bone marrow core biopsy collection methodology between the sites in the US and France, the core biopsy collection will be considered an optional procedure for subjects enrolled in France in the dose escalation portion, but required at Screening in the safety expansion and VenDex combination. For subjects enrolled in the Phase 2 portion, the bone marrow biopsy should be collected at screening, unless not recommended per institutional guidelines. This will enable testing by immunohistochemistry of key biomarkers (BCL-2, BCL-XL, and MCL-1) that have been identified preclinically to be associated with single agent sensitivity to venetoclax.

Blood Collection for Immuno-Phenotyping (US Only, Phase 2 Portion Only)

Blood samples will be collected according to Table 10 as applicable.

Note: Immuno-Phenotyping sample collection at Final Visit will be discontinued after implementation of Protocol Amendment 11.

Blood Collection for Immuno-Sequencing (US Only, Phase 2 Portion Only)

Blood samples will be collected according to Table 10 as applicable.

5.3.1.6 Samples for Exploratory Research

For all subjects in the study that consent to optional exploratory research, blood, bone marrow core biopsy and bone marrow aspirate samples will be collected per Table 9 and Table 10. Please contact the AbbVie TA MD or designee if necessary for additional information.

Blood Collection for Pharmacogenetic Analysis

An optional 4 mL whole blood sample for DNA isolation will be collected at Screening or prior to the first dose of study drug from each subject who consents to provide samples for exploratory research. If the sample is not collected prior to the first dose of study drug, the sample may be collected at any time throughout the study.

Final Visit Bone Marrow Core (BMC) Biopsy Tissue Collection

Bcl-2 Family Member Protein Analysis

A bone marrow core biopsy sample may be collected at Final Visit (prior to the initiation of a new anti-myeloma treatment) if deemed feasible by the Investigator. Tissue should be fixed, decalcified and embedded in paraffin according to institutional procedures. While sending FFPE blocks is preferred, slides prepared by the local pathology laboratory are acceptable and should be prepared 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.

Final Visit Bone Marrow Aspirate Collection

Sample may be collected at Final Visit, if deemed feasible by the Investigator.

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

- Cytogenetics/FISH
- Translational Research
- BCL-2 Family Member Analysis

Note: Cytogenetics/FISH and Translational Research sample collection at Final Visit will be discontinued after implementation of Protocol Amendment 11.

In Vitro Sensitivity of MM Cells (France Only, Optional Collection, Phase 1 Portion Only)

Bone marrow aspirate samples will be collected according to Table 9 as applicable.

Instructions for collection and processing of the in vitro sensitivity sample are as follows:

- Collect 2 – 3 mL of bone marrow aspirate into an EDTA tube.
- Ship ambient on day of collection to:

  Dr. [redacted]
  U892 Equipe 10
  Centre de Recherche Contre le Cancer Nantes/Angers
  8, quai Moncousu
  44007 Nantes
  France

Collection should only be completed if subject agrees and is undergoing aspirate for reasons other than in vitro sensitivity sample collection.

BH3 Profiling (US Only, Optional Collection, Phase 1 Portion Only)

Bone marrow aspirate samples will be collected according to Table 9 as applicable.

Collection should only be completed if subject agrees and is undergoing aspirate for reasons other than BH3 Profiling sample collection.

BH3 Profiling aspirate samples will be shipped directly from the site to the central laboratory per the current laboratory manual.

COVID-19 Pandemic-Related Acceptable Protocol Modifications

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, laboratory and/or research samples will not be collected.

5.3.2 Drug Concentration Measurements

5.3.2.1 Collection of Samples for Analysis

Immediately after collection, the blood samples will be inverted several times to ensure good mixing of the blood and anticoagulant, and will be placed in an ice bath.

The timing of blood collections will take priority over all other scheduled study activities except for dosing. The order of blood collections will be maintained to the minute such that the time intervals relative to the preceding dosing will be the same for all subjects. The date and time (to the nearest minute) of each blood sample collection will be recorded on the eCRF.

The date and time (to the nearest minute) of each dose of venetoclax and whether or not the dose was taken within 30 minutes after the completion of breakfast will be recorded on the scheduled PK days and for the last 2 dosess prior to every scheduled PK day. Sites will ensure that all information is captured through source documents (site or subject calendar/diary provided by AbbVie).

Blood Samples for Venetoclax Assay

Blood samples (3 mL) for venetoclax assay will be collected by venipuncture into evacuated potassium (K_2) EDTA tube at the following times:

Dose Escalation Cohort

- Lead-in Day 1: $8^{\dagger}$ hours post-dose (if Lead-in period is utilized)
- Lead-in Day 8: $8^{\dagger}$ hours post-dose (if Lead-in period is utilized)
- Cycle 1 Day 1: $8^{\dagger}$ hours post-dose

- Cycle 2 Day 1: 0-hour (pre-dose) and at 2, 4, 6, 8† hours post-dose
- Cycle 2 Day 2: 24 hours post Cycle 2 Day 1 dose (pre-dose of Cycle 2 Day 2)
- Cycles 3, 5, 7 and 9 Day 1: 0-hour (pre-dose)
- *Intrasubject dose escalation, if applicable, optional:
  - 8† hours post-escalated dose
  - 0-hour (pre-dose) at next scheduled visit

Safety Expansion Cohort

- Lead-in Day 1: 8† hours post-dose (if Lead-in period is utilized)
- Lead-in Day 8: 8† hours post-dose (if Lead-in period is utilized)
- Cycle 1 Day 1: 8† hours post-dose
- Cycles 2, 3, 5, 7 and 9 Day 1: 0-hour (pre-dose)
- *Intrasubject dose escalation, if applicable, optional:
  - 8† hours post-escalated dose
  - 0-hour (pre-dose) at next scheduled visit

Venetoclax-Dexamethasone Combination Cohort

- Cycle 1 Day 1: 8† hours post-dose
- Cycles 2, 3, 5, 7 and 9 Day 1: 0-hour (pre-dose)

Phase 2 Portion

- Cycles 2, 3, 5, and 7 Day 1: 0-hour (pre-dose)

† The 8 hour post-dose PK sample collection may be collected up to 1 hour earlier, if necessary, to facilitate sample processing.

* Refer to Section 5.1 Intrasubject Dose Escalation.

All 0-hr (pre-dose) samples are relative to the start of venetoclax administration. Refer to Table 8 for a schedule of the blood collection for venetoclax assay.

A total of 13 blood samples are planned to be collected per subject for PK analysis in the dose escalation cohort. A total of 8 blood samples are planned to be collected per subject for PK analysis in the safety expansion cohort. A total of 6 blood samples are planned to be collected per subject for PK analysis in the VenDex combination cohort. A total of 4 blood samples are planned to be collected per subject for PK analysis in the Phase 2 portion.

5.3.2.2 Handling/Processing of Samples

Blood Samples for Venetoclax PK Assay

Immediately after collection, the blood samples for venetoclax will be inverted 8 to 10 times to ensure good mixing of the blood and anticoagulant, and will be placed in an ice bath. The blood samples will be centrifuged using a refrigerated centrifuge (2° to 8°C) to separate the plasma at 1100 to 1600 × g for 15 minutes within 1 hour of blood collection. The plasma samples will be transferred using plastic pipettes into screw-capped polypropylene tubes (cryovials) labeled with the drug number name, assay type, type of sample (plasma), the protocol number, the subject number, the study cycle and day, and the planned time of sampling relative to dosing and then frozen at –20°C or colder. The entire process should be completed within 2 hours of draw. Samples should be maintained at –20°C or colder until shipped to the central laboratory.

5.3.2.3 Disposition of Samples

The frozen plasma samples for venetoclax assays will be packed in dry ice sufficient to last during transport and shipped from the study site to the central laboratory according to instructions included in the laboratory manuals for this study. An inventory of the samples included will accompany the package. The central laboratory will be responsible for shipping the plasma samples to AbbVie for testing.

5.3.2.4 Measurement Methods

Plasma concentrations of venetoclax will be determined under the supervision of the Drug Analysis Department at AbbVie.

5.3.3 Efficacy Variables

In the Phase 1 portion, all efficacy endpoints are secondary, and therefore exploratory in nature. In the Phase 2 portion, confirmatory testing will be conducted for ORR and VGPR+, the primary efficacy endpoints. Secondary efficacy endpoints include PFS, DOR, TTR, TTP, OS, and the following PROs: Worst Pain (BPI-SF), Physical Functioning and GHS/QoL (EORTC QLQ-C30), and Fatigue (PROMIS Cancer Fatigue SF). Tertiary efficacy endpoints include the PROs based on the remaining subscales of BPI-SF, EORTC QLQ-C30, EORTC QLQ-M20, and EQ-5D-5L.

5.3.3.1 IMWG Criteria for Tumor Response

Subjects with multiple myeloma with measurable disease at baseline will be evaluated using the 2011 IMWG criteria[23-25] (Phase 1 subjects) or 2016 standard IMWG criteria[30] (Phase 2 subjects) provided in Appendix E.

Eligibility: Only subjects with measurable disease at baseline can have objective response evaluated as an end point. All baseline evaluations should be performed during the screening period and prior to the first dose of study drug.

IMWG Criteria

Subjects will be assessed for response using the IMWG response criteria. All response categories require two consecutive assessments made at any time before the institution of any new therapy. All response categories (i.e., stringent complete response, complete response, very good partial response, partial response, minimal response, and stable disease) 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. Response criteria for all categories and subcategories of response except CR are applicable only to subjects who have 'measurable' disease defined by at least one of the following three measurements:

- Serum M-protein ≥ 1.0 g/dL (≥ 10 g/L)
- Urine M-protein ≥ 200 mg/24 hr

- Serum FLC assay: involved FLC level ≥ 10 mg/dL (≥ 100 mg/L) provided serum FLC ratio is abnormal

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, Serum quantitative immunoglobulins). 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. For Phase 1 subjects local IMWG assessments are allowable per protocol prior to the COVID-19 Pandemic.

5.3.3.2 Evaluation of Disease

IMWG response assessments will be reviewed by the Investigator per the 2011 IMWG criteria[23-25] (Phase 1 subjects) or 2016 standard IMWG criteria[30] (Phase 2 subjects) provided in (Appendix E). 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.

Phase 1 portion: All IMWG laboratory 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.

Phase 2 portion: All IMWG response assessments are to be based on the central laboratory results, with the exception of imaging and bone marrow assessments which are performed locally.

COVID-19 Pandemic-Related Acceptable Protocol Modifications

If travel restrictions or other changes in local regulations in light of the COVID-19 pandemic prevent the subject from 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, Serum quantitative immunoglobulins). 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. For Phase 1 subjects local IMWG assessments are allowable per protocol prior to the COVID-19 Pandemic.

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, MUGA/2D echocardiogram, (Phase 1 portion only), and laboratory assessments.

5.3.5 Pharmacokinetic Variables

Values for the PK parameters of venetoclax, including the maximum observed plasma concentration (C_{max}), the time to C_{max} (peak time, T_{max}) and the area under the plasma concentration-time curve (AUC) over a 24-hour dose interval (AUC_{0-24}) will be determined using noncompartmental methods for doses administered on the intensive PK day (i.e., Cycle 2 Day 1 in the dose escalation cohorts). 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 drug (or drugs of the same or

similar class) or and progression of the subjects' disease related conditions. The information learned from analyzing these samples may be used to investigate factors influencing response to treatment, scientific questions related to MM, and/or in the development of new therapies and diagnostic tests, 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 family member expression at baseline as a predictive biomarker of response. BCL-2 family member mRNA expression will be determined by qPCR analysis in CD138-enriched samples from bone marrow aspirates. BCL-2 family member protein expression will be evaluated in bone marrow core biopsies by IHC. 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), del 17p, and +5, +9, or +15. The VenDex combination cohort and Phase 2 portion will evaluate safety and efficacy of venetoclax at the RPTD in subjects with t(11;14)-positive MM. Subjects MM tumor cells with the t(11;14) translocation were found to be associated with increased sensitivity to venetoclax in preclinical studies of MM.[8] t(11;14)-positive samples also demonstrated a high median BCL-2/MCL-1 mRNA ratio.[8] MRD is an emerging component of response assessment in MM subjects. Exploratory analysis of MRD negativity in the bone marrow at 10^{-4}, 10^{-5} and 10^{-6} thresholds may be performed.

Additional exploratory evaluations may include biomarkers related to pathway(s) targeted by the study drug, 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). Blood may also be analyzed by immune cell phenotyping and quantification, and T-cell clonality assed by immune-sequencing. 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.

Blood samples may also be sequenced and data 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. Such genetic factors may include genes for drug metabolizing enzymes, drug transport proteins, genes within the target pathway, genes believed to be related to the disease or to drug response. Some genes currently insufficiently characterized or unknown may be understood to be important at the time of analysis. The results are exploratory in nature, and may not be included with the study summary.

5.4 Removal of Subjects from Therapy or Assessment

5.4.1 Discontinuation of Individual Subjects

Each subject has the right to withdraw from the study at any time. In addition, the investigator will discontinue a subject from the study at any time if the investigator considers it necessary for any reason, including:

- The investigator believes it is in the best interest of the subject;
- The subject's response to therapy is unsatisfactory, as evidenced by progression of disease while on study drug;
    - However, during dose escalation and safety expansion portion, the subject can be considered for venetoclax in combination with dexamenthasone upon failing venetoclax monotherapy;
- The subject's response to combination therapy is unsatisfactory, as evidenced by progression of disease while on combination therapy;
- The subject experiences toxicities related to study drug as clinically significant abnormal laboratory results or AEs, which rule out continuation of the study drugs, as determined by the investigator or the AbbVie Therapeutic Area Medical Director.

- The subject requires more than 2 dose reductions of venetoclax, in the absence of objective response to study treatment;
- The subject requires radiotherapy, cancer-related surgery as a result of disease progression, or alternate anti-neoplastic agents during the study period;
- The subject becomes pregnant or begins breast-feeding;
- Subject is significantly noncompliant with the study procedures, which would put the subject at risk for continued participation in the trial.

All subjects will be included for analysis of safety data. Subjects who withdraw from the study will not be replaced unless they are not evaluable.

During the Phase 1 portion, evaluable subjects are defined as those subjects who:

- Experience a DLT, or
- Complete approximately 80% or more of the treatment regimen during the DLT assessment period.

In the event that a subject withdraws or is discontinued from the study, the reason(s) for the discontinuation from the study and primary reason will be recorded. Final visit procedures per Table 5 and Table 7, as applicable, will be performed as soon as possible after discontinuation from the study. Additional blood samples for drug measurement may be collected at the time of discontinuation from subjects who are discontinued due to adverse events; the clock time, time in relation to dose, and date the sample was taken will be recorded.

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

At the end of the subject's participation in the study, the calendars/diaries are to be returned to the site and appropriately filed with the subject's source documents for this study.

A Safety Follow-up Visit should be performed for all subjects approximately 30 days following discontinuation of study drug and then as clinically appropriate for safety assessment. The subject will be followed until a satisfactory clinical resolution of the adverse event is achieved.

A separate Safety Follow-up Visit does not need to be performed for subjects who had a Final Visit conducted ≥ 30 days after discontinuation of study drug and did not require additional adverse event follow-up. 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 study drug 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 6.1.6 or Section 7.0.

If a subject withdraws from study follow up or withdraws permission for the collection of their personal data, the study staff may still use available public records to obtain information about survival status only, as appropriate per local regulations.

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 above to ensure all acceptable mitigation steps have been explored.

All efforts should be made to obtain safety and disease response information at the End of Treatment 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 End of Treatment and/or Safety Follow-Up Visit, if possible, arrange for subjects to have laboratory work done at a local lab, hospital, or other facility. Local lab results should be obtained along with reference ranges and kept within the subjects' source documentation. Local lab results should be reviewed by the investigator as soon as possible. Before starting another MM therapy, the site shall make all effort to complete Final Visit and Safety Follow Up Visit procedures to obtain safety and disease response information.

5.4.2 Discontinuation of Entire Study

AbbVie may terminate this study prematurely, either in its entirety or at any 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 drug 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 treatment regimen, if applicable, by other appropriate regimens.

5.5 Treatments

5.5.1 Treatments Administered

Each dose of venetoclax will be taken with approximately 240 mL of water. On days that pre-dose PK sampling is required (refer to Table 8), dosing will occur in the morning at the clinic at approximately 0900 (± 1 hour) to facilitate PK sampling. Dose Escalation cohort subjects will take venetoclax within 30 minutes after the completion of a **standard** low-fat breakfast (Appendix D) with approximately 240 mL of water on Cycle 2 Day 1. On all other dosing days, subjects will be instructed to take venetoclax orally QD within 30 minutes after the completion of a low-fat breakfast.

In cases of vomiting, no replacement dose is to be given. 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.

During dose escalation and safety expansion, upon assessment of progressive disease and discussion with the AbbVie TA MD, the investigator may add dexamethasone treatment starting at 40 mg PO on Days 1, 8, 15 of each 21-day cycle per the dexamethasone prescribing information.

During the VenDex combination and Phase 2 cohorts, subjects will receive venetoclax, daily (Day 1 – 21), at the RPTD with dexamethasone (40 mg PO) on Days 1, 8, and 15 of each 21-day cycle, per the dexamethasone prescribing information. All subjects who are ≥ 75 years old may start dexamethasone at a 20 mg dose. During the VenDex combination and Phase 2 cohorts, in cases where a dexamethasone dose is missed or

forgotten, the subject should take the dose as soon as possible, ensuring the dose is taken within 48 hours of the missed dose. Otherwise, the dose should not be taken. Subjects will be instructed to take each dose of venetoclax orally QD with approximately 240 mL of water and within 30 minutes after the 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.

COVID-19 Pandemic-Related Acceptable Protocol Modifications

If a subject is unable to come to the study site to pick up their study drug (venetoclax and dexamethasone) due to COVID-19, a direct-to-patient (DTP) study drug shipment can be made from the study site to the subject if allowed by local regulations. 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 on treatment via onsite (preferred), phone or video conference visit, or local assessments as permitted through COVID-19 Pandemic-Related Acceptable Protocol Modifications. These assessments shall be documented in the source data 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 their home
- Assessment of the following procedures prior to dispensing venetoclax to subjects: AE/CM review, safety labs reviewed [hematology, chemistry, Coagulation panel], urine pregnancy testing (women of childbearing potential), IMWG disease assessment (central lab collection preferred, local laboratory acceptable if not possible to collect centrally), 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 study supplies (e.g., drug dosing diaries). Subjects should provide dosing updates to site staff during remote phone or video conference visits and return diaries to the 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 patient 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 site will work directly with the courier.

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

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. The subject shall return the study drug bottles to the site at the time of the next onsite study visit unless the study site is directed otherwise by AbbVie.

5.5.2 Identity of Investigational Product

Information about the formulations to be used in this study is presented in Table 16.

Table 16. Identity of Investigational Product

Study Drug	Trademark	Formulation	Route of Administration	Manufacturer	Location
Venetoclax (ABT-199)	N/A	10 mg Tablet	Oral	AbbVie/Abbott	North Chicago, IL
Venetoclax (ABT-199)	N/A	50 mg Tablet	Oral	AbbVie/Abbott	North Chicago, IL
Venetoclax (ABT-199)	N/A	100 mg Tablet	Oral	AbbVie/Abbott	North Chicago, IL
Dexamethasone±	N/A	4 mg Tablet	Oral	N/A	N/A

± Dexamethasone is considered Investigational Product during the VenDex combination and Phase 2 cohorts.

Table 17. Identity of Non-Investigational Product

Study Drug	Trademark	Formulation	Route of Administration	Manufacturer	Location
Dexamethasone[a]	N/A	Tablet	Oral	N/A	N/A

a. Dexamethasone formulations may vary based on the source. Dexamethasone is considered Non-Investigational Product during the dose escalation and safety expansion cohorts.

During the dose escalation and safety expansion cohorts, dexamethasone should be obtained commercially via the site pharmacy. For operational or regulatory purposes, AbbVie may provide non investigational products depending on local requirements.

5.5.2.1 Packaging and Labeling

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

For the VenDex combination and Phase 2 cohorts, AbbVie will provide dexamethasone. It will be packaged in blistercards or bottles to accommodate study design. Each blistercard or bottle will be labeled per local regulatory requirements.

5.5.2.2 Storage and Disposition of Study Drug

The venetoclax and dexamethasone study drug must be stored at 15° to 25°C (59° to 77°F). Dexamethasone should also be protected from moisture. The investigational products (Table 16) are for investigational use only and are to be used only within the context of this study. The study drug(s) supplied for this study must be maintained under adequate security and stored under the conditions specified on the label until dispensed for subject use or returned to AbbVie.

5.5.3 Method of Assigning Subjects to Treatment Groups

All subjects will be assigned a unique subject number on the first day of screening via IRT. Since this is an open-label study, subjects will maintain the same subject number regardless of the number of re-screens and through the duration of the study.

5.5.4 Selection and Timing of Dose for Each Subject

Selection of the dose for this study is discussed in Section 5.6.4. The same dose will be administered to all subjects in each dose level within each portion. Once the MTD is declared for dose escalation or safety expansion portion, subjects who remain on study and continue to tolerate the drug may escalate to the dose level determined to be the MTD or any dose level below the MTD, provided they have completed at least 2 cycles at their originally assigned dose level. For Dose Escalation subjects, Cycle 2 Day 1 dosing will occur in the morning at the clinic (refer to Section 5.5.1) when subjects will receive

venetoclax within 30 minutes after the completion of a **standard** low-fat breakfast (Appendix D). On all other dosing days, subjects will be instructed to take venetoclax tablets orally within 30 minutes after the completion of a low-fat breakfast once daily (QD). All doses of venetoclax will be taken with approximately 240 mL of water.

5.5.5 Blinding

This is an open-label study.

5.5.6 Treatment Compliance

The investigator or his/her designated and qualified representatives will administer/dispense study drug only to subjects enrolled in the study in accordance with the protocol. The study drug must not be used for reasons other than that described in the protocol.

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

5.5.7 Drug Accountability

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

An overall accountability of study drug 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 drug) 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 drug bottles will be performed at the site. Empty containers will be destroyed at the site. Labels must remain attached to the containers.

5.5.8 Safety Review Committee

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

5.6 Discussion and Justification of Study Design

5.6.1 Discussion of Study Design and Choice of Control Groups

During the dose escalation portion of the study, dose cohorts (dose levels) will contain a minimum of 3 subjects each for evaluation and safety assessments which will be crucial for determining drug dose escalation as described in Section 5.1. There are no control groups in this study.

5.6.2 Appropriateness of Measurements

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

5.6.3 Suitability of Subject Population

Subjects with relapsed or refractory MM will be selected to participate in this study. Subjects with MM must have relapsed following or be refractory to standard treatments

such as melphalan, bortezomib, and lenalidomide. In addition, the subject should be unable to tolerate other available therapies or no other therapies are available. Preclinical findings support the possibility of efficacy in this patient population. 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.

Subjects who harbor t(11;14) assessed by the central laboratory will be eligible for the VenDex combination cohort and Phase 2 portion of this study.

5.6.4 Selection of Doses in the Study

The 800 mg QD RPTD of venetoclax in the VenDex combination cohort was selected based on the results from a Phase 1b study (Study M12-901) of venetoclax plus bortezomib and dexamethasone in relapsed or refractory MM subjects and the venetoclax monotherapy portions of this study (Study M13-367). An exposure-response analysis of the efficacy (best response) and safety (grade ≥ 3 anemia, thrombocytopenia, and neutropenia) from Study M12-901 indicated that a venetoclax dosage regimen of 600 mg QD or higher in combination with bortezomib and dexamethasone would likely result in a substantial VGPR or better response rate with these response rates increasing through 1200 mg QD. No relationship was observed between venetoclax exposure and anemia or thrombocytopenia, but the neutropenia (grade ≥ 3) rates began to increase at doses above 800 mg QD. Similar exploratory exposure-response analyses from the venetoclax monotherapy portions of this study (Study M13-367) indicated a trend of increasing response rates through 1200 mg QD in the t(11;14) positive subjects. However, with venetoclax monotherapy in MM, no relationship was observed between venetoclax exposure and anemia, thrombocytopenia, or neutropenia. The 40 mg once weekly dexamethasone dose in the VenDex combination cohort was selected as it is a commonly used dexamethasone dose in MM combination therapy, such as with daratumumab and lenalidomide or bortezomib.

Subsequent to completion of the VenDex combination cohort of the study, additional venetoclax exposure-response analyses were conducted using both the monotherapy and dexamethasone combination therapy portions of this study. These analyses confirmed the benefit of the addition of dexamethasone to the venetoclax regimen, that response rates (ORR and VGPR+) were expected to increase with higher venetoclax doses in combination with dexamethasone in t(11;14) positive patients, and that no relationship was evident between venetoclax exposure and anemia, thrombocytopenia, or neutropenia. Based on these efficacy and safety results, and considering treatment compliance considerations, a venetoclax dose of 800 mg QD with 40 mg dexamethasone once weekly was selected to be used in the Phase 2 portion of the study.

The maximum dose of venetoclax for this protocol will not exceed 1200 mg/day.

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 6.1.6). For adverse events, please refer to Section 6.1 through 6.1.12. For product complaints, please refer to Section 6.2.

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 drug, and any action(s) taken. For serious adverse events considered as having "no reasonable possibility" of being associated with study drug, the investigator will provide an other cause of the event. For adverse events to be considered

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

All adverse events will be followed to a satisfactory conclusion.

6.1.1 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 6.1.8 regarding toxicity management) and/or if the investigator considers them to be adverse events.

An elective surgery/procedure scheduled to occur during a study will not be considered an adverse event if the surgery/procedure is being performed for a pre-existing condition and/or 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 study drug is administered until 30 days have elapsed following discontinuation of study drug 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 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.

Hospitalization for a subject with high disease burden as indicated by elevated white blood cells, bulky disease and/or hyperuricemia who require observation and management (e.g., for IV hydration) for the purpose of TLS prophylaxis will not be captured as a serious adverse event (SAE), unless there is an additional reason for hospitalization or an additional criterion for seriousness other than hospitalization.

Hospitalization of a subject within 30 days following discontinuation of study drug for subsequent line of therapy will not be recorded as serious adverse events.

Certain adverse events are anticipated to occur in the study population (MM) at some frequency independent of the study drug exposure. Such events include known consequences of the underlying disease or condition under investigation (e.g., symptoms, disease progression) and events unlikely to be related to the underlying disease or condition under investigation but common in the study population independent of the study drug (e.g., cardiovascular events in an elderly population).

Cytopenias (anemia, neutropenia, or thrombocytopenia) are part of the natural history of MM. Persistent cytopenias at the same CTCAE grade as at baseline are not to be reported as adverse events, unless they fulfill a seriousness criteria, result in permanent discontinuation of a study drug, or the investigator had an identifiable cause other than the underlying disease. However, all laboratory data should be entered regardless of whether an adverse event is reported.

These events are listed in Appendix H (Adverse Events Commonly Associated with MM Study Population or Progression of MM).

These adverse events may occur alone or in various combinations and are considered expected for reporting purposes for this protocol.

Although exempted from expedited reporting to Health Authorities and IRBs as individual cases, if an event commonly associated with MM or progression of MM meets seriousness criteria it must be reported to AbbVie within 24 hours of the site being made aware of the serious adverse event (Refer to Section 6.1.6). For deaths related to disease progression (coded to malignant neoplasm progression), the date and cause of death will be recorded on the appropriate case report form, but the event will not be expedited as an individual case safety report to regulatory authorities.

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 4.0).[26] If a reported adverse event **increases** in severity, the initial adverse event should be given an outcome date and a new adverse event reported on a different onset date than the end date of the previous adverse event 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 Adverse Events Expected Due to Study Related Endpoints

6.1.3.1 Deaths

Deaths that occur during the protocol specified adverse event reporting period (see Section 6.1.5) that are more likely related to disease progression will therefore be an expected adverse event and will not be subject to expedited reporting.

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.

6.1.3.2 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.

6.1.4 Relationship to Study Drug

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

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

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

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

6.1.5 Adverse Event Collection Period

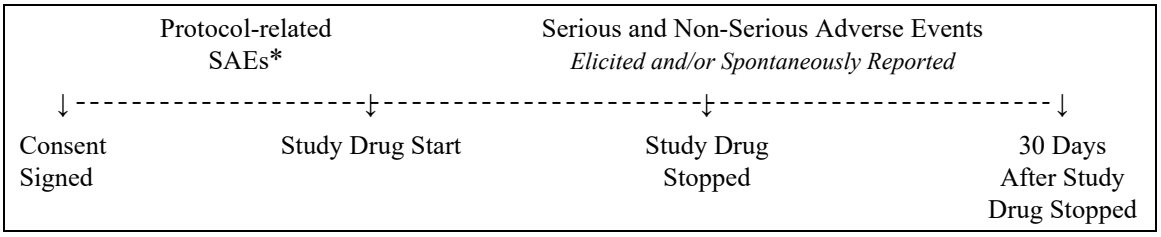
All protocol-related serious adverse events must be collected from the signing of the study specific informed consent until study drug administration.

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

In addition, all serious and non-serious adverse events reported from the time of study drug administration until 30 days or 5 half lives, whichever is longer, following discontinuation of study drug administration have elapsed will be collected, whether elicited or spontaneously reported by the subject.

Adverse event information will be collected as shown in Figure 6.

Figure 6. Adverse Event Collection



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

During the Phase 2 Portion, after the end of the adverse event reporting period (30 days after the final dose of study drug):

- All deaths, including any relevant clinical information leading to death, regardless of cause, should be reported on the appropriate eCRF.

Adverse events will be monitored throughout the study to identify any of special interest that may indicate a trend or risk to subjects.

Adverse Events of Special Interest (AESI)

The following AESI (serious and non-serious) is to be entered into the EDC system immediately (i.e., no more than 24 hours after the site becoming aware of the event):

- Tumor lysis syndrome

6.1.6 Adverse Event Reporting

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

Email:	**PPDINDPharmacovigilance@AbbVie.com**
FAX to:	**+1 (847) 938-0660**

For safety concerns, contact the Therapeutic Area Safety Team at:

Oncology Safety Team
1 North Waukegan Road
North Chicago, IL 60064-6146
Toll-Free: +1 (833) 942-2226
Safety E-mail: SafetyManagement_Oncology@abbvie.com

For any emergent subject safety concerns, please contact the AbbVie TA MD listed below:

[redacted] MD
Medical Director, TA Oncology
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 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 AbbVie TA MD.

Phone: +1 (973) 784-6402

AbbVie will be responsible for Suspected Unexpected Serious Adverse Reaction (SUSAR) reporting for the Investigational Medicinal Product (IMP) in accordance with global and local guidelines, 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.

COVID-19 Pandemic-Related Acceptable Protocol Modifications

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

COVID-19 infections should be captured as adverse events. If the event meets the criteria for a serious adverse event (SAE), then follow the SAE reporting directions per the protocol and above. The following COVID-19 related supplemental eCRFs should be completed (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 6.1.8.5 are met. There are no time limits for study drug interruption if no permanent study discontinuation criteria have been met. The investigator should notify the AbbVie TA MD or designee listed above when reintroducing any study drugs in subjects with confirmed or suspected COVID-19 infection.

6.1.7 Pregnancy

Pregnancy in a study subject must be reported to an AbbVie representative (Section 6.1.6 or Section 7.0) 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 should be taken throughout the study and for 30 days after discontinuing study drug. Male subjects should be informed that contraceptive measures should be taken by their female partner. Information regarding a pregnancy occurrence in a study subject and the outcome of the pregnancy will be collected. In the event of pregnancy occurring in the partner of an enrolled subject, written informed consent for release of medical information form 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.

Although no potential risks have been identified in nonclinical studies (please refer to Investigator Brochure Section 7.4) the effect of Bcl-2 inhibition on pregnancy has not been fully characterized. Venetoclax resulted in increased postimplantation loss and decreased fetal body weights were observed in the mouse embryofetal development study at the highest dosage administered. Venetoclax is not advised in pregnancy or lactation.

6.1.8 Toxicity Management

6.1.8.1 Definition – Dose Limiting Toxicity (DLT)

Dose limiting toxicities (DLTs) for dose-escalation purposes will be determined during the lead-in period (if applicable) plus the first cycle (21 days) of study drug administration at the designated cohort dose. Adverse events occurring following Cycle 1 will also be evaluated by the investigator and the AbbVie TA MD and may be considered as dose limiting. Any of the following events that are considered to have a "reasonable possibility" of relationship to the administration of venetoclax, which cannot be attributed by the investigator to a clearly identifiable cause such as disease progression, concurrent illness, or concomitant medication, will be considered a DLT:

- Grade 4 neutropenia lasting more than 7 days
- Grade 3 or Grade 4 neutropenia with fever
- Grade 4 thrombocytopenia
- Grade 2 or higher bleeding associated with Grade ≥ 3 thrombocytopenia
- Unexpected Grade 2 or higher toxicity which requires dose modification or delay of ≥ 1 week, will be considered a DLT (e.g., peripheral neuropathy)

- Clinical TLS will be considered a DLT. Laboratory TLS will be considered a DLT if the metabolic abnormalities are deemed clinically significant by the investigator.
- All other Grades 3, 4, or 5 adverse events will be considered a DLT with the exception of the following:
  - Grade 3 thrombocytopenia that does not result in bleeding
  - Grades 3, 4 lymphopenia
  - Grades 3, 4 leukopenia
  - Grade 3 neutropenia
  - Grade 3 nausea, vomiting, and/or diarrhea that is responsive to treatment
  - Grade 3 or 4 hyperuricemia or hypocalcemia or Grade 3 hyperkalemia, if transient (i.e., lasting < 48 hours) and without manifestations of clinical TLS (e.g., creatinine ≥ 1.5 × ULN, cardiac arrhythmias, seizures, or sudden death)

If a DLT of TLS is observed during the lead-in period, it will be attributed to the lead-in period and a modification will be made to the lead-in period regimen for subsequent cohorts. Any other DLTs observed during the lead-in and/or designated cohort dosing period will require a modification of the designated cohort dose (and/or lead-in period regimen, if appropriate) as directed per the Dose Escalation Guidelines (Section 5.1 and Table 2).

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

Drug interruption for up to 72 hours following transient (i.e., lasting < 48 hours) chemical changes and laboratory TLS may be allowed and may not be considered a DLT or require a dose reduction. If the TLS has not resolved within 72 hours then a dose reduction should be considered. The subject may be allowed to re-escalate to the final dose based on a risk assessment (including tumor burden status).

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

6.1.8.2 Management of Infection and Lymphopenia

There is a potential for clinically significant infection and lymphopenia (B and T lymphocyte subtypes) in this study.

It is recommended that subjects should receive anti-infective prophylaxis (e.g., amoxicillin/clavulanic acid or levofloxacin or equivalent per institutional guidelines) at least during the first 90 days of study and upon disease progression for at least 30 days, unless contraindicated per investigator discretion. Furthermore, it is recommended that subjects deemed at high risk of infection receive immunoglobulin replacement therapy (i.e., IVIG) per institutional guidelines or at the Investigator's discretion.

The use of antibiotics that are moderate or strong CYP3A inhibitors (See Section 5.2.4.3 and Appendix C) should be avoided or used with caution and with appropriate venetoclax dose modification (See Table 4) as per protocol.

All subjects with MM receiving venetoclax should be closely monitored for infections. In the event of a Grade ≥ 3 infection or any serious infection, treatment with venetoclax should be interrupted. Upon resolution, treatment can either be resumed at a reduced dose (see Table 18 or Table 19) or discontinued at the discretion of the Investigator. Please refer to Table 20 for guidance on dose interruptions and/or reductions related to venetoclax toxicities. All anti-infective measures should be appropriately recorded on the eCRF. Potential for drug-drug interactions should be considered. Please refer to Appendix C for a description of excluded and cautionary medications.

6.1.8.3 Management of Neutropenia

There is a potential for clinically significant neutropenia in this study. If clinically indicated, standard management practices for neutropenia should be implemented at the investigator's discretion.

Anti-infective prophylaxis and granulocyte-colony stimulating factor (G-CSF) for management of neutropenia should be considered per institutional guidelines and appropriately recorded on the eCRF. It is recommended that subjects should receive anti-infective prophylaxis (e.g., amoxicillin/clavulanic acid or levofloxacin or equivalent per institutional guidelines) when Grade 4 neutropenia develops (ANC < 500 cells/uL) and continued until the neutropenia improves to Grade 3 or better (ANC >500 cells/uL).

6.1.8.4 Management of Tumor Lysis Syndrome

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

Multiple myeloma patients with high tumor burden (e.g., high bone marrow plasma cell infiltration, plasma cell leukemia or bulky plasmacytoma), rapidly increasing M-protein or light chains or high proliferative activity, plasmablastic morphology, or compromised renal function (CrCl < 50 mL/minute) may be at higher risk of developing TLS.[31] Also, subjects with t(11;14) and high bone marrow plasma cell infiltration or a significant number of circulating plasma cells appear to have an increased risk for TLS when treated with venetoclax.

Consider TLS prophylaxis with oral hydration (at least 1 – 2 liters, as tolerable, daily) in all subjects at least 72 hours prior to the first day of dosing with venetoclax. 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 according to

institutional guidelines (Guidance also available in Appendix G Recommendations for Initial Management of Electrolyte Imbalances and Prevention of Tumor Lysis Syndrome (TLS) in Multiple Myeloma Subjects).

For subjects with t(11;14) and > 50% bone marrow plasma cell infiltration or CrCl < 50 mL/min, oral hydration as asforementioned is required and chemistry labs (phosphate, potassium, calcium, uric acid, creatinine, LDH, and AST at a minimum) should be done at approximately 6 hours after the first dose of venetoclax. More intensive measures (e.g., intravenous hydration, frequent monitoring of labs, hospitalization, etc.) should be considered at the Investigator discretion or in accordance with institutional guidelines. All TLS prophylaxis measures should be appropriately recorded in the eCRF.

In case of evidence of TLS, dosing with venetoclax should be interrupted. Drug interruption for up to 72 hours following transient (i.e., lasting < 48 hours) chemical changes and laboratory TLS will not require a dose reduction.

If the TLS has not resolved within 72 hours, then a dose reduction should be considered. The subject may be allowed to re-escalate to the final dose based on a risk assessment (including tumor burden status). If active correction of electrolytes was performed, the first dose of venetoclax should only be given when electrolytes have been stable without additional treatment for at least 24 hours.

If a subject meets criteria for clinically significant laboratory or clinical TLS, the subject must dose reduce (Refer to Table 19 as applicable). The subject may be allowed to re-escalate to the intended cohort dose based on a risk assessment (including tumor burden status) after discussion between the Investigator and the TA MD.

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

6.1.8.5 Guidelines for Dose Modifications and Treatment

During the VenDex combination and Phase 2 cohorts, if the dose of dexamethasone 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 dexamethasone is held and not completed within 48 hours, Cycle 2 Day 1 would be considered missed and subject would continue to be evaluated for dosing at Cycle 2 Day 8). If a dose is held, all assessments listed for that day would still be completed.

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

Subjects with a confirmed (SARS-Cov-2 test positive) or suspected COVID-19 infection must interrupt all study drugs until the following SARS-Cov-2 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 SARS-Cov-2 testing is pending. Treatment may be

reinitiated upon confirmation of negative SARS-Cov-2 test result and notification to the AbbVie TA MD or designee.

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. Follow protocol Section 5.3.1, Section 5.4.1, Section 5.4.2, Section 6.1.1, Section 6.1.5 and Appendix C 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.

6.1.8.6 Dose Modifications or Delays for Venetoclax Toxicities

Dose modifications and treatment guidelines for venetoclax monotherapy, Table 18, venetoclax with dexamethasone, Table 19, and venetoclax-related toxicities, Table 20 are provided below.

Table 18. Venetoclax Monotherapy Dose Levels

Designated Venetoclax Dose Level	Dose Level –1	Dose Level –2
1200 mg QD	800 mg QD	400 mg QD
900 mg QD	600 mg QD	300 mg QD
600 mg QD	300 mg QD	100 mg QD
300 mg QD	200 mg QD	100 mg QD

If the dose of venetoclax at the lowest dose level is not tolerable, then no further reductions will be allowed and venetoclax should be discontinued. Upon resolution of the AE leading to dose reduction, the dose of venetoclax can be increased following Table 18

guidelines, based on the Investigator's clinical judgment. If the AE recurs upon increasing the dose of venetoclax, then the subject should remain at the reduced and tolerated dose level. Guidelines in Table 4 should also be followed for venetoclax-toxicity related dose reductions when moderate or strong CYP3A inhibitors are concomitantly administered.

Table 19. Venetoclax Combined with Dexamethasone Dose Levels

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

Table 20. Hematological and Non-Hematological Toxicities Related to Venetoclax

Toxicities	Recommended Action
Grade 3 or Grade 4 neutropenia with infection or fever; or Grade 4 hematologic toxicities (except for lymphopenia)	• G-CSF or growth factors for neutropenia should be administered with venetoclax if clinically indicated. • For Grade 4 neutropenia (ANC < 500 cells/uL) without infection, anti-infective prophylaxis (e.g., amoxicillin/clavulanic acid or levofloxacin or equivalent per institutional guidelines) is recommended until the neutropenia improves to Grade 3 or better (ANC > 500 cells/uL) • First episode: Interrupt venetoclax and once the toxicity has resolved to Grade 1 or baseline level, venetoclax may be resumed at the same dose. • For subsequent episodes: Interrupt venetoclax. Consider using G-CSF as clinically indicated. Follow dose reduction guidelines in Table 18 and Table 19, as applicable when resuming treatment with venetoclax after resolution. A larger dose reduction may occur at the discretion of the physician and according to the dose reduction guidelines in Table 18 and Table 19, as applicable.
Grade ≥ 3 or Serious Infection	• Interrupt venetoclax and upon resolution, treatment can either be resumed at a reduced dose (See Table 18 or Table 19, as applicable) or discontinued, at the discretion of the Investigator.
Grade 3 or 4 non hematologic events	• First episode: Interrupt venetoclax. Once toxicity has resolved to Grade ≤ 1 or baseline, venetoclax may be resumed at the same dose. No dose modification is required. • For subsequent episodes: Interrupt venetoclax. Follow dose reduction guidelines in Table 18 and Table 17, as applicable when resuming treatment with venetoclax after resolution. A larger dose reduction may occur at the discretion of the physician and according to the dose reduction guidelines in Table 18 and Table 19, as applicable.
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 18 and Table 19, as applicable). • For any events of clinical TLS, resume at a reduced dose following resolution.

6.1.9 Management of Decreased Spermatogenesis

Based on findings in a preclinical study, there is a potential for decreased spermatogenesis. Male subjects should consider sperm banking before treatment with venetoclax if they are considering preservation of fertility.

6.1.10 Toxicities Related to Dexamethasone

All VenDex combination and Phase 2 cohort subjects should start dexamethasone at 40 mg. All subjects who are ≥ 75 years old may start at a 20 mg dose. Dose reduction levels and treatment guidelines for dexamethasone-related toxicities are provided in Table 21 and Table 22.

Table 21. Dose Reductions for Dexamethasone

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

Table 22. Treatment Guidelines for Toxicity Related to Dexamethasone

Body System	Symptom	Recommended Action
Gastrointestinal	Dyspepsia, gastric or duodenal ulcer, gastritis Grade 1 – 2 (requiring medical management)	Treat with H_2 blockers, sucralfate, or omeprazole. 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 omeprazole. If symptoms persist despite above measures, 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, 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.

6.1.11 Determination of the MTD

Escalation of venetoclax to the next designated cohort dose level will proceed if all assigned subjects at a dose level complete the lead-in period (if applicable) plus one cycle (21 days) at the designated cohort dose without experiencing a DLT (refer to Section 6.1.8.1). If one (1) subject within any dose level experiences a DLT, up to 6 subjects will be enrolled at that dose level. Additional subjects may be enrolled at the

current dose level at the discretion of the AbbVie TA MD. If < 33% of the subjects enrolled at a dose level experience a DLT, then escalation of the designated cohort dose may continue. If ≥ 33% of the subjects enrolled at a dose level experience a DLT, dose escalation will stop and the previous lead-in period and designated cohort dosing regimen will be considered the MTD. Dose de-escalation of the designated cohort dose, and/or a modified lead-in period may be explored if MTD is not declared.

If dose de-escalation or modification of the lead-in period occur and < 33% of subjects enrolled experience a DLT at the reduced designated cohort dose and/or the modified lead-in period regimen, this dosing regimen will be declared the MTD. If ≥ 33% of the subjects enrolled at the reduced designated cohort dose and/or the modified lead-in period regimen still experience a DLT, dose de-escalation of the designated cohort dose and/or modified lead-in period regimen will continue to be explored.

The MTD will be defined as the highest designated cohort dose level (and corresponding lead-in period regimen, if applicable) at which < 33% of the subjects enrolled experience a DLT.

6.1.12 Determination of the RPTD

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

6.2 Product Complaint

6.2.1 Definition

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

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.

6.2.2 Reporting

Product Complaints concerning the investigational product and 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 occurring 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 (syringe, pen, etc.). 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 except when necessary to eliminate an immediate hazard to study subjects. The principal investigator is responsible for complying with all protocol requirements, written instructions, and applicable laws regarding protocol deviations. If a protocol deviation occurs (or is identified, including those that may be due to the COVID-19 pandemic) after a subject has been enrolled, the principal investigator is responsible for notifying Independent Ethics Committee (IEC)/Independent Review Board (IRB) regulatory authorities (as applicable), and their assigned CRO clinical monitor or the following AbbVie clinical representative(s):

Primary Contact:

[redacted]
Study Project Manager I
AbbVie House
Vanwall Business Park
Vanwall Road
Maidenhead
SL6 4UB

Office:
Email:

AbbVie TA MD:

[redacted], MD
Medical Director, TA Oncology
Pharmacyclics Switzerland GmbH
An AbbVie Company
Mühlentalstrasse 36
CH-8200 Schaffhausen

Office:
Mobile:
Email:

Alternate Contact:

[redacted]
Study Management Associate III
AbbVie, on assignment from Syneos Health
1 North Waukegan Road
North Chicago, IL 60064

Cell:
Email:

Program Lead:

[redacted]
Program Lead II
AbbVie
[redacted]
1 North Waukegan Rd
North Chicago, IL 60064

Office:
Fax:
E-mail:

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. Any significant protocol deviations affecting subject eligibility and/or safety must be reviewed and/or approved by the IEC/IRB and regulatory authorities, as applicable, prior to implementation.

8.0 Statistical Methods and Determination of Sample Size

8.1 Statistical Analysis Plans

8.1.1 Definition of Analysis Population

All analyses will be performed for all subjects who take at least one dose of study drug.

8.1.2 Baseline Characteristics

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

Continuous baseline characteristics 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, prior therapies, cytogenetics).

8.1.3 Pharmacokinetics

8.1.3.1 Tabulations and Summary Statistics

Plasma concentrations and PK parameter values of venetoclax will be tabulated for each subject and each dose level, and summary statistics will be computed for each sampling time and each parameter.

8.1.3.2 Model and Tests

Dose Proportionality

Pharmacokinetic parameters of venetoclax from the dose escalation subjects assessed on Cycle 2 Day 1 will be analyzed as follows. An analysis will be performed for T_{max}, dose normalized C_{max}, dose-normalized AUC_{24} and β provided that they can be adequately determined from the data. The model used for the statistical analyses will include dose

level. This may be done by classifying subjects by dose level or, if appropriate, using dose level as a continuous variable. Covariates such as age, body weight, body surface area, gender, and perhaps others that might explain some of the variability in the population will be included in the model initially. However, a covariate may be dropped from the model if the regression coefficient is not significant at alpha level 0.10. The natural logarithmic transformation will be employed for C_{max} and the AUC's unless the data clearly indicate that other transformation or the untransformed variable provides more nearly symmetric probability distributions and/or more nearly homogenous variances across dose levels. Within the framework of the model, tests that have good power for a trend with dose will be performed on the effect of dose level.

Steady State Trough Hour 0 Concentrations

Exploratory analyses of trough (pre-dose) concentrations of venetoclax on Day 1 of Cycle 2, 3, 5, 7 and 9 for Phase 1 and Phase 2 portion subjects combined may be done to characterize the achievement of steady-state pharmacokinetics. Cycle may be included in the model as a categorical variable (to generate pairwise comparisons of various time points), or it may be treated as a continuous variable in a regression analysis framework (where a slope of zero indicates steady-state pharmacokinetics). The term for dose will also be included in the model, and the potential interaction between cycle and dose will be evaluated.

Additional analyses will be performed if useful and appropriate.

8.1.3.3 Missing Values and Model Violations

The possibility of bias from missing data of subjects who prematurely discontinue due to an adverse event will be addressed. Normally values of PK variables (C_{max}, AUC, etc.) will be determined without replacing missing individual concentration values, simply using the available data, and if necessary doing the analysis with some missing values for a PK variable. However, missing concentration values for isolated individual blood samples may be replaced (imputed) if such might affect study conclusions or meaningfully affect point estimates.

8.1.4 Efficacy Endpoints

8.1.4.1 Objective Response Rate and Very Good Partial Response or Better Rate

The ORR is defined as the proportion of subjects with documented PR or better (i.e., PR, VGPR, CR, or sCR) based on IMWG criteria in Section 5.3.3.1. VGPR+ is defined as the proportion of subjects with documented VGPR or better (i.e., VGPR, CR, or sCR) based on IMWG criteria in Section 5.3.3.1.

8.1.4.2 Time to Disease Progression

For a given subject, TTP is defined as the number of days from the date of the first dose of study drug to the date of first documented PD or death due to MM, whichever occurs first. If the subject does not have an event of PD and the subject has not died due to MM, the subject's data will be censored. Detailed event and censoring information for TTP are provided in Table 23.

Table 23. Event and Censoring Date Used in TTP

Situation	Option for End-Date	Outcome
No baseline assessment	Date of first dose of study drug	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 missing assessments	If no adequate assessment is available prior to PD/death then date of first dose of study drug. 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 first dose of study drug. Otherwise, date of the last adequate assessment	Censor

8.1.4.3 Duration of Response

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 MM, whichever occurs first. If the subject does not have an event of PD and the subject has not died due to MM, the subject's data will be censored. Detailed event and censoring information for DOR are provided in Table 24.

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

Table 24. Event and Censoring Date Used in DOR

Situation	Option for End-Date	Outcome
No baseline assessment	Date of first dose of study drug	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 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

8.1.4.4 Progression-Free Survival

For a given subject, PFS is defined as the number of days from the date of the first dose of study drug 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 with an outcome 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 25.

Table 25. Event and Censoring Date Used in PFS

Situation	Option for End-Date	Outcome
No baseline assessment	Date of first dose of study drug	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 missing assessments	Date of the last adequate assessment prior to PD/death	Censor
No PD and no death	Date of the last adequate assessment	Censor

8.1.4.5 Overall Survival

For a given subject, OS is defined as the number of days from the date of the first dose of study drug 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 dies, the data will be censored at the date they were last known to be alive.

8.1.4.6 Time to Response

For a given subject, TTR is defined as the number of days from the date of the first dose of study drug until the date of their first favorable response (i.e., PR, VGPR, CR, or sCR). If a subject does not experience a favorable response, they will be censored at the date of last adequate assessment.

8.1.5 Statistical Analysis of Efficacy

For the Phase 2 portion, confirmatory testing will be performed for ORR and VGPR+ rate, i.e.,:

1. H_{0a}: ORR $\leq$ 30% vs H_{1a}: ORR > 30%
2. H_{0b}: VGPR+ $\leq$ 12% vs H_{1b}: VGPR+ > 12%

Because two tests are being performed, multiplicity control must be implemented. The Hochberg procedure will be used, as follows:

- Calculate the p-value for each test, i.e., p_{ORR} and p_{VGPR+}
  - If p_{ORR} and p_{VGPR+} are both less than 0.025, reject both H_{0a} and H_{0b}, and declare efficacy.
  - Else, if min(p_{ORR}, p_{VGPR+}) is less than 0.0125, reject either H_{0a} or H_{0b} (as appropriate), and declare efficacy, where min() denotes the minimum.
  - Otherwise, do not declare efficacy.

This procedure controls the family-wise error rate at 0.025 and is uniformly more powerful than the Bonferroni correction.

In addition, point estimates and 95% exact confidence intervals of ORR and VGPR+ rate will be determined for different dose groups and treatments (venetoclax and venetoclax in combination with dexamethasone). The distribution of PFS, OS, TTR, TTP and DOR will be estimated for all subjects using Kaplan-Meier product-limit methodology. If reached, median time to event and a corresponding 95% confidence interval will be estimated.

DOR will be analyzed only based on data from responders (PR or better).

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

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.

Additional analysis may be performed if deemed necessary and helpful in understanding the drug effect.

8.1.5.1 Phase 2 Efficacy Subgroup Analysis

The Phase 2 portion of this study may explore potential differences in efficacy for various subgroups. Subjects may be compared by: age (< 65 years vs ≥ 65 years), ISS stage (I vs II/III), cytogenetic factors, the nature of subjects' previous therapies, and high versus low BCL-2:BCL-XL ratio.

In particular, the presentation of IMWG response rates (including ORR and VGPR+ rates) and time-to-event endpoints (PFS, OS, and DOR) may be broken down by subgroup membership.

8.1.6 Statistical Analysis of Safety

The safety of venetoclax monotherapy and venetoclax plus dexamethasone (combination and Phase 2) will be assessed by evaluating study drug exposure, adverse events, serious adverse events, deaths, and changes in laboratory values and vital sign parameters.

8.1.6.1 Duration of Study Drug Exposure

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

8.1.6.2 Adverse Events

Analyses of adverse events will include only "treatment-emergent" events, i.e., those that have an onset on or after the day of the first dose of the study drug. 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)[27] adverse event coding dictionary. The percentage of subjects experiencing an adverse event will be provided by relationship to study drug and by NCI CTCAE version 4.03[26] toxicity.

8.1.6.3 Serious Adverse Events

Serious adverse events will be summarized using the same methods as adverse events described above in Section 8.1.6.2.

8.1.6.4 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.

8.1.6.5 Longitudinal Analyses of Laboratory and Vital Signs Data

Changes from baseline will be summarized for each scheduled post-baseline visit and for the Final Visit blood chemistry, hematology, urinalysis, and vital sign parameters, where applicable. 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 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.

8.1.6.6 Analyses of Laboratory Data Using NCI CTCAE

Where applicable, laboratory values will be categorized according to the NCI CTCAE version 4.03)[26] 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 study drug, and as the grade of the last post-baseline measurement collected no more than 30 days after the last dose of study drug. If multiple values are available for a post baseline measurement, then the value with the highest NCI CTCAE grade will be used in the assessment of shift. The percentage of subjects experiencing a shift from baseline grades of 0 to 2 to maximum post-baseline grades of 3 to 4, and from baseline grades of 0 to 2 to final post-baseline grades of 3 to 4 will be summarized.

Detailed listings of data for subjects experiencing NCI CTCAE grades 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.

8.1.6.7 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 Biomarkers and Exploratory Research Variables

If biomarkers and/or exploratory end point data are determined from the collected samples, any statistical analyses of these data are outside the scope of this protocol and may be reported separately from the final clinical study report.

8.2 Determination of Sample Size

The Phase 1 portion is a dose escalation study. The number of subjects required will depend upon the toxicities observed as the trial progresses. Once MTD is reached and RPTD is determined, approximately 36 additional subjects will be enrolled at the MTD (or RPTD) of venetoclax into the safety expansion portion.

The safety expansion portion will evaluate the MTD (or RPTD) defined during the dose escalation portion of the study to provide increased precision in the estimation of safety parameters for different Bcl-2 family expression profiles. Each of these Bcl-2 expression family profiles will include approximately 12 additional subjects, as the probablilty of observing at least one dose-limiting adverse event in 12 subjects is 99% if the true but unknown dose limiting adverse event rate is 33%.

The VenDex combination portion will explore the safety and efficacy of venetoclax in combination with dexamethasone in subjects with t(11;14)-positive MM. Approximately 18 additional subjects will be enrolled as the probability to observe at least one occurrence of an adverse event is ≥ 85%, if the true incidence of the respective adverse event rate is ≥ 10%.

The primary objective of the Phase 2 portion of the study is to test (a) H_{0a}: ORR ≤ 30% against H_{1a}: ORR > 30% and (b) H_{0b}: VGPR+ rate ≤ 12% against H_{1b}: VGPR+ rate > 12%. These hypotheses will be tested using a family-wise one-sided type-I error rate of 0.025. The Hochberg procedure will be used to control for multiplicity. This part of the study is powered for a true ORR of 50% and a true VGPR+ rate of 30%. Under the considerations above, if at least 80 subjects are enrolled in the Phase 2 portion of the study, there will be over 95% power to reject H_{0a}, 96% power to reject H_{0b}, 92% power to reject both H_{0a} and H_{0b}, and 99% power to declare efficacy (due to high ORR, high VGPR+ rate, or high values of both).

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 and approval by Regulatory Authority (ies), if required by local regulations, prior to implementation of any changes made to the study design. The investigator will be required to submit, maintain

and archive study essential documents according to ICH GCP and all other applicable regulatory requirements.

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

9.2 Ethical Conduct of the Study

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

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 may engage with study site personnel in efforts to ensure the safety of subjects, maintain protocol compliance, and minimize risks to the integrity of the study while trying to best manage subject continuity of care. This may include alternative methods for assessments (e.g., phone contacts or virtual site visits), alternative locations for data collection (e.g., use of a local lab instead of a central lab), and shipping investigational product and/or supplies direct to subjects to ensure continuity of treatment where allowed. 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.

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 procedure being performed on the subject the informed consent statement will be reviewed, signed and dated by the subject, the person who administered the informed consent, and any other signatories according to local requirements. 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.

Pharmacogenetic analysis will only be performed if the subject has voluntarily signed and dated a pharmacogenetic informed consent, approved by an IRB/IEC, after the nature of the testing has been explained and the subject has had an opportunity to ask questions. The pharmacogenetic informed consent must be signed before the pharmacogenetic testing is performed. If the subject does not consent to the pharmacogenetic testing, it will not impact the subject's participation in the study.

In the event a subject withdraws consent to participate from the study, stored biomarker and exploratory research 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 and exploroatory research 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 IEC/IRB, 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.

If a subject specifically requests to withdraw consentfrom survival follow up, study sites may enter confirmation of death using source documentation from available public records such as death registries or funeral notices, as appropriate per local regulations.

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, subject diaries or evaluation checklists, pharmacy dispensing and other records, recorded data from automated instruments, microfiches, photographic negatives, microfilm or magnetic media, and/or x-rays. Data collected during this study must be recorded to 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 Awareness Date (SAE CRF) may serve as the source for this data point. This adverse event data point required for eCRF completion can be entered directly in the eCRF.

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 monitoring of data may be employed if allowed by the local regulatory authority, IRB/IEC, and the study site.

10.2 Case Report Forms

Case report forms (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 electronic data capture (EDC) system called Rave® provided by the technology vendor Medidata Solutions Incorporated, NY, USA. The EDC system and the study-specific electronic case report forms (eCRFs) will comply with Title 21 CFR Part 11. The documentation related to the validation of the EDC system is available through the vendor, Medidata, while the validation of the study-specific eCRFs will be conducted by AbbVie and will be maintained in the Trial Master File at AbbVie.

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

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

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

Patient-reported data have been completed for Phase 2 subjects. These data have been collected with an Electronic Patient Reported Outcome (ePRO) system called Trialmax, provided by the technology vendor CRF 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, CRF Health, while the user acceptance testing of the study specific PRO design will be conducted and maintained at AbbVie.

The subjects have been entering the data on an electronic device; the data has been uploaded to a server. The data on the server will be considered source, and maintained and managed by CRF Health.

Internet access to the ePRO data has been provided by CRF 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 has been collected electronically via a tablet device into which the patient has directly enter the required pieces of information. The electronic device has been programmed to allow data entry for only the visits specified in the protocol and did not allow for patients to complete more than one of the same assessments at any one visit. All data entered on the device has been immediately stored to the device itself and

automatically uploaded to a central server administrated by CRF 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, an initiation meeting will be held with AbbVie personnel, the investigator(s), and the study coordinators/project manager(s). This meeting will include a detailed discussion and review of the protocol and essential documents, performance of study procedures, case report form completion and specimen collection methods.

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

The information developed during the conduct of this clinical study is also considered confidential and will be used by AbbVie in connection with the development of 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 optional exploratory 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. Aggregate data from optional exploratory research may be provided to investigators used in scientific publications or presented at medical conventions. Optional exploratory 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 time frame specified in the contract between the investigator and AbbVie. Continuation of this study beyond this date must be mutually agreed upon in writing by both the investigator and AbbVie. The investigator will provide a final report to the IEC/IRB following conclusion of the study, and will forward a copy of this report to AbbVie or their representative.

The investigator must submit, maintain and archive any records related to the study according to ICH GCP and all other applicable regulatory requirements. If the investigator is not able to retain the records, he/she must notify AbbVie to arrange alternative archiving options.

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

The end of study is defined as the date of the last subject's last visit, including Safety Follow Up.

14.0 Investigator's Agreement

1. I have received and reviewed the Investigator's Brochure for venetoclax and product labeling for 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 1/2 Study Evaluating the Safety and Pharmacokinetics of ABT-199 in Subjects with Relapsed or Refractory Multiple Myeloma
Protocol Date:	17 February 2021

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 International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practices (GCP) and local regulations and guidelines governing the study at the site location. In signing the Investigator's Agreement in Section 14.0 of this protocol, the investigator is agreeing to the following:

1. Conducting the study in accordance with ICH GCP, the applicable regulatory requirements and current protocol, and making changes to a protocol only after notifying AbbVie and the appropriate Institutional Review Board (IRB)/ Independent Ethics Committee (IEC), except when necessary to protect the subject from immediate harm.
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 its amendments.
4. Reporting complaints that occur in the course of the investigation(s) to AbbVie.
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 protocol and all of its 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. Providing direct access to source data documents for study-related monitoring, audits, IEC/IRB review, and regulatory inspection(s).

Appendix B. List of Protocol Signatories

Name	Title	Functional Area
[redacted]	Study Project Manager I	Clinical
[redacted]	Director	Statistics
[redacted]	Medical Director	Clinical
[redacted]	Executive Medical Director, Hematology	Clinical
[redacted]	Director	Clinical Pharmacology and Pharmacometrics
[redacted]	Senior Principal Research Scientist	Precision Medicine, Oncology

Appendix C. Sample List of Cautionary Medications

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[2] **P-gp substrates** Aliskiren, ambrisentan, colchicine, dabigatran etexilate, digoxin, everolimus,* fexofenadine, lapatinib,* loperamide, maraviroc, nilotinib,* ranolazine, saxagliptin, sirolimus,* sitagliptin, talinolol, tolvaptan, topotecan* **BCRP substrates** Methotrexate,* mitoxantrone,* irrinotecan,* lapatinib,* rosuvastatin, sulfasalazine, topotecan* **OATP1B1/1B3 substrates** Atrasentan, atorvastatin, ezetimibe, fluvastatin, glyburide, rosuvastatin, simvastatin acid, pitavastatin, pravastatin, repaglinide, telmisartan, valsartan, olmesartan **P-gp inhibitors** Amiodarone, azithromycin, captopril, carvedilol, dronedarone, felodipine, quercetin, ronalzine, ticagrelor **BCRP inhibitors** Geftinib* **Corticosteroids** Cortisone, Hydrocortisone, Methylprednisolone, Prednisolone, Prednisone, Triamcinolone, Betamethasone, Dexamethsone

* These are anticancer agents; contact AbbVie TA MD (refer to Section 6.1.6) before use.

** If subject requires use of these medications, use with caution and contact AbbVie TA MD or designee (refer to Section 6.1.6) for guidance.

† If subject requires use of these medications, use with caution and reduce the venetoclax dose by 75%. 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 target dose.

‡ If subject requires use of these medications, use with caution and reduce the venetoclax dose by 50%. 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 target dose.

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 should not consume grapefruit, grapefruit products, Seville oranges (including marmalade containing Seville oranges) or starfruits.

Appendix D. Sample Meal Description

Standard American Heart Association Healthy (Low-Fat) Breakfast

1 box cereal (30 – 40 g)
Skim milk (240 mL)
1 boiled egg
1 slice toast (15 g)
Margarine (10 g)

Total calories, approximately 520 Kcal; 30% of the total caloric content of the meal is from fat; total grams of fat, approximately 17 grams.

Appendix E. IMWG Response Criteria for Multiple Myeloma

IMWG 2011[23-25] Response Criteria

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 plasma 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 • ≥ 90% reduction in 24-hr urinary M-protein 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, 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 dose 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 any time 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 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 is defined as meeting at least one of the following four measurements: serum M-protein ≥ 1 g/dL (≥ 10 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 ration is abnormal or bone marrow plasma cells ≥ 30%.

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

* 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.

** Clarification to IMWG criteria for coding CR and VGPR in patients in whom the only measurable disease is by serum FLC levels: CR in such patients is defined as a normal FLC ratio of 0.26 – 1.65 in addition to CR criteria listed above. VGPR in such patients is defined as a > 90% decrease in the difference between involved and uninvolved free light chain FLC levels.

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: o Serum M-protein[a] absolute increase ≥ 0.5 g/dL, and/or o Urine M-protein absolute increase ≥ 200 mg/24 hr, and/or o 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, and/or • 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). • 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 (≥ 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.

* 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.

Standard IMWG 2016[30] Response Criteria

Note: MRD IMWG[30] criteria will be evaluated as an exploratory endpoint.

Response Subcategory	**Response Criteria[a]**
Stringent complete response*	• Negative immunofixation on the serum and urine (regardless of whether disease at baseline was measurable in serum, urine, both, or neither) and • Disappearance of any soft tissue plasmacytomas and • < 5% plasma cells in bone marrow[b] and • Normal FLC ratio** and • Absence of clonal cells in bone marrow[b] by immunohistochemistry (κ/λ ratio ≤ 4:1 or ≥ 1:2 for κ and λ patients, respectively, after counting ≥ 100 plasma cells)[c]
Complete response*[,c]	• Negative immunofixation on the serum and urine (regardless of whether disease at baseline was measurable on serum, urine, both, or neither) and • Disappearance of any soft tissue plasmacytomas and • < 5% plasma cells in bone marrow[b] and • For subjects in whom the only measurable disease is by serum FLC levels, a normal FLC ratio** is also required

Response Subcategory	Response Criteria[a]
Very good partial response*	• Serum and urine M-protein detectable by immunofixation but not on electrophoresis or • ≥ 90% reduction in serum M-protein plus urine M-protein < 100 mg per 24 hours • For subjects in whom the only measurable disease is by serum FLC levels, VGPR is defined as: o ≥ 90% decrease in the difference between involved and uninvolved FLC levels
Partial response	• ≥ 50% reduction of serum M-protein and • Reduction in 24-hour urinary M-protein by ≥ 90% or to < 200 mg per 24 hours o 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 o If the serum and urine M-protein are unmeasurable,[d] and serum-free light assay is also unmeasurable, a ≥ 50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma-cell percentage was ≥ 30% • ≥ 50% reduction in the size of soft tissue plasmacytomas is also required, if present at baseline
Minimal response	• 25% – 49% reduction of serum M-protein and • 50% – 89% reduction in 24-hour urinary M-protein and • ≥ 50% reduction in the size (SPD)[f] of soft tissue plasmacytomas if present at baseline
Stable disease[e]	• Not meeting criteria for CR, VGPR, PR, MR or progressive disease

Response Subcategory	Response Criteria[a]
Progressive disease	• Any one or more of the following criteria: o Increase of 25% from lowest confirmed response value in one or more of the following criteria: • Serum M-protein (absolute increase must be ≥ 0.5 g/dL); • Serum M-protein increase ≥ 1 g/dL, if the lowest M component was ≥ 5 g/dL; • Urine M-protein (absolute increase must be ≥ 200 mg/24 h); o In patients without measurable serum and urine M-protein levels, the difference between involved and uninvolved FLC levels (absolute increase must be > 10 mg/dL); o In patients without measurable serum and urine M-protein levels and without measurable involved FLC levels, bone marrow plasma-cell percentage irrespective of baseline status (absolute increase must be ≥ 10%); o Appearance of a new lesion(s), ≥ 50% increase from nadir in SPD[f] of > 1 lesion, or ≥ 50% increase in the longest diameter of a previous lesion > 1 cm in short axis; o ≥ 50% increase in circulating plasma cells (minimum of 200 cells per μL) if this is the only measure of disease
Clinical Relapse	• Clinical relapse requires one or more of the following criteria: o Direct indicators of increasing disease and/or end organ dysfunction (CRAB features) related to the underlying clonal plasma-cell proliferative disorder. It is not used in calculation of time to progression or progression-free survival but is listed as something that can be reported optionally or for use in clinical practice; o Development of new soft tissue plasmacytomas or bone lesions (osteoporotic fractures do not constitute progression); o Definite increase in the size of existing plasmacytomas or bone lesions. A definite increase is defined as a 50% (and ≥ 1 cm) increase as measured serially by the SPD[f] of the measurable lesion; o Hypercalcemia (>11 mg/dL); o Decrease in hemoglobin of ≥ 2 g/dL not related to therapy or other non-myeloma-related conditions; o Rise in serum creatinine by 2 mg/dL or more from the start of the therapy and attributable to myeloma; • Hyperviscosity related to serum paraprotein

CR = complete response; FLC = free light chain; IMWG = International Myeloma Working Group; M-protein = myeloma protein; MR = minimal response; PR = partial response; sCR = stringent complete response; SPD = sum of the products of the maximal perpendicular diameters of measured lesions; VGPR = very good partial response

Notes:

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

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

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

b. Confirmation with repeat bone marrow biopsy not needed.

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

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

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

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

Appendix F. Howard Definition of Tumor Lysis Syndrome

Table 1. 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 calcium = measured calcium level in mg/dL + 0.8 × (4 – albumin in gm/dL).

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

* Not directly or probably attributable to therapeutic agent.

Note: Laboratory tumor lysis syndrome and at least one clinical complication.

Source: Howard 2011[28]

Appendix G. Recommendations for Initial Management of Electrolyte Imbalances and Prevention of Tumor Lysis Syndrome (TLS) in Multiple Myeloma Subjects

Section 1: First Dose of Venetoclax or Dose Escalation

- Within the first 24 hours after either the first dose or dose escalation, if any laboratory criteria below are met, the subject should be hospitalized for monitoring and the Investigator notified. No additional venetoclax doses should be administered until resolution. A rapidly rising serum potassium is a medical emergency.
- Nephrology (or acute dialysis service or other) should be contacted/consulted on admission (per institutional standards to ensure emergency dialysis is available) for any subject who is high risk for TLS being hospitalized in response to laboratory changes or per Investigator discretion.
- IV fluids (e.g., D5 1/2 normal saline) initiated at a rate of at least 1 mL/kg/hr rounded to the nearest 10 mL (target 150 to 200 mL/hr; not < 50 mL/hr). Modification of fluid rate should also be considered for individuals with specific medical needs.
- Monitor for symptoms or signs of TLS (e.g., fever, chills, tachycardia, nausea, vomiting, diarrhea, diaphoresis, hypotension, muscle aches, weakness, paresthesias, mental status changes, confusion, seizures). If any clinical features are observed, recheck potassium, phosphorus, uric acid, calcium and creatinine within 1 hour immediately.
- Vital signs should be taken at time of all blood draws or any Intervention.
- The management recommendations below focus on the minimum initial responses required. If a diagnosis of TLS is established, ongoing intensive monitoring and multi-disciplinary management will be per institutional protocols.

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

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

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

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

Section 2: Ongoing Dosing of Venetoclax

Management of electrolyte changes from last value at intervals > 24 hours after either the first dose or dose escalation (e.g., 48 or 72 hours) is as below.

***Note*:** If the patient is hospitalized, no additional venetoclax doses should be administered until resolution.

- For potassium, admit patient for any increase ≥ 1.0 mmol/L (1.0 mEq/L), or any level > upper limit of normal.
  - Refer to the management guidelines for electrolyte changes observed within the first 24 hours after either the first dose or dose escalation (see prior table).
- If a smaller potassium increase is observed that does not meet the criteria for admission above, recheck potassium, phosphorus, uric acid, calcium and creatinine in 24 hours and confirm no evidence of tumor lysis prior to further venetoclax dosing.
- For uric acid, calcium, phosphorus and creatinine, refer to the management guidelines for electrolyte changes observed within the first 24 hours after either the first dose or dose escalation (see prior table).

Appendix H. Adverse Events Commonly Associated with MM Study Population or Progression of MM

Disease-Related Events
Renal Insufficiency
Bone Complications (pathologic fractures, spinal cord compressions, hypercalcemia, bone pain)
Neurologic complications (spinal cord and nerve root compression, intracranial plasmacytomas, leptomeningeal involvement [increased intracranial pressure, cranial nerve palsies, confusion])
Peripheral neuropathy
Paraesthesia
Cytopenia (neutropenia, anaemia, thrombocytopenia)
Febrile neutropenia
Infections (bacterial, viral, and fungal)
Second primary cancers, all types
Fatigue
Unexplained weight loss
Intermittent fever
Bruising
Minor hemorrhages
Pain, all types
Malignant neoplasm progression, including death

Population-Related Comorbidities
Hypertension
Rheumatoid arthritis/osteoarthritis
Hyperlipidemia
Peptic ulcer
Inflammatory bowel disease
Coronary artery disease
Peripheral vascular disease
Cardiomyopathy
Valvular disease
Atrial fibrillation
Diabetes mellitus
Chronic obstructive pulmonary disease
Cerebrovascular accident
Transient ischemia attack

Appendix I. Corticosteroid Conversion Table

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

Reference:

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

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

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