Title Page

Protocol Title:		A Phase 1 First in Human Study Evaluating the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of AMG 176 in Subjects With Relapsed or Refractory Multiple Myeloma and Subjects With Relapsed or Refractory Acute Myeloid Leukemia
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Sponsor	**Name of Sponsor:**	Amgen, Inc.
	Address:	One Amgen Center Drive Thousand Oaks, CA 91320**, USA**
	Telephone Number:	+1-805-447-1000
Key Sponsor Contacts	**Name:**	[redacted], MD, PhD
	Address:	One Amgen Center Drive Thousand Oaks, CA 91320**, USA**
	Telephone Number:	[redacted]
	Email Address:	[redacted]
Protocol Approver	**Name:**	[redacted], MD
	Function:	Vice President, Early Development
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This protocol was developed, reviewed, and approved in accordance with Amgen's standard operating procedures. This format and content of this protocol is aligned with Good Clinical Practice: Consolidated Guidance (ICH E6).

Confidentiality Notice

Investigator's Agreement:

I have read the attached protocol entitled A Phase 1 First in Human Study Evaluating the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of AMG 176 in Subjects With Relapsed or Refractory Multiple Myeloma and Subjects With Relapsed or Refractory Acute Myeloid Leukemia, dated **13 July 2023**, and agree to abide by all provisions set forth therein.

I agree to comply with the International Council for Harmonisation (ICH) Tripartite Guideline on Good Clinical Practice (GCP), Declaration of Helsinki, and applicable national or regional regulations/guidelines.

I agree to ensure that Financial Disclosure Statements will be completed by: me (including, if applicable, my spouse [or legal partner] and dependent children) and my subinvestigators (including, if applicable, their spouses [or legal partners] and dependent children) at the start of the study and for up to 1 year after the study is completed, if there are changes that affect my financial disclosure status.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Amgen Inc.

_____

Signature

_____ _____

Name of Investigator Date (DD Month YYYY)

_____

Title and Role of Investigator

_____

Institution Name

_____

Address and Telephone Number of Institution

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1. Protocol Summary

1.1 Synopsis

Protocol Title: A Phase 1 First in Human Study Evaluating the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of AMG 176 in Subjects With Relapsed or Refractory Multiple Myeloma and Subjects With Relapsed or Refractory Acute Myeloid Leukemia

Study Phase: 1

Indication: Multiple myeloma (MM) and acute myeloid leukemia (AML)

Rationale

Acute Myeloid Leukemia (AML) is a clonal disorder characterized by ineffective hematopoiesis and an accumulation of abnormal blasts in the bone marrow (Albitar et al, 2002; Doll and List, 1989). The combination of azacitidine and venetoclax represents the current standard frontline therapy for newly diagnosed patients considered unfit for intensive chemotherapy due to either age or medical comorbidity (DiNardo et al, 2020). While remission rates and median overall survival (OS) represent a significant improvement compared to prior therapy, the regimen is not curative. Primary resistance may occur, with a mean OS of less than 3 months observed for patients upon relapse (Prebet et al, 2011; Jabbour et al, 2010; Fenaux et al, 2009). Recent studies demonstrate that the myeloid cell leukemia sequence 1 (MCL1) protein, an intrinsic anti-apoptotic protein within the B-cell lymphoma/leukemia 2 (BCL2) family, may drive the resistance to BCL2 inhibition by venetoclax.

The upregulation of MCL1 has been described in many human malignant subtypes, including AML and myelodysplastic syndrome**s** (MDS) (Fischer et al, 202**3**; Caenepeel et al, 2018), highlighting MCL1 as a promising target for the next generation of therapy for these malignancies. MCL1-dependency was observed in AML mouse models as well as in human AML-derived cell lines (Glaser et al, 2012), and inhibition of MCL1 induced leukemic cell death in these models. Preclinical investigations have also demonstrated that MCL1 inhibition synergizes with standard of care (SOC) therapy and increases antileukemic activity by sensitizing leukemic cells towards apoptosis (Kelly et al, 2014; Phillips et al, 2015; Caenepeel et al, 2018). As evidence of this, combination of MCL1 inhibition with venetoclax overcomes BCL2 inhibitor resistance and is active in venetoclax-resistant cell lines and patient samples (Zhang et al, 2020). In the current study, AMG 176, an MCL1 inhibitor, is combined with azacitidine to overcome treatment resistance in subjects with relapsed or refractory AML. In support of this expectation, preliminary efficacy results demonstrate clinical responses in subjects previously treated and refractory to azacitidine and venetoclax therapy (see Table 2-1).

In this study, Part 1 and Part 2 were initially designed to investigate AMG 176 as monotherapy and combinational therapy in subjects with multiple myeloma (MM). As of December 2019, 48 subjects were enrolled in Part 1 where clinical responses were observed at dose levels > 240 mg/m^2. However, AMG 176 associated elevations of

troponin were observed at dose levels of 360 and 480 mg/m² in MM patients. In contrast, clinical responses in AML were observed at lower dose levels, indicating that AML may be more susceptible to MCL1 inhibition and can be treated with lower doses compared to subjects with MM. The combination of these observations led to further development in AML and a pause in MM development for now; Part 1 will remain closed to enrollment and Part 2 was removed from the protocol during Amendment 10. To avoid the potential for troponin elevations, only doses ≤ 240 mg/m² will be further investigated. Furthermore, since preclinical data demonstrates that MCL1 inhibition as more efficacious in combination with other antileukemic therapies, combinational therapy will be prioritized in this study (Parts 4 and 5) to optimize the clinical benefit to subjects. Monotherapy dose escalation will be performed only to inform the combinational study, and not to confirm the likely monotherapy maximum tolerated dose (MTD) of 240 mg/m². As of November 2022, 33 subjects have been enrolled in monotherapy (Part 3b) and combination therapy (Part 4) cohorts at dose levels of ≤ 240 mg/m²; no concerning safety events (including elevations of troponin) and no Dose-Limiting Toxicities (DLTs) were observed. See also Section 6.1 and Section 6.2.

Objective(s)/Endpoint(s)

Objectives	Endpoints
Primary	
Multiple Myeloma Part 1a (BIW)	
• Evaluate the safety and tolerability of AMG 176 monotherapy in subjects with relapsed or refractory multiple myeloma (MM) and determine the maximum tolerated dose (MTD) for twice weekly (BIW) dosing schedule	• Incidence of Dose-Limiting Toxicities (DLTs), treatment-related and treatment-emergent adverse events, and clinically significant changes in vital signs, electrocardiograms (ECGs), and clinical laboratory tests
• Evaluate the pharmacokinetics (PK) of AMG 176 when administered as monotherapy (BIW)	• PK parameters for AMG 176, including, but not limited to, maximum observed concentration (C_{max}), area under the concentration-time curve (AUC), clearance (CL), and half-life ($t_{½}$)
Multiple Myeloma Part 1b (QW)	
• Evaluate the safety and tolerability of AMG 176 monotherapy in subjects with relapsed or refractory MM and determine the MTD for a once weekly (QW) dosing schedule	• Incidence of DLTs, treatment-related, treatment-emergent adverse events and clinically significant changes in vital signs, ECGs, and clinical laboratory tests
• Evaluate the PK of AMG 176 when administered as monotherapy (QW)	• PK parameters for AMG 176 including, but not limited to C_{max}, AUC, CL, and $t_{½}$

Acute Myeloid Leukemia Part 3a (BIW)	
• Evaluate the safety and tolerability of AMG 176 monotherapy in subjects with relapsed or refractory acute myeloid leukemia (AML) and determine the MTD for BIW dosing as a monotherapy in subjects with relapsed or refractory AML	• Incidence of DLTs, treatment-related, treatment-emergent adverse events and clinically significant changes in vital signs, ECGs, and clinical laboratory tests
• Evaluate the PK of AMG 176 when administered as monotherapy (BIW)	• PK parameters for AMG 176 including, but not limited to C_{max}, AUC, CL, and $t_{½}$
Acute Myeloid Leukemia Part 3b (QW)	
• Evaluate the safety and tolerability of AMG 176 QW monotherapy in subjects with relapsed or refractory AML	• Incidence of DLTs, treatment-related, treatment-emergent adverse events and clinically significant changes in vital signs, ECGs, and clinical laboratory tests
• Evaluate the PK of AMG 176 when administered as monotherapy (QW)	• PK parameters for AMG 176 including, but not limited to C_{max}, AUC, CL, and $t_{½}$
Acute Myeloid Leukemia Part 3c (QW) in Japan	
• Evaluate the safety and tolerability of AMG 176 QW monotherapy in subjects in Japan with relapsed or refractory AML	• Incidence of DLTs, treatment-related, treatment-emergent adverse events and clinically significant changes in vital signs, ECGs, and clinical laboratory tests
• Evaluate the PK of AMG 176 when administered as monotherapy (QW) in Japan	• PK parameters for AMG 176 including, but not limited to C_{max}, AUC, CL, and $t_{½}$
Acute Myeloid Leukemia Part 3d - Drug-drug Interaction (DDI) Assessment with Itraconazole in United States (US)	
• Evaluate the PK of AMG 176 when given alone and in combination with itraconazole in subjects with AML	• PK parameters for AMG 176 including, but not limited to C_{max}, AUC, CL, and $t_{½}$
Acute Myeloid Leukemia Parts 4 and 5 (QW, BIW, and conventional AML dosing) in combination with azacitidine	
• Evaluate the safety and tolerability of AMG 176 in combination with azacitidine in subjects with relapsed or refractory AML and in Part 4 only, determine the maximum tolerated combination dose (MTCD) of AMG 176 in combination with azacitidine	• Incidence of DLTs (Part 4 only), treatment-related, treatment-emergent adverse events and clinically significant changes in vital signs, ECGs, and clinical laboratory tests
• Evaluate the PK of AMG 176 and azacitidine when administered in combination	• PK parameters for AMG 176 and azacitidine including, but not limited to, C_{max}, AUC, CL, and $t_{½}$

Secondary	
Multiple Myeloma Part 1a (BIW)	
• Demonstrate inactivation of myeloid cell leukemia sequence 1 (MCL1) by the increase of active B-cell lymphoma/leukemia 2 associated X protein (BAX) and caspase 3 in circulating monocytes and/or the decrease of circulating monocytes in AMG 176 BIW treated subjects	• BAX and caspase 3 expression in circulating monocytes and/or circulating monocyte counts
• Evaluate preliminary efficacy of AMG 176 BIW when given as monotherapy in relapsed or refractory MM	• Overall response (OR) according to International Myeloma Working Group uniform response criteria (IMWG-URC) for MM subjects, progression-free survival (PFS), time to response, and duration of response (DOR)
Multiple Myeloma Part 1b (QW)	
• Demonstrate inactivation of MCL1 by the increase of active BAX and caspase 3 in circulating monocytes and /or the decrease of circulating monocytes in AMG 176 QW treated subjects	• BAX and caspase 3 expression in circulating monocytes and /or circulating monocyte counts
• Evaluate preliminary efficacy of AMG 176 QW when given as monotherapy in relapsed or refractory MM	• Overall response according to IMWG-URC for MM subjects, PFS, time to response, and DOR
Acute Myeloid Leukemia Part 3a (BIW), Part 3b (QW), and Part 3c (QW)	
• Evaluate preliminary efficacy of AMG 176 when given as monotherapy in relapsed or refractory AML (For Part 3c: Japan subjects only)	• Overall response according to the 2017 European LeukemiaNet (ELN) criteria (Döhner et al, 2017) in AML subjects, event-free survival (EFS), time to response, and DOR (see Section 11.15)
Acute Myeloid Leukemia Part 3d - DDI Assessment with Itraconazole in US	
• Evaluate the safety and tolerability of AMG 176 when given alone and in combination with itraconazole in subjects with AML	• Treatment-emergent adverse events and changes in vital signs, ECGs, and clinical laboratory tests
Acute Myeloid Leukemia Parts 4 and 5 (QW and BIW)	
• Evaluate preliminary efficacy of AMG 176 when given in combination with azacitidine in relapsed or refractory AML	• Overall response according to the 2017 ELN criteria in AML subjects, EFS, time to response, and DOR (see Section 11.15)

Overall Design

This is a phase 1, multicenter, open-label, dose-escalation study to define the MTD or recommended dose and maximum tolerated combination dose (MTCD), as well as the safety, tolerability, PK, pharmacodynamics (PD), and efficacy of AMG 176 administered as monotherapy or in combination with SOC. The study will be conducted in multiple parts as shown in the table below.

A dose-level review team (DLRT) will be responsible for dosing recommendations, which may include escalation to the next nominal or intermediate dose, de-escalation to a lower nominal or intermediate dose; modifications of the ramp-up dosing, alternative dose frequencies, continuation, delay or termination of dosing; or repetition or expansion of a cohort; or determination of recommended dose. For definition of the DLT evaluation period and of a DLT-evaluable subject refer to Section 6.2.1.2.1.

Cycles of AMG 176 treatment may continue until confirmed progressive disease (PD) defined by 2017 European LeukemiaNet (ELN) criteria for AML subjects [Section 11.15]), the subject becomes intolerant to the study medication, signs and symptoms of clinical progression are evident as determined by the principal investigator, or the subject withdraws consent. Evaluation of disease response will be performed every 28 days (± 7 days) until PD irrespective of cycle duration including dose delays or treatment discontinuation. The disease assessment schedule is independent of treatment schedules. Ramp-up dosing in cycle 1 will be utilized whenever the AMG 176 target dose level is at 180 mg/m^2 or higher to mitigate the risk of tumor lysis syndrome (TLS) (see Section 6.1.1).

A safety follow-up (SFU) visit must be performed 30 days (+3 days) after the last dose of protocol-required therapies. Long term follow-up assessments will occur every 3 months (± 14 days) after end of treatment (EOT) for 1 year and include survival, subsequent anti-cancer therapy, and any cardiac associated serious adverse event or studies performed.

Overview of Study Design			
Part	Indication/ Number of Subjects	Cohort/ Treatment Group[a]	Design
CLOSED TO ENROLLMENT			
1a	*Multiple Myeloma (36 subjects enrolled)*	*AMG 176 BIW IV monotherapy (30 to 480 mg/m^2)*	*A standard 3+3 design was used to identify the MTD (or recommended dose), safety, tolerability, PK, and PD of AMG 176 administered BIW.*
1b	*Multiple Myeloma (12 subjects enrolled)*	*AMG 176 QW IV monotherapy (180 to 480 mg/m^2)*	*A standard 3+3 design was used to identify the MTD (or recommended dose), safety, tolerability, PK, and PD of AMG 176 administered QW. The starting dose level will be 180 mg/m^2.*

Overview of Study Design			
3a	*AML (17 subjects enrolled)*	*AMG 176 BIW IV monotherapy (60 to 180 mg/m^2)*	*A standard 3+3 design was used to identify the MTD, as well as the safety, tolerability, PK, and PD of AMG 176 administered BIW. The starting dose level will be 60 mg/m^2.*
3c	*AML (4 subjects enrolled in Japan)*	*AMG 176 QW IV monotherapy (120 mg/m^2)*	*A standard 3+3 design without dose escalation was used to evaluate the safety, tolerability, PK, and PD of AMG 176 administered QW in subjects with AML in Japan.*
3b	AML (11 subjects)	AMG 176 QW IV monotherapy (120, 180, and 240 mg/m^2)	A modified toxicity probability interval (mTPI) model design will be used to evaluate the safety, tolerability, PK, and PD of AMG 176 administered QW.
Part	Indication/ Number of Subjects	Cohort/ Treatment Group[a]	Design
OPEN TO ENROLLMENT			
3d	AML (**approximately** 11 subjects in US)	AMG 176 QW IV 60 mg/m^2 in combination with itraconazole (200 mg) once daily (QD) starting on day -3 through day 4 (total of 7 days) only in cycle 1	A fixed sequence design (itraconazole plus AMG 176 in week 1, followed by AMG 176 in subsequent weeks) will be used to evaluate the effect of itraconazole (strong cytochrome P450 3A4 [CYP3A4] inhibitor) on the PK of AMG 176.
4	AML (approximately 60 subjects)	AMG 176 QW and BIW IV (60, 120, 180, and 240 mg/m^2) in combination with azacitidine, with ramp-up dosing of AMG 176 as described for target doses ≥ 180 mg/m^2.	An mTPI design will be used to define the combination RP2D. All subjects will receive azacitidine at a dose of 75 mg/m^2 either IV or SC, as recommended in the prescribing information, daily for the first 7 days of a 28-day cycle. Safety, tolerability, PK, and PD of AMG 176 in combination with azacitidine will also be established. Part 4 enrollment will begin after the DLRT established the 120 mg/m^2 dose of AMG 176 as safe and tolerable in combination with azacitidine.

Overview of Study Design			
Part	Indication/ Number of Subjects	Cohort/ Treatment Group[a]	Design
OPEN TO ENROLLMENT			
5	AML (approximately 68 subjects **[**24 per cohort **in Part 5A, 20 in Part 5B]**)	Part 5**A**: AMG 176 in combination with azacitidine Cohorts 1 and 2: OBD Selection (QW or BIW). Part 5**B**: Conventional AML Dosing Schedule (5 consecutive days)	Part 5 will begin after the completion of Part 4. Part 5**A**: • Two cohorts will be enrolled to determine the combination RP2D/OBD on either a QW or BIW dosing schedule. • **Simon's two-stage minimax design (Simon, 1989) will be used in each cohort of Part 5A for conducting the trial.** • Enrollment will be restricted to subjects with persisting or recurring AML ≤ 2 prior lines of therapy. Part 5**B (The enrollment of Part 5B will start after Part 5A is complete)**: • Two regimens will be tested, both continuing to utilize a 28-day cycle. • All subjects will receive 7 days of azacitidine IV or SC daily at 75 mg/m² on Days 1 - 5, 8 - 9 of each 28-day cycle. • Regimen 1 will administer AMG 176 at 240 mg/m² QD for 3 days + 4 days off followed by BIW dosing on weeks 2 and 3. • Regimen 2 will administer AMG 176 at 240 mg/m² QD for 5 consecutive days, and then BIW on week 2 (no administration on weeks 3 and 4). Regimen 2 will only enroll if no safety issues arise after 6 subjects have enrolled in Regimen 1. • Doses other than the stated 240 mg/m² based on emerging data.

AML = acute myeloid leukemia; BIW = twice weekly; DLRT = dose-level review team; IV = intravenous; MM = multiple myeloma; MTD = maximum tolerated dose; mTPI = modified toxicity probability interval; PD = pharmacodynamics; PK = pharmacokinetics; QD = once daily; QW = once weekly; RP2D = recommended phase 2 dose; SC = subcutaneous; US = United States

Note: Part 2 was designed to be a combination treatment for MM in a previous amendment. It was removed due to a change in AMG 176 clinical development.

Number of Subjects

Subjects with relapsed or refractory MM and subjects with relapsed or refractory AML are eligible for this study (see Section 5). It is anticipated that **approximately** 21**9** subjects will be enrolled in the different parts of this study.

CLOSED TO ENROLLMENT: Multiple myeloma Part 1a enrolled 36 subjects for dose escalation. Multiple myeloma Part 1b enrolled 12 subjects for dose escalation. Acute myeloid leukemia Part 3a enrolled 17 subjects for dose escalation. Part 3b enrolled 11 subjects. Acute myeloid leukemia Part 3c enrolled 4 subjects in Japan.

OPEN TO ENROLLMENT: Part 3d will enroll **about** 11 subjects in the United States. Part 4 will enroll approximately 60 subjects. Part 5 will enroll approximately 6**8** subjects. The rationale for the number of subjects required is detailed in Section 9.2.

Summary of Subject Eligibility Criteria

Multiple Myeloma

Subjects ≥ 18 years of age with relapsed or refractory MM.

Subjects must have a pathologically documented, definitively diagnosed, MM relapse or refractory PD and have received at least 2 therapeutic treatments or regimens for MM.

Subjects must have measurable disease per the International Myeloma Working Group (IMWG) response criteria.

Acute Myeloid Leukemia

Subjects ≥ 18 years of age with AML as defined by the World Health Organization (WHO) Classification (Section 11.14) persisting or recurring following 1 or more treatment courses except acute promyelocytic leukemia (APL). The investigator must be of the opinion that no other treatment option will result in a durable response (DR). In Part 5**A** cohorts 1 and 2, enrollment will be restricted to subjects with persisting or recurring AML ≤ 2 prior lines of therapy.

For a full list of eligibility criteria, please refer to Section 5.1 to Section 5.2.

Treatments

AMG 176 will be supplied as either a 10 mL liquid deliverable volume in a single use **(**20 **R)** glass vial or a 14.4 mL liquid deliverable volume in a single use **(**30 **R)** glass vial. Vials are to be stored at temperatures at or below 25ºC and protected from light. AMG 176 is formulated as a sterile solution for infusion at a concentration of 25 mg/mL in 10% w/w 2-hydroxypropyl beta-cyclodextrin, buffered with 100 mM glycine to pH 9.0. The AMG 176 drug product is diluted in normal saline prior to infusion. AMG 176 is administered as an **intravenous (**IV**)** infusion on a 28-day cycle as per the schedules shown in Table 1-1.

Table 1-1. AMG 176 Dosing Schedule

	AMG 176 dosing (IV infusion on a 28-day cycle)
Part 1b, 3b, 3c, 3d, and 4 (cohort 1 through 4)	QW, day 1 of every week of the 28-day cycle
Part 4 (cohorts 5a and 5b)	BIW, days 1 and 2 each week for the first 3 weeks of each 28-day cycle
Part 3d	QW for 3 weeks only, after which subjects may crossover to Part 3b or Part 4 for continued treatment if approved by the investigator and Amgen medical monitor
Part 5**A** (cohorts 1 and 2)	QW or BIW
Part 5**B**	Regimen 1: Day 1 - 3 (3 consecutive days) the first week, and BIW on weeks 2 and 3 each cycle in the first 6 subjects. If this schedule is deemed safe by the DLRT, the next 6 subjects will receive **R**egimen 2 Regimen 2: Day 1 - 5 (5 consecutive days) the first week, and BIW dosing week 2 for each cycle

BIW = twice weekly; DLRT = dose-level review team; IV = intravenous; QW = once weekly

Procedures

After written informed consent has been obtained, all screening tests and procedures will be performed within 14 days of administration of the first dose of AMG 176 (day 1), or itraconazole (ie, day -17 to day -3) for Part 3d, unless otherwise noted. Subjects will be seen in clinic where critical clinical safety and study evaluations will be performed including physical examination, vital signs, clinical laboratory tests, electrocardiograms (ECGs), PK, and [redacted]r sample collections and disease assessments.

For a full list of study procedures, including the timing of each procedure, please refer to Section 8.2 and the Schedule of Activities in Section 1.3.

Statistical Considerations

All subjects who are enrolled and receive at least 1 administration of the investigational product (AMG 176) will be included in the Full Analysis Set (FAS). The analyses will be performed on FAS, unless otherwise specified. The analyses of DLT will include only DLT-evaluable subjects.

Descriptive statistics will be provided for selected demographics, safety, PK, PD and [redacted] data by dose, dose schedule, and time as appropriate. Descriptive statistics on continuous data will include means, medians, standard deviations and ranges, while categorical data will be summarized using frequency counts and percentages. Graphical summaries of the data may also be presented.

The proportion of subjects with overall response per IMWG criteria for MM subjects or with complete remission per 2017 ELN criteria for AML subjects with corresponding 2-sided exact 95% CI will be calculated using the Clopper-Pearson method (Clopper and Pearson, 1934).

For a full description of statistical analysis methods, please refer to Section 9.

Statistical Hypotheses

At least 1 dose level of AMG 176 administered as monotherapy will achieve acceptable safety and tolerability in subjects with relapsed or refractory MM with evidence of biologic impact as shown by either evidence of reduction in MCL1 activity in circulating monocytes/circulating blasts and/or evidence of anti-tumor activity.

At least 1 dose level of AMG 176 administered as a monotherapy or in combination with azacitidine will achieve acceptable safety and tolerability in subjects with relapsed or refractory AML with evidence of biologic impact, as shown by either evidence of reduction in MCL1 activity in circulating monocytes/circulating blasts and/or evidence of anti-tumor activity.

Dose Optimization Plan to **i**nform Recommended Phase 2 Dose (RP2D) for the Combination of AMG 176 with Azacitidine

The data to date support a monotherapy MTD of 360 mg/m² and a monotherapy recommended phase 2 dose (RP2D) of 240 mg/m² for AMG 176. Given the limited monotherapy activity, further development has since proceeded utilizing combination therapy of AMG 176 with azacitidine. Preclinical models have demonstrated synergistic anticancer activity with this combination.

The RP2D for the combination of AMG 176 with azacitidine (here from referred to as the "combination RP2D") will be estimated using the totality of data from across the first in human (FIH) study, including the PK, safety, efficacy, PD [redacted] for efficacy, and other results from the dose escalation and dose expansion.
Dose-exposure-response analyses for safety and efficacy will be conducted to inform the combination RP2D.

Two dose levels will be selected for the expansion phase based on the preliminary dose-exposure–response analyses and PK/PD modeling using available data from preclinical and dose escalation phase. In order to minimize bias, assignments will be randomized to each dose level **in Part 5A**. Pharmacokinetic exposure separation, minimal dose expected to achieve efficacy, highest dose with acceptable safety profile and other aspects will be considered for dose selection of the expansion phase.

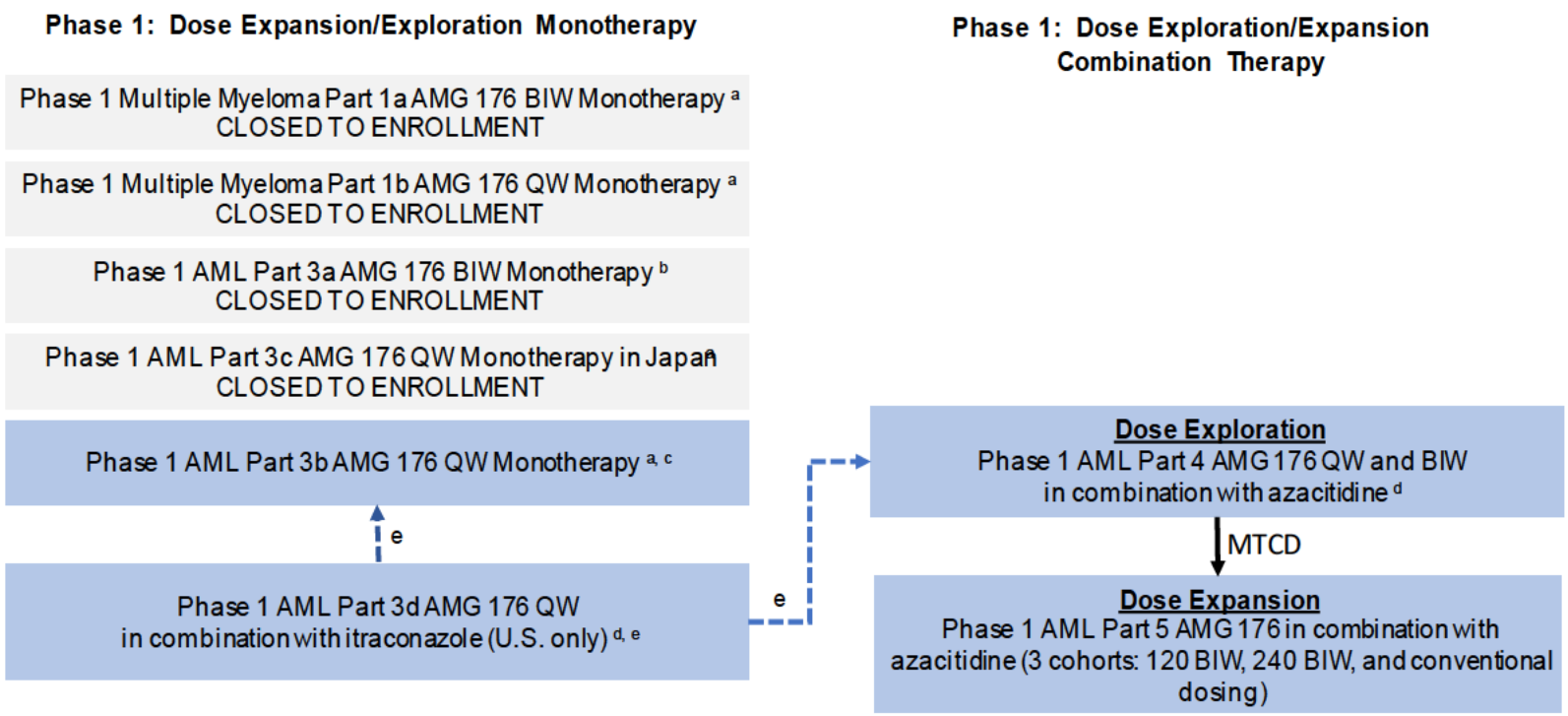
AMG 176 has exhibited a predictable PK/PD profile. Based on the available data from the dose escalation part of Study 20150161, preliminary dose-exposure analyses indicated dose-related increases in exposure with mean terminal elimination half-life (t½) of approximately 4 to 23 hours in AML subjects. Preliminary dose-exposure-response analyses in subjects with relapsed or refractory (R/R) MM and in subjects with R/R AML demonstrated no concerning safety signals, including troponin elevations, at AMG 176 doses of 240 mg/m² or less (QW or BIW) when administered as monotherapy or in combination with azacitidine. Preliminary efficacy is observed at a range of dose levels from 60 to 240 mg/m² AMG 176 monotherapy and in combination with azacitidine in AML subjects.

Further dose-exposure-response analyses and PK/PD modeling based on the totality of data (PK, safety, efficacy, PD [redacted] for efficacy), using all data from dose escalation and dose expansion, will be conducted to develop robust dose-exposure-response relationships to guide the selection of the combination RP2D (the dose that achieves maximum efficacy with acceptable toxicity in the target AML population).

Sponsor Name: Amgen, Inc.

1.2 Study Schema

Figure 1-1. Overall Study Design and Treatment Schema



AML = acute myeloid leukemia; BIW = twice weekly; MTCD = maximum tolerated combination dose; QW = once weekly; US = United States

[a] Ramp-up dosing in cycle 1 will be utilized whenever the target dose level is at 180 mg/m² or higher. Ramp-up dosing consists of an initial dose at cycle 1 week 1 of 120 mg/m² followed by an increase to the target dose level for subsequent doses.

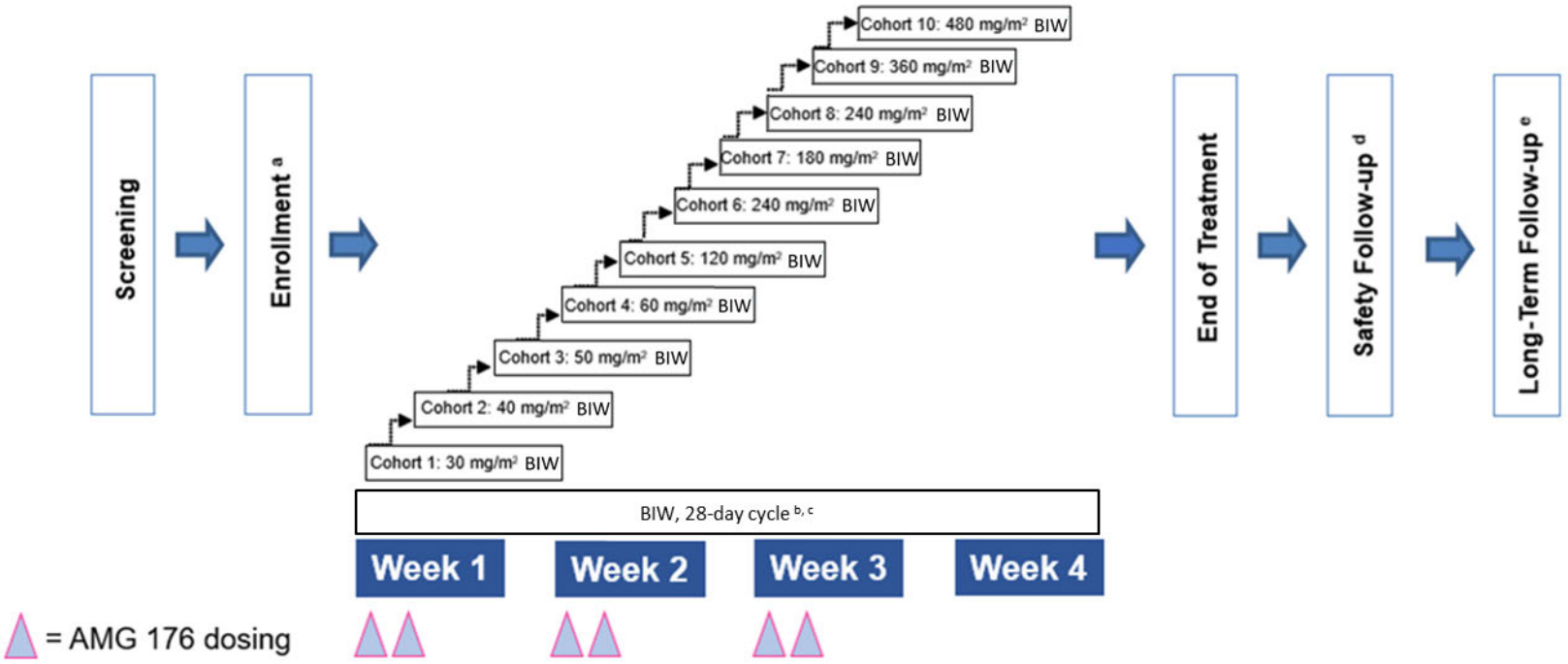
[b] The AMG 176 starting dose level will be 60 mg/m² BIW.

[c] The AMG 176 starting dose level will be 120 mg/m² QW.

[d] The AMG 176 starting dose level was 60 mg/m² QW.

[e] After week 3, subjects may crossover to Part 3b or Part 4 for continued treatment if approved by the investigator and Amgen medical monitor. Subjects from Part 3d who crossover to Part 3b, will not crossover (for the second time) to Part 4.

Figure 1-2. Study Design and Treatment Schema – Multiple Myeloma Part 1a AMG 176 BIW Monotherapy Dose Escalation (CLOSED TO ENROLLMENT)



BIW = twice weekly; IV = intravenous; MTD = maximum tolerated dose.

[a] Enrolled 36 subjects. A standard 3+3 design will be used to identify the MTD or recommended dose.

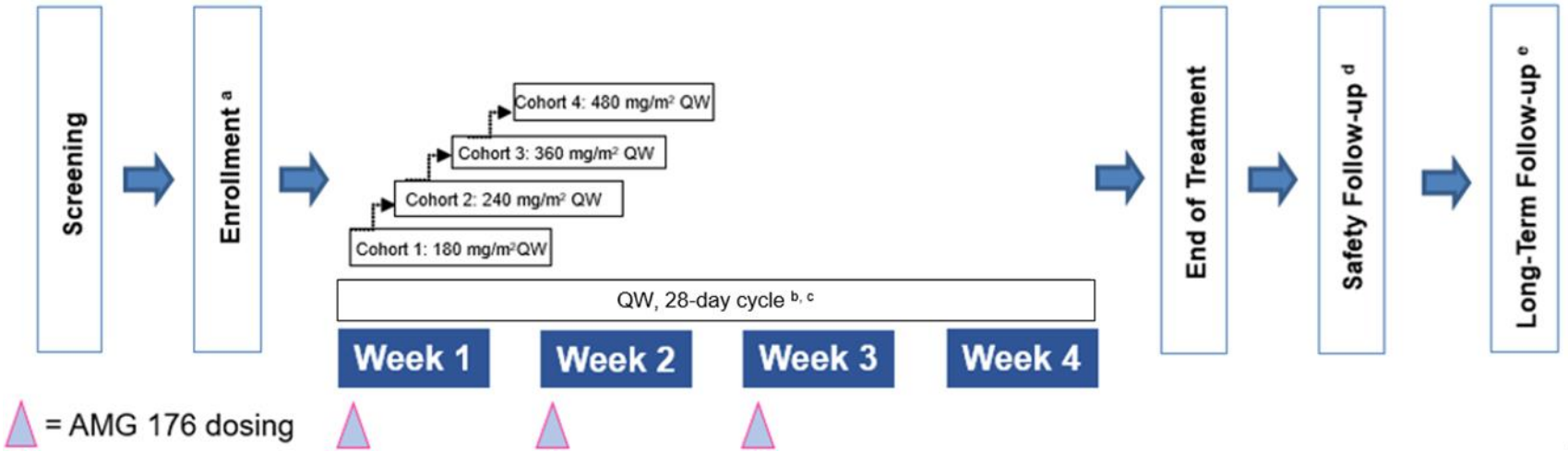
[b] Ramp-up dosing in cycle 1 will be utilized whenever the target dose level is at 180 mg/m² or higher (cohort 7 or higher). Ramp-up dosing consists of an initial dose at cycle 1 week 1 of 120 mg/m^2 followed by an increase to the target dose level for subsequent doses.

[c] AMG 176 will be administered in monthly cycles of treatment. Each cycle AMG 176 BIW is defined as an IV infusion once daily for two consecutive days followed by a 5-day break and repeated each week for 3 weeks followed by one week with no treatment.

[d] A safety follow-up visit will take place 30 days (+3 days) after the last dose of protocol-required therapies.

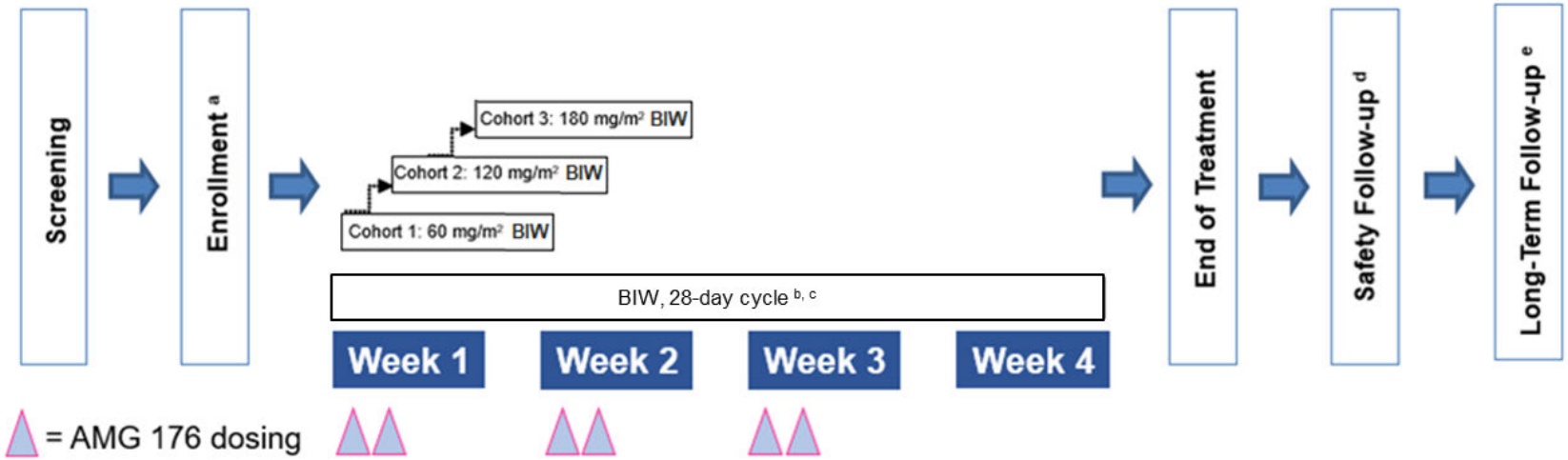
[e] Long-term follow-up assessments will occur every 3 months (± 14 days) after end of treatment (EOT) for 1 year.

Figure 1-3. Study Design and Treatment Schema – Multiple Myeloma Part 1b AMG 176 QW Monotherapy Dose Escalation (CLOSED TO ENROLLMENT)



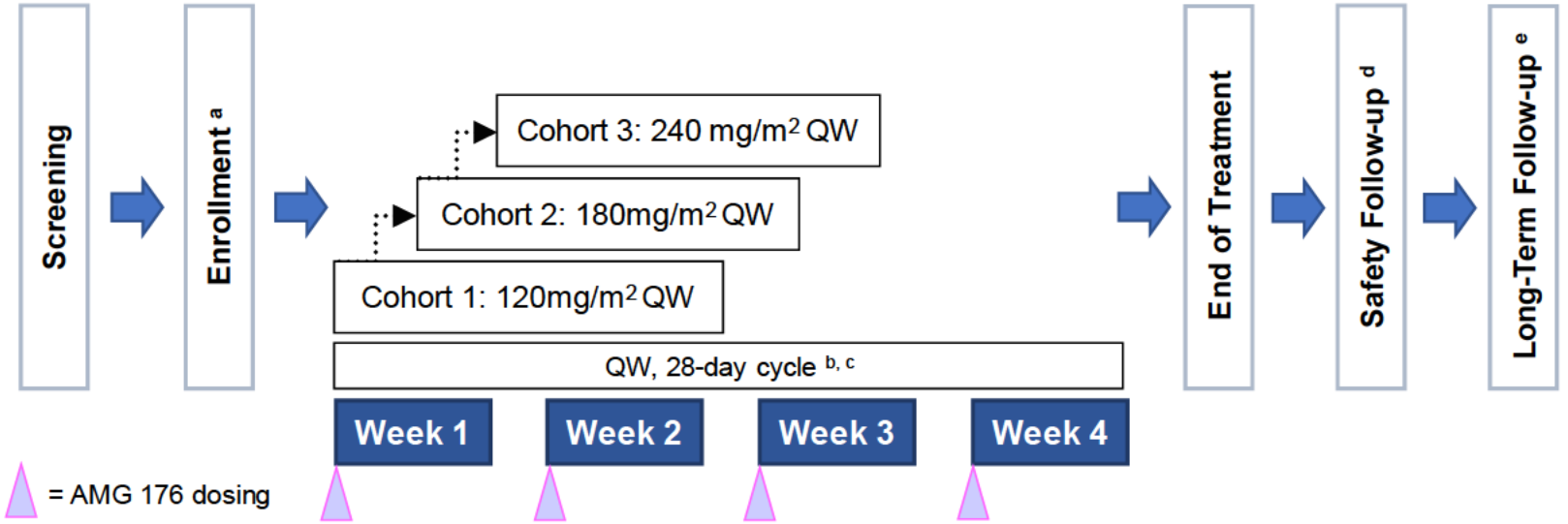
IV = intravenous; MTD = maximum tolerated dose; QW = once weekly.
[a] Enrolled 12 subjects. A standard 3+3 design will be used to identify the MTD or recommended dose.
[b] The starting dose level will be 180 mg/m^2 QW. AMG 176 will be administered in monthly cycles of treatment. Each cycle AMG 176 QW is defined as an IV infusion once weekly followed by a 6-day break and repeated each week for 3 weeks followed by one week with no treatment.
[c] Ramp-up dosing in cycle 1 will be utilized whenever the target dose level is at 180 mg/m^2 or higher. Ramp-up dosing consists of an initial dose at cycle 1 week 1 of 120 mg/m^2 followed by an increase to the target dose level for subsequent doses.
[d] A safety follow-up visit will take place 30 days (+3 days) after the last dose of protocol-required therapies.
[e] Long-term follow-up assessments will occur every 3 months (± 14 days) after end of treatment (EOT) for 1 year.

Figure 1-4. Study Design and Treatment Schema – Acute Myeloid Leukemia Part 3a AMG 176 BIW Monotherapy Dose Escalation (CLOSED TO ENROLLMENT)



BIW = twice weekly; IV = intravenous
[a] Enrolled 17 subjects. A standard 3+3 design will be used to identify the maximum tolerated dose.
[b] The starting dose level will be 60 mg/m^2 BIW. AMG 176 will be administered in monthly cycles of treatment. Each cycle AMG 176 BIW is defined as an IV infusion once daily for two consecutive days followed by a 5-day break and repeated each week for 3 weeks followed by one week with no treatment.
[c] Ramp-up dosing in cycle 1 will be utilized whenever the target dose level is at 180 mg/m^2 or higher. Ramp-up dosing consists of an initial dose at cycle 1 week 1 of 120 mg/m^2 followed by an increase to the target dose level for subsequent doses.
[d] A safety follow-up visit will take place 30 days (+3 days) after the last dose of protocol-required therapies.
[e] Long-term follow-up assessments will occur every 3 months (± 14 days) after end of treatment (EOT) for 1 year.

Figure 1-5. Study Design and Treatment Schema – Acute Myeloid Leukemia Part 3b AMG 176 QW Monotherapy Dose Escalation (CLOSED TO ENROLLMENT)



IV = intravenous; mTPI = modified toxicity probability interval; PD = pharmacodynamics; PK = pharmacokinetics; QW = once weekly

[a] Enrolled 11 subjects. An mTPI design will be used to evaluate the safety, tolerability, PK, and PD.

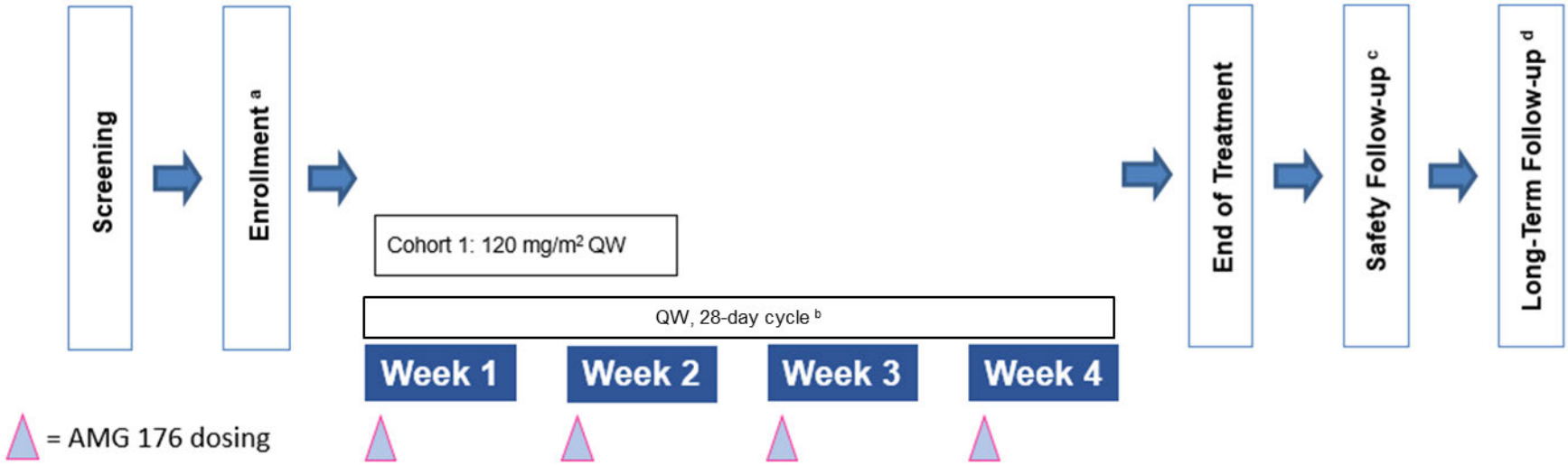
[b] Ramp-up dosing in cycle 1 will be utilized whenever the target dose level is at 180 mg/m² or higher (cohorts 2 and 3). Ramp-up dosing consists of an initial dose at cycle 1 week 1 of 120 mg/m² followed by an increase to the target dose level for subsequent doses.

[c] The starting dose level will be 120 mg/m² QW. AMG 176 will be administered in monthly cycles of treatment. Each cycle AMG 176 QW is defined as an IV infusion once weekly followed by a 6-day break and repeated each week for 4 consecutive weeks.

[d] A safety follow-up visit will take place 30 days (+3 days) after the last dose of protocol-required therapies.

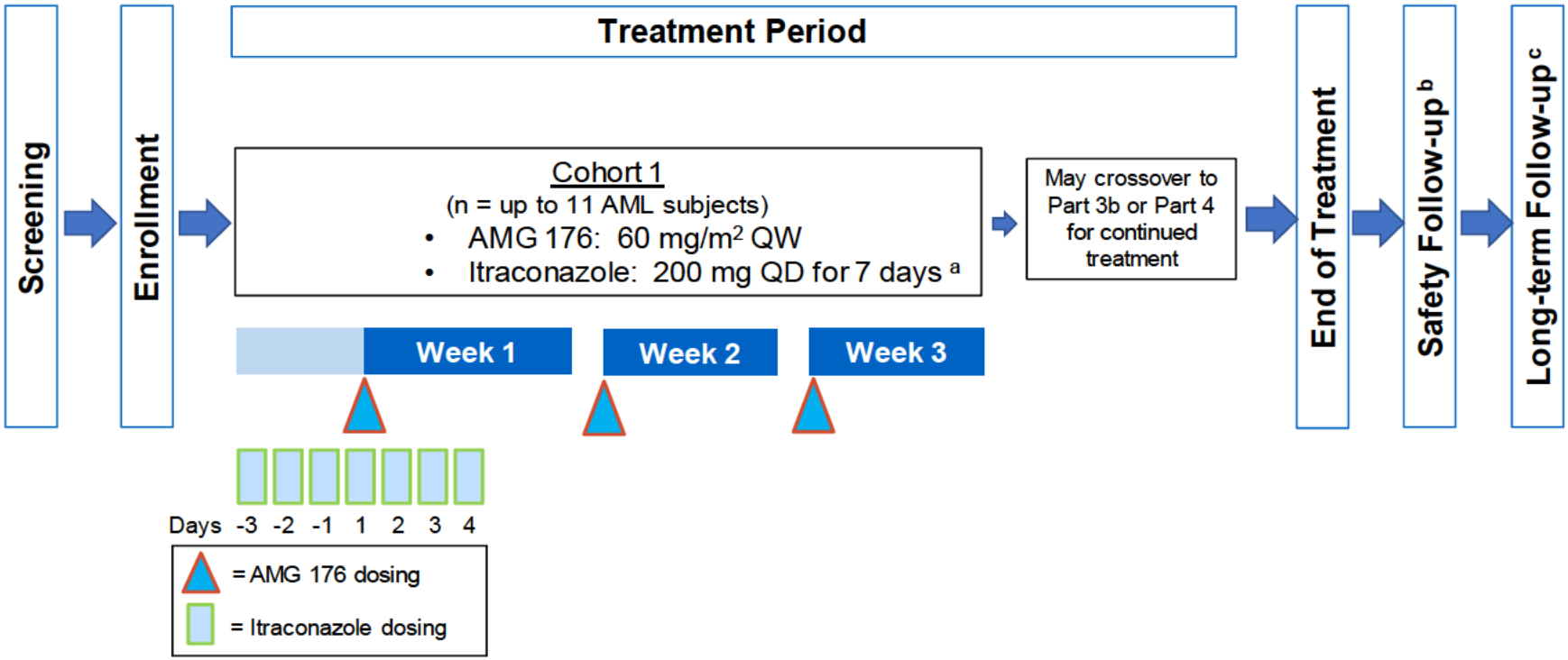
[e] Long-term follow-up assessments will occur every 3 months (± 14 days) after end of treatment (EOT) for 1 year.

Figure 1-6. Study Design and Treatment Schema – Acute Myeloid Leukemia Part 3c AMG 176 QW Monotherapy Dose Escalation in Japan (COMPLETED)



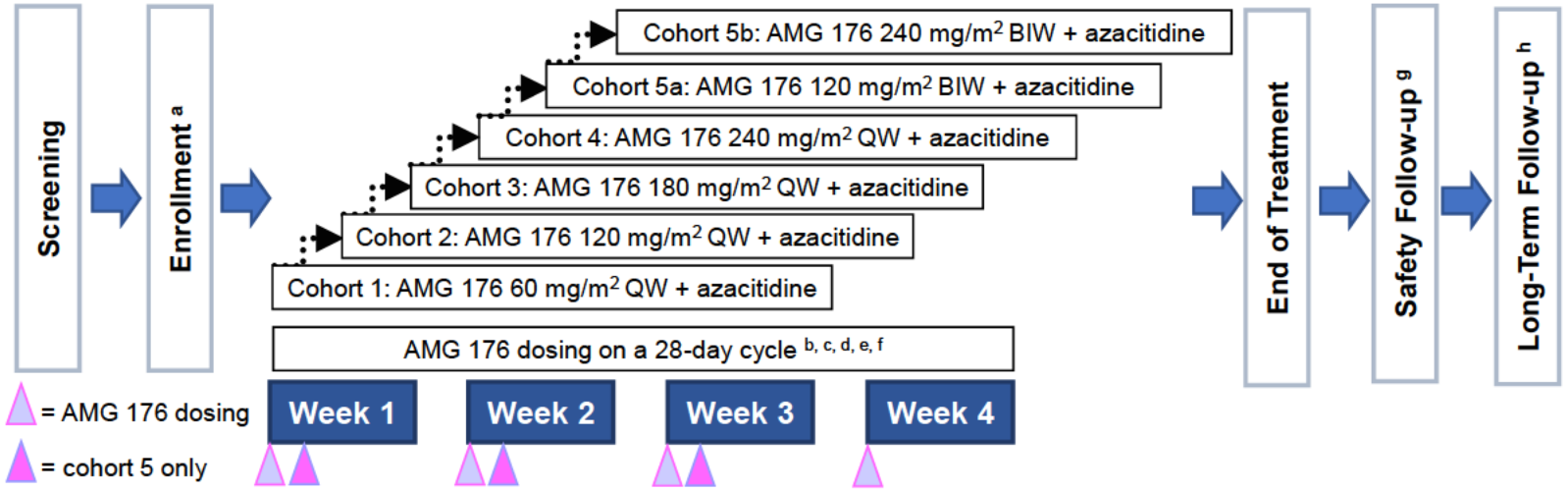
IV = intravenous; PD = pharmacodynamics; PK = pharmacokinetics; QW = once weekly
[a] Enrolled 4 subjects. A standard 3+3 design without dose escalation will be used to evaluate the safety, tolerability, PK, and PD of AMG 176 administered QW in AML subjects in Japan.
[b] AMG 176 will be administered in monthly cycles of treatment. Each cycle AMG 176 QW is defined as an IV infusion once weekly followed by a 6-day break and repeated each week for 4 consecutive weeks.
[c] A safety follow-up visit will take place 30 days (+3 days) after the last dose of protocol-required therapies.
[d] Long-term follow-up assessments will occur every 3 (± 14 days) months after end of treatment (EOT) for 1 year.

Figure 1-7. Study Design and Treatment Schema – Acute Myeloid Leukemia Part 3d – DDI Assessment With Itraconazole in the United States



DDI = drug-drug interaction; PK = pharmacokinetics; QD = once daily; QW = once weekly
[a] Oral itraconazole capsules (200 mg) QD starting at 8 am on day -3 through day 4 (total of 7 days) to achieve adequate cytochrome P450 3A4 (CYP3A4) inhibition prior to, and following, AMG 176 administration. The DDI assessment may be modified or discontinued as safety and PK data emerge.
[b] A safety follow-up visit will take place 30 days (+3 days) after the last dose of AMG 176.
[c] Long-term follow-up assessments will occur every 3 months (± 14 days) after end of treatment for 1 year.

Figure 1-8. Study Design and Treatment Schema – Acute Myeloid Leukemia Part 4 AMG 176 QW and BIW in Combination With Azacitidine (DOSE EXPLORATION)



BIW = twice weekly; IV = intravenous; MTCD = maximum tolerated combination dose; mTPI = modified toxicity probability interval; QW = once weekly; RP2D = recommended phase 2 dose; SC = subcutaneous

[a] Approximately 60 subjects will be enrolled. An mTPI design will be used to define the combination RP2D.

[b] The starting dose level was 60 mg/m^2 QW (NOTE: Lower starting or planned dose levels may be investigated). AMG 176 will be administered in 28-day cycles of treatment. Each cycle AMG 176 QW is defined as an IV infusion once weekly followed by a 6-day break and repeated each week for 4 consecutive weeks.

[c] The BIW dose levels for Cohorts 5a and 5b are 120 mg/m^2 and 240 mg/m^2. (NOTE: Additional cohorts with lower starting or planned dose levels may be investigated, such as 120 mg/m^2). AMG 176 will be administered in monthly cycles of treatment. Each cycle AMG 176 BIW is defined as an IV infusion once daily for 2 consecutive days followed by a 5-day break and repeated each week for 3 weeks followed by one week with no treatment.

[d] Ramp-up dosing in cycle 1 will be utilized whenever the target dose level is at 180 mg/m^2 or higher (cohorts 3, 4, and 5). Ramp-up dosing consists of an initial dose at cycle 1 week 1 of 120 mg/m^2 followed by an increase to the target dose level for subsequent doses.

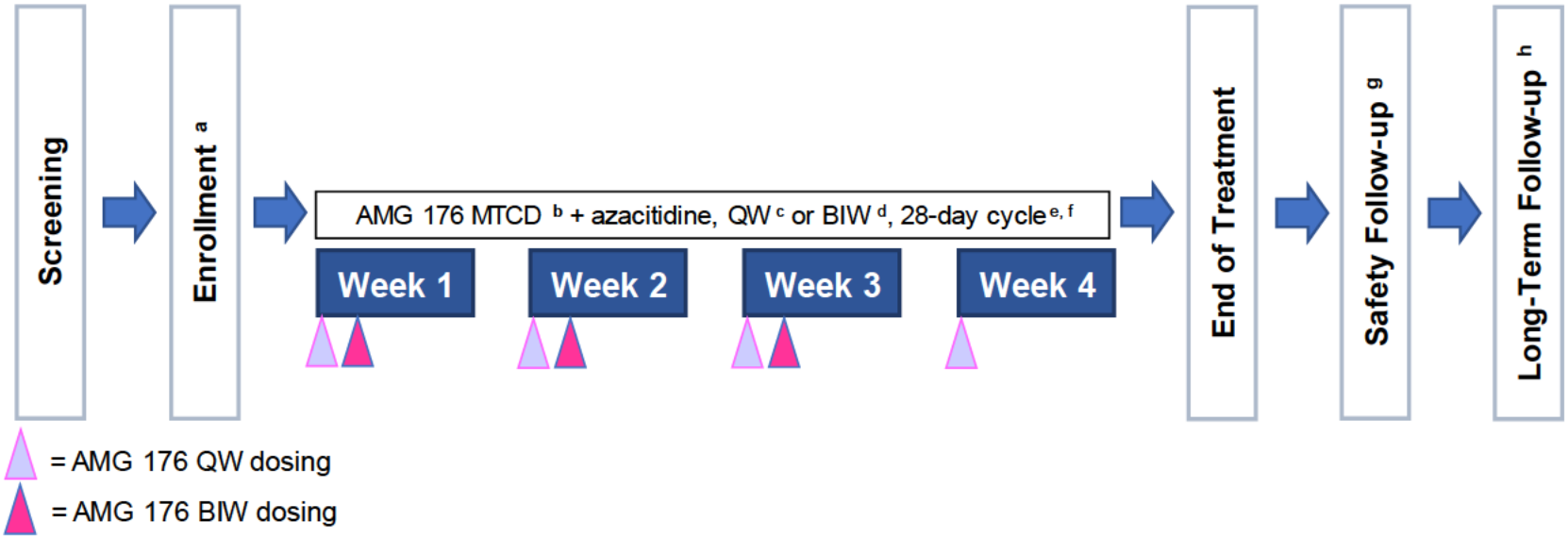
[e] Azacitidine will be administered at a dose of 75 mg/m^2 either IV or SC, as recommended in the prescribing information, daily for the first 7 days of a 28-day cycle.

[f] AMG 176 QW and BIW cohorts may be conducted in parallel.

[g] A safety follow-up visit will take place 30 days (+3 days) after the last dose of AMG 176.

[h] Long-term follow-up assessments will occur every 3 months (± 14 days) after end of treatment (EOT) for 1 year.

Figure 1-9. Study Design and Treatment Schema – Acute Myeloid Leukemia Part 5A AMG 176 QW or BIW in Combination With Azacitidine (DOSE EXPANSION)



BIW = twice weekly; IV = intravenous; MTCD = maximum tolerated combination dose; QW = once weekly; SC = subcutaneous

[a] Approximately 48 subjects will be enrolled for Part 5**A**.

[b] Ramp-up dosing in cycle 1 will be utilized if the MTCD target dose level is at 180 mg/m² or higher. Ramp-up dosing consists of an initial dose at cycle 1 week 1 of 120 mg/m² followed by an increase to the target dose level for subsequent doses.

[c] AMG 176 will be administered in monthly cycles of treatment. Each cycle AMG 176 QW is defined as an IV infusion once weekly followed by a 6-day break and repeated each week for 4 consecutive weeks.

[d] AMG 176 will be administered in monthly cycles of treatment. Each cycle AMG 176 BIW is defined as an IV infusion once daily for two consecutive days followed by a 5-day break and repeated each week for 3 consecutive weeks followed by one week with no treatment.

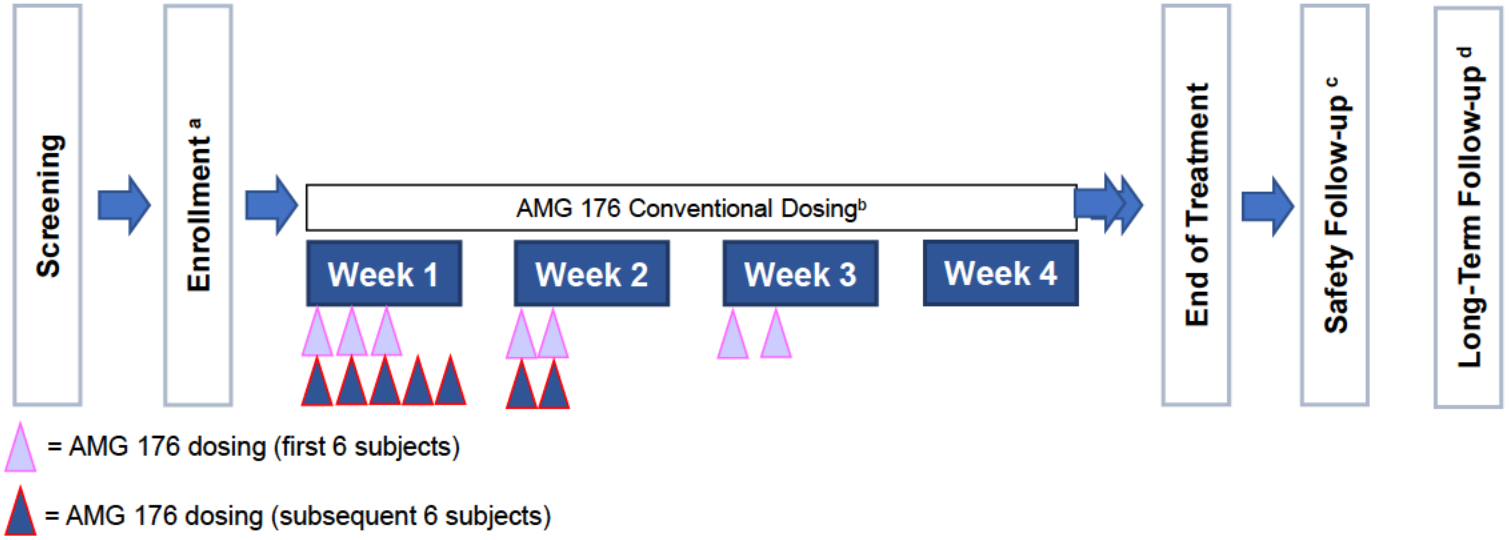
[e] Azacitidine will be administered at a dose of 75 mg/m² either IV or SC, as recommended in the prescribing information, daily for the first 7 days of a 28-day cycle.

[f] AMG 176 QW and BIW cohorts may be conducted in parallel.

[g] A safety follow-up visit will take place 30 days (+3 days) after the last dose of AMG 176.

[h] Long-term follow-up assessments will occur every 3 months (± 14 days) after end of treatment (EOT) for 1 year.

Figure 1-10. Study Design and Treatment Schema – Acute Myeloid Leukemia Part 5B AMG 176 Conventional Dosing



BIW = twice weekly; DLRT = dose-level review team; IV = intravenous
[a] Approximately 20 subjects will be enrolled for Part 5**B**.
[b] AMG 176 is administered as an IV infusion on a 28-day cycle for 3 consecutive days the first week, and BIW on weeks 2 and 3 each cycle of each 28-day cycle in the first 6 subjects (Regimen 1). If this schedule is deemed safe by the DLRT, the next 6 subjects will receive dosing on 5 consecutive days the first week, and BIW in week 2 for each 28-day cycle (Regimen 2). If Regimen 2 is deemed safe by the DLRT, then further enrollment to Part 5**B** may proceed at either Regimen 1 or Regimen 2, as determined by the study team.
[c] A safety follow-up visit will take place 30 days (+3 days) after the last dose of AMG 176.
[d] Long-term follow-up assessments will occur every 3 months (± 14 days) after end of treatment (EOT) for 1 year.

1.3 Schedule of Activities (SoA)

Quick Link	Schedule of Activities	Status
	Part 1a (Multiple Myeloma BIW) and Part 3a (AML BIW)	Closed to Enrollment
Table 1-3	Part 1b (Multiple Myeloma QW),	
	Part 3b (AML QW; Cohorts 1-3 Only), and	
	Part 3c (AML QW in Japan)	
Table 1-4	Part 3d (AML in United States) DDI Assessment with Itraconazole	Open to Enrollment
Table 1-5	Part 4 (Cohorts 1-4 Only) and	
	Part 5**A** (AML) AMG 176 QW in Combination with Azacitidine	
Table 1-6	Part 4 (Cohorts 5a and 5b Only) and	
	Part 5**A** (AML) AMG 176 BIW in Combination with Azacitidine	
Table 1-7	Part 5**B** (AML) Conventional Dosing – Regimen 1	
Table 1-8	Part 5**B** (AML) Conventional Dosing – Regimen 2	
Table 1-9	Schedule of Activities Notes and Abbreviation Definitions	

Table 1-2. Schedule of Activities: Part 1a (Multiple Myeloma BIW) and Part 3a (AML BIW)

	Screen	Treatment																																																
Cycle		**Cycle 1**																																																
Weeks		**W1**																				**W2**																				**W3**								
Days	**D-14 to D-0**	**D1**										**D2**									**D3**	**D8**										**D9**									**D10**	**D15**				**D16**				**D17**
Hours (relative to start of dosing)		**pre-dose**	**0**	**EOI**	**3**	**4**	**5**	**7**	**8**	**12**	**24**	**pre-dose**	**0**	**EOI**	**3**	**4**	**5**	**7**	**8**	**12**	**24h after D2**	**pre-dose**	**0**	**EOI**	**3**	**4**	**5**	**7**	**8**	**12**	**24**	**pre-dose**	**0**	**EOI**	**3**	**4**	**5**	**7**	**8**	**12**	**24h after D9**	**pre-dose**	**0**	**EOI**	**8**	**pre-dose**	**0**	**EOI**	**8**	**24h after D16**
GENERAL AND SAFETY ASSESSMENTS																																																		
Informed consent	X																																																	
Clinical evaluation	X	X										X										X										X										X				X				
Vital signs	X	X		X								X		X								X		X								X		X								X		X		X		X		
12-lead ECG	X	X		X	X		X	X	X		X	X		X			X	X	X		X	X		X	X		X	X	X	X	X	X		X	X		X	X	X	X	X	X		X	X	X		X	X	X
ECHO/MUGA	X																																																	
Hospitalization		Hospitalization days																				Hospitalization days																												
TLS prophylaxis		X										X										X										X																		
Peripheral neuropathy assessment (MM subjects only)	X																																																	
Prior / Conmed reporting	Prior & Concomitant Medication Reporting																																																	
AE / SAE reporting	AE/SAE Reporting																																																	
STUDY TREATMENT																																																		
AMG 176 dosing			X										X										X										X										X				X			
LABORATORY ASSESSMENTS																																																		
Local Labs																																																		
Safety lab tests	X	X										X										X										X										X				X				
TLS monitoring test	X	X		X		X			X	X	X	X		X		X			X	X	X	X		X		X			X	X	X	X		X		X			X	X	X									
Cardiac monitoring test		X							X		X	X							X		X	X							X		X	X							X		X	X			X	X			X	X
Pregnancy test	X	X																																																
Hepatitis serology	X																																																	

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See Table 1-9 or assessment notes and abbreviation definitions.

	Screen	Treatment																																																
Cycle		**Cycle 1**																																																
Weeks		**W1**																				**W2**																				**W3**								
Days	**D-14 to D-0**	**D1**										**D2**									**D3**	**D8**										**D9**									**D10**	**D15**				**D16**				**D17**
Hours (relative to start of dosing)		pre-dose	0	EOI	3	4	5	7	8	12	24	pre-dose	0	EOI	3	4	5	7	8	12	24h after D2	pre-dose	0	EOI	3	4	5	7	8	12	24	pre-dose	0	EOI	3	4	5	7	8	12	24h after D9	pre-dose	0	EOI	8	pre-dose	0	EOI	8	24h after D16
Central Labs																																																		
AMG 176 PK		X		X	X		X	X				X		X			X	X			X	X		X	X		X	X	X	X		X		X	X		X	X	X	X	X	X		X		X		X		
Biomarker - Whole blood NaHep		X		X	X							X										X		X	X							X																		
Biomarker - Whole blood immune cell subsets		X					X					X									X	X					X					X									X	X								
Biomarker - PBMC		X																																							X									
Biomarker - Plasma	X																																																	
Biomarker - Serum	X																																																	
Biomarker - Pharmacogenetics (saliva sample)	X																																																	
Bone marrow aspirate/biospy	X																																																	
DISEASE AND IMAGING ASSESSMENTS																																																		
MM SUBJECTS ONLY																																																		
SPEP/UPEP/ Immunofixation	X																																																	
SFLC	X																																																	
Quantitative Ig	X																																																	
Beta-2 microglobulin	X																																																	
Bone marrow biopsy/aspirate	X																																																	
Plasmacytoma survey	X																																																	
Skeletal survey	X																																																	
AML SUBJECTS ONLY																																																		
Bone marrow aspirate/biopsy	X																																																	
Peripheral blood count	X	X																				X																				X								

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See Table 1-9 for assessment notes and abbreviation definitions.

	TREATMENT																												
Cycles (every 28 days)	**Cycle 2-4**														**≥ Cycle 5**														
Weeks	**W5-16**														**Q4W**														
Days	**D1**			**D2**			**D3**	**D8&15**			**D9&16**			**D10&17**	**D1**		**D2**		**D3**	**D8&15**		**D9&16**		**D10&17**		**EOT**	**SFU**	**LTFU/EOS**	
Hours (relative to start of dosing)	**pre-dose**	**0**	**EOI**	**pre-dose**	**0**	**EOI**	**24h after D2**	**pre-dose**	**0**	**EOI**	**pre-dose**	**0**	**EOI**	**24h after D9 & D16**	**pre-dose**	**0**	**pre-dose**	**0**	**24h after D2**	**pre-dose**	**0**	**pre-dose**	**0**	**24h after D9 & D16**					
GENERAL ASSESSMENTS																													
Clinical evaluation	X			X				X			X				X		X			X		X			X	X		
Vital signs	X		X	X		X	X	X		X	X		X		X		X		X	X		X			X	X		
12-lead ECG	X		X	X		X	X	X		X	X		X	X	X		X		X	X		X		X	X	X		
ECHO/MUGA																									X		X		
Peripheral neuropathy assessment (MM subjects only)																										X			
Conmed reporting	Concomitant Medication Reporting																												
AE / SAE reporting	AE & SAE Reporting																											X	
Subsequent anti-cancer therapy & Survival																												X	
STUDY TREATMENT																													
AMG 176 dosing		X			X				X			X				X		X			X		X						
LABORATORY ASSESSMENTS																													
Local Labs																													
Safety lab tests	X			X				X			X				X		X			X		X			X	X		
Cardiac monitoring test	X			X			X	X			X			X	X		X		X	X		X		X	X	X		
Pregnancy test	X														X										X	X		

See Table 1-9 for assessment notes and abbreviation definitions.

	Treatment																													
Cycles (every 28 days)	**Cycle 2-4**														**≥ Cycle 5**														
Weeks	**W5-16**														**Q4W**														
Days	**D1**			**D2**			**D3**	**D8&15**			**D9&16**			**D10&17**	**D1**		**D2**		**D3**	**D8&15**		**D9&16**		**D10&17**		**EOT**	**SFU**	**LTFU/EOS**		
Hours (relative to start of dosing)	pre-dose	0	EOI	pre-dose	0	EOI	24h after D2	pre-dose	0	EOI	pre-dose	0	EOI	24h after D9 & D16	pre-dose	0	pre-dose	0	24h after D2	pre-dose	0	pre-dose	0	24h after D9 & D16					
Central Labs																														
AMG 176 PK	X		X	X		X		X		X	X		X																	
Biomarker PBMC	X																									X				
Part 3a: Biomarker bone marrow/aspirate	C2D1, C3D1, and thereafter prior to every other cycle or when clinically indicated until disease progression and to confirm CR and MRD status																													
DISEASE AND IMAGING ASSESSMENTS																														
MM SUBJECTS ONLY																														
SPEP/UPEP/ Immunofixation	Every 28 days (± 7 days) until confirmed progressive disease irrespective of cycle duration including dose delays and treatment discontinuation. For subjects who do not progress during treatment, continue to be measure every 28 days (± 7 days) until progressive disease																									X				
SFLC																										X				
Quantitative Ig																										X				
Beta-2 microglobulin																										X				
Bone marrow aspirate/biopsy	Repeat to confirm CR and MRD status																													
Plasmacytoma survey	Repeat to confirm PR or better, PD, or as clinically indicated																													
Skeletal survey	Repeat if PD suspected or as clinically indicated																													
AML SUBJECTS ONLY																														
Bone marrow aspirate/biopsy	C2D1, C3D1, and thereafter prior to every other cycle or when clinically indicated until disease progression and to confirm CR and MRD status																													
Peripheral blood count	X							X							X					X					X				
Overall disease response	Assessed and documented at every cycle and at time of PD																													

See Table 1-9 for assessment notes and abbreviation definitions.

Table 1-3. Schedule of Activities: Part 1b (Multiple Myeloma QW), Part 3b (AML QW; Cohorts 1-3 Only), and Part 3c (AML QW in Japan)

	Screen	Treatment																												
Cycle		Cycle 1																												
Study Part		Parts 1b, 3b, and 3c																										Parts 3b and 3c		
Weeks		W1									W2										W3					W4				
Days	D-14 to D-0	D1								D2	D8									D9	D15				D16	D22				D23
Hours (relative to start of dosing)		pre-dose	0	EOI	3	4	5	7	8	12	24h after D1	pre-dose	0	EOI	3	4	5	7	8	12	24h after D8	pre-dose	0	EOI	8	24h after D15	pre-dose	0	EOI	8	24h after D22
GENERAL ASSESSMENTS																															
Informed consent	X																														
Clinical evaluation	X	X									X	X										X					X				
Vital signs	X	X		X							X	X		X								X		X			X		X		
12-lead ECG	X	X		X	X		X	X	X		X	X		X	X		X	X	X	X	X	X		X	X	X	X		X	X	X
ECHO/MUGA	X																														
Part 1b, 3b: Hospitalization		Hospitalization										Hospitalization																			
Part 3c: Hospitalization		Hospitalization																													
TLS prophylaxis		X										X																			
Peripheral neuropathy assessment (MM subjects only)	X																														
Prior / Conmeds reporting		Prior & Concomitant Medications Reporting																													
AE & SAE reporting		AE & SAE Reporting																													
STUDY TREATMENT																															
AMG 176 dosing			X										X										X					X			
LABORATORY ASSESSMENTS																															
Local Labs																															
Safety lab tests	X	X										X										X					X				
TLS monitoring test		X		X		X			X	X	X	X		X		X			X	X	X	X				X	X				X
Cardiac monitoring tests	X	X							X		X	X							X		X	X			X	X	X			X	X
Pregnancy test	X	X																													
Hepatitis serology	X																														

See Table 1-9 for assessment notes and abbreviation definitions.

Table 1-3. Schedule of Activities: Part 1b (Multiple Myeloma QW), Part 3b (AML QW; Cohorts 1-3 Only), and Part 3c (AML QW in Japan)

	Screen	Treatment																												
Cycle		Cycle 1																												
Study Part		Parts 1b, 3b, and 3c																										Parts 3b and 3c		
Weeks		W1									W2									W3					W4				
Days	D-14 to D-0	D1								D2	D8								D9	D15				D16	D22				D23
Hours (relative to start of dosing)		pre-dose	0	EOI	3	4	5	7	8	12	24h after D1	pre-dose	0	EOI	3	4	5	7	8	12	24h after D8	pre-dose	0	EOI	8	24h after D15	pre-dose	0	EOI	8	24h after D22
Central Labs																														
AMG 176 PK		X		X	X		X	X	X		X	X		X	X		X	X	X	X	X	X		X	X	X	X		X	X	X
Biomarker - Whole blood NaHep		X		X	X						X	X		X	X						X										
Biomarker - Whole blood immune cell subsets		X					X				X	X					X				X	X									
Biomarker - PBMC		X										X									X										
Biomarker - Plasma	X																														
Biomarker - Serum	X																														
Biomarker - Pharmacogenetics (saliva sample) - Part 1b and 3b only	X																														
Biomarker bone marrow aspirate/biopsy	X																														
DISEASE AND IMAGING ASSESSMENTS																														
MM SUBJECTS ONLY																														
SPEP/UPEP/ Immunofixation	X																														
SFLC	X																														
Quantitative Ig	X																														
Beta-2 microglobulin	X																														
Bone marrow aspirate/biopsy	X																														
Plasmacytoma survey	X																														
Skeletal survey	X																														
AML SUBJECTS ONLY																														
Bone marrow aspirate/biopsy	X																														
Peripheral blood count	X	X										X										X					X				

See Table 1-9 for assessment notes and abbreviation definitions.

Table 1-3. Schedule of Activities: Part 1b (Multiple Myeloma QW), Part 3b (AML QW; Cohorts 1-3 Only), and Part 3c (AML QW in Japan)

	Treatment																													
Cycles (every 28 days)	Cycle 2 - 4											≥Cycle 5																		
Study Part	Parts 1b, 3b, and 3c								Parts 3b and 3c			Parts 1b, 3b, and 3c											Parts 3b and 3c							
Weeks	W5-16											Q4W																		
Days	D1			D2	D8&15		D9	D16	D22		D23	D1		D2	D8		D15		D9	D16	D22		D23							
Hours (relative to start of dosing)	pre-dose	0	EOI	24 h after D1	pre-dose	0	24 h after D8	24 h after D15	pre-dose	0	24 h after D22	pre-dose	0	24 h after D1	pre-dose	0	pre-dose	0	24 h after D8	24 h after D15	pre-dose	0	24 h after D22	EOT	SFU	LTFU/EOS				
GENERAL AND SAFETY ASSESSMENT																														
Clinical evaluation	X				X				X			X			X		X				X			X	X				
Vital signs	X		X		X				X			X			X		X				X			X	X				
12-lead ECG	X		X	X	X		X	X	X		X	X		X	X		X		X	X	X		X	X	X				
ECHO/MUGA																								X		X			
Peripheral neuropathy assessment (MM subjects only)																									X				
Part 3b: Patient interview substudy	X																												
Conmeds reporting	Concomitant Medications Reporting																												
AE / SAE Reporting	AE & SAE Reporting																									X			
Subsequent anti-cancer therapy & Survival																										X			
STUDY TREATMENT																													
AMG 176 dosing		X				X				X			X			X		X				X							
LABORATORY ASSESSMENTS																													
Local Labs																													
Safety lab tests	X				X				X			X			X		X				X			X	X				
Cardiac monitoring tests	X			X	X		X	X	X		X	X		X	X		X		X	X	X		X	X	X				
Pregnancy test	X											X												X	X				

See Table 1-9 for assessment notes and abbreviation definitions.

Table 1-3. Schedule of Activities: Part 1b (Multiple Myeloma QW), Part 3b (AML QW; Cohorts 1-3 Only), and Part 3c (AML QW in Japan)

	Treatment																							EOT	SFU	LTFU/EOS
Cycles (every 28 days)	Cycle 2 - 4											≥Cycle 5														
Study Part	Parts 1b, 3b, and 3c								Parts 3b and 3c			Parts 1b, 3b, and 3c									Parts 3b and 3c					
Weeks	W5-16											Q4W														
Days	D1			D2	D8&15		D9	D16	D22		D23	D1		D2	D8		D15		D9	D16	D22		D23			
Hours (relative to start of dosing)	pre-dose	0	EOI	24 h after D1	pre-dose	0	24 h after D8	24 h after D15	pre-dose	0	24 h after D22	pre-dose	0	24 h after D1	pre-dose	0	pre-dose	0	24 h after D8	24 h after D15	pre-dose	0	24 h after D22			
Central Labs																										
AMG 176 PK	X		X	X																						
Biomarker - PBMC	X																							X		
Parts 3b, 3c: Biomarker bone marrow aspirate/biopsy	C2D1, C3D1, and thereafter prior to every other cycle or when clinically indicated until disease progression and to confirm CR and MRD status																									
DISEASE AND IMAGING ASSESSMENTS																										
MM SUBJECTS ONLY																										
SPEP/UPEP/ Immunofixation	Every 28 days (± 7 days) until confirmed progressive disease irrespective of cycle duration including dose delays and treatment discontinuation. For subjects who do not progress during treatment, continue to be measure every 28 days (± 7 days) until progressive disease																							X		
SFLC																								X		
Quantitative Ig																								X		
Beta-2 microglobulin																								X		
Bone marrow aspirate/biopsy	Repeat to confirm CR and MRD status																									
Plasmacytoma survey	Repeat to confirm PR or better, PD, or as clinically indicated																									
Skeletal survey	Repeat if PD suspected or as clinically indicated																									
AML SUBJECTS ONLY																										
Bone marrow aspirate/biopsy	C2D1, C3D1, and thereafter prior to every other cycle or when clinically indicated until disease progression and to confirm CR and MRD status																									
Peripheral blood count	X				X				X			X			X		X				X			X		
Overall disease response	Assessed and documented at every cycle and at time of PD																									

See Table 1-9 for assessment notes and abbreviation definitions.

Table 1-4. Schedule of Activities: Part 3d (AML in United States) DDI Assessment With Itraconazole

	Screen	Treatment																																For subjects that do not crossover		
Cycle		Cycle 1																															*Cycle ≥ 2*			
Weeks		W1														W2									W3								W4	*Week ≥ 5*			
Days	D-17 to D-3	D-3	D-2	D-1	D1									D2	D3	D4	D8								D9	D15							D16	D17	D22				
Hours (relative to start of dosing)					pre-dose	0	EOI	3	4	5	7	8	12	24h after D1	48h after D1	72h after D1	pre-dose	0	EOI	3	5	7	8	12	24h after D8	pre-dose	0	EOI	3	5	7	8	24h after D15	48h after D15	168h after D15	EOT	SFU	LTFU / EOS
GENERAL AND SAFETY ASSESSMENT																																					
Informed consent	X																																				
Clinical evaluation	X				X									X			X									X									X	X	
Vital signs	X				X		X							X			X		X	X	X	X		X		X		X							X	X	
12-lead ECG	X				X		X	X		X	X	X		X			X		X				X		X		X	X	X	X	X	X			X	X	
ECHO/MUGA	X																																			X		X
Hospitalization					Hospitalization												Hospitalization																					
TLS prophylaxis					X												X																				
Prior / Concomitant medication reporting		X		X			X																													X		
Adverse event reporting		X		X																																X		
Serious adverse event reporting		X		X																																	X	
STUDY TREATMENT																																					
AMG 176 dosing						X												X									X										
Itraconazole dosing		X	X	X		X								X	X	X																					
LABORATORY ASSESSMENTS																																					
Local Labs																																					
Safety lab tests	X				X												X									X									X	X	
TLS test monitoring					X		X		X			X	X	X			X		X				X	X	X	X							X					
Cardiac monitoring tests	X				X							X		X			X						X		X	X						X	X		X	X	
Pregnancy test	X				X																															X	X	
Hepatitis serology	X																																				
Central Labs																																					
AMG 176 PK					X		X	X		X	X	X	X	X	X		X		X				X		X	X		X	X	X	X	X	X	X	X			
Bone marrow aspirate/biopsy	X																																				
[redacted]																																					
DISEASE ASSESSMENTS																																					
Bone marrow aspirate/biopsy	X																																			X		
Peripheral blood count	X				X												X									X									X		

For subjects that crossover: Follow time points and assessments in Table 1-5 or Table 1-6, as applicable to crossover, starting after Week 3. (*Note: the AMG 176 PK sample must be collected 168 hours after the day 15 dose as part of Part 3d*).

See Table 1-9 for assessment notes and abbreviation definitions.

Table 1-5. Schedule of Activities: Parts 4 (Cohorts 1-4 Only) and 5A (AML) AMG 176 QW in Combination With Azacitidine

Note: Timepoints shown in the schedule of activities are relative to start of dosing of the corresponding treatment: AMG 176 or azacitidine.

	Screen	Treatment																																				
Cycle		Cycle 1																																				
Weeks		1													2											3				4								
Days	D-14 to D0	D1												D2	D3-7	D8									D9	D15				D16	D22					D23		
Hours (relative to start of dosing)		pre-dose	0	5m	EOI	1	2	3	4	5	7	8	12	24h after D1		pre-dose	0	EOI	3	4	5	7	8	12	24h after D8	pre-dose	0	EOI	8	24h after D15	pre-dose	0	EOI	8	24h after D22			
GENERAL AND SAFETY ASSESSMENT																																						
Informed consent	X																																					
Clinical evaluation	X	X												X		X										X					X							
Vital signs	X	X			X									X		X		X								X		X			X		X				
12-lead ECG	X	X			X			X		X	X	X		X		X		X	X		X	X	X	X	X	X		X	X	X	X		X		X	X	X
ECHO/MUGA	X																												X								
Hospitalization		Hospitalization														Hospitalization																						
TLS prophylaxis		X														X																						
Prior / Conmeds reporting		Prior & Concomitant Medications Reporting																																				
AE / SAE reporting		AE & SAE Reporting																																				
STUDY TREATMENT																																						
AMG 176 dosing			X														X										X					X						
Azacitidine dosing			X											X	X																							
LABORATORY ASSESSMENTS																																						
Local Labs																																						
Safety lab tests	X	X														X										X					X							
TLS test monitoring		X			X				X			X	X	X		X		X					X	X	X				X	X							X
Cardiac monitoring tests	X	X										X		X		X							X		X	X			X	X	X			X			X
Pregnancy test	X	X																																				
Hepatitis serology	X																																					

See Table 1-9 for assessment notes and abbreviation definitions.

Table 1-5. Schedule of Activities: Parts 4 (Cohorts 1-4 Only) and 5A (AML) AMG 176 QW in Combination With Azacitidine

Note: Timepoints shown in the schedule of activities are relative to start of dosing of the corresponding treatment: AMG 176 or azacitidine.

	Screen	Treatment																																
Cycle		Cycle 1																																
Weeks		W1													W2										W3					W4				
Days	D-14 to D-0	D1											D2	D3-7	D8									D9	D15				D16	D22				D23
Hours (relative to start of dosing)		pre-dose	0	5m	EOI	1	2	3	4	5	7	8	12	24h after D1		pre-dose	0	EOI	3	4	5	7	8	12	24h after D8	pre-dose	0	EOI	8	24h after D15	pre-dose	0	EOI	8	24h after D22
Central Labs																																		
Azacitidine PK		X		X	X	X	X		X			X				X		X	X		X	X	X	X	X	X		X	X	X	X		X	X	X
AMG 176 PK		X			X			X		X	X	X		X		X		X	X		X	X	X	X	X	X		X	X	X	X		X	X	X
Biomarker bone marrow aspirate/biopsy	X																																	
Biomarker - Whole blood NaHep	X	X			X			X						X		X		X	X						X										
Biomarker - Whole blood immune cell subsets		X								X				X		X						X			X	X									
Biomarker - PBMC		X														X									X										
Biomarker - Plasma	X																																		
Biomarker - Serum	X																																		
Biomarker - Pharmacogenetics (saliva sample)	X																																		
DISEASE ASSESSMENTS																																			
Bone marrow aspirate/biopsy	X																																		
Peripheral blood count	X	X														X										X					X				

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See Table 1-9 for assessment notes and abbreviation definitions.

Table 1-5. Schedule of Activities: Parts 4 (Cohorts 1-4 Only) and 5A (AML) AMG 176 QW in Combination With Azacitidine

	Treatment																														
Cycles (every 28 days)	**Cycle 2**								**Cycle 3-4**								**Cycle 5 and Beyond**														
Weeks	**5-8**								**9-16**								**Q4W**														
Days	**D1**			**D2,9,16&23**	**D3-7**	**D8,15&22**			**D1**			**D2,9,16&23**	**D3-7**	**D8,15&22**			**D1**		**D2,9,16&23**	**D3-7**	**D8,15&22**				**EOT**	**SFU**	**LTFU/EOS**				
Hours (relative to start of dosing)	**pre-dose**	**0**	**EOI**	**24 h after dose**		**pre-dose**	**0**	**EOI**	**pre-dose**	**0**	**EOI**	**24 h after dose**		**pre-dose**	**0**	**EOI**	**pre-dose**	**0**	**24 h after dose**		**pre-dose**	**0**	**EOI**								
GENERAL AND SAFETY ASSESSMENT																															
Clinical evaluation	X					X			X					X			X				X				X	X					
Vital signs	X		X			X		X	X		X			X		X	X				X				X	X					
12-lead ECG	X		X	X		X			X		X	X		X			X		X		X				X	X					
ECHO/MUGA																X									X		X				
Patient interview substudy	X																														
Conmed reporting	Concomitant Medication Reporting																														
AE & SAE reporting	AE & SAE Reporting																														X
Subsequent anti-cancer therapy & Survival																															X
STUDY TREATMENT																															
AMG 176 dosing		X					X			X					X			X					X								
Azacitidine dosing		X		D2	X					X		D2	X					X	D2	X										
LABORATORY ASSESSMENTS																															
Local Labs																															
Safety lab tests	X					X			X					X			X				X				X	X					
Cardiac monitoring tests	X			X		X			X			X		X			X		X		X				X	X					
Pregnancy test	X								X								X								X	X					
Central Labs																															
AMG 176 PK	X		X	D2					X		X	D2																			
[redacted]	[redacted]																									X					
Bone marrow aspirate/biospy	C2D1, C3D1, and thereafter prior to every other cycle or when clinically indicated until disease progression and to confirm CR and MRD status																														
DISEASE ASSESSMENTS																															
Bone marrow aspirate/biopsy	C2D1, C3D1, and thereafter prior to every other cycle or when clinically indicated until disease progression and to confirm CR and MRD status																														
Peripheral blood counts	X					X			X					X			X				X				X						
Overall disease response	Assessed and documented at every cycle and at time of PD																														

See Table 1-9 for assessment notes and abbreviation definitions.

Table 1-6. Schedule of Activities: Parts 4 (Cohorts 5a and 5b Only) and 5A (AML) AMG 176 BIW in Combination With Azacitidine

	Screen	Treatment																																																								
Cycle		Cycle 1																																																							
Weeks		W1																			W2																			W3									W4								
Days	D-14 to D0	D1									D2									D3	D4-7	D8									D9									D10	D15				D16				D17	D22				D23				D24
Hours (relative to start of dosing)		pre-dose	0	EOI	3	4	5	7	8	12	24h after D1/ pre-dose	0	EOI	3	4	5	7	8	12	24h after D2		pre-dose	0	EOI	3	4	5	7	8	12	24h after D8/ pre-dose	0	EOI	3	4	5	7	8	12	24h after D9	pre-dose	0	EOI	8	pre-dose	0	EOI	8	24h after D16	pre-dose	0	EOI	8	pre-dose	0	EOI	8	24h after D23
GENERAL AND SAFETY ASSESSMENTS																																																									
Informed consent	X																																																								
Randomization (Part 5a only)																																																	X								
Clinical evaluation	X	X									X											X									X										X				X					X				X				
Vital signs	X	X		X							X		X									X		X							X		X								X		X		X		X			X		X		X		X		
12-lead ECG	X	X		X	X		X	X	X		X		X			X	X	X		X	X	X		X	X		X	X	X	X	X		X	X		X	X	X	X	X	X		X	X	X		X	X	X	X		X	X	X		X	X	X
ECHO/MUGA	X																																											X									X					
Hospitalization		Hospitalization days																				Hospitalization days																																				
TLS prophylaxis		X									X											X									X																											
Prior / Conmed reporting	Prior & Concomitant Medication Reporting																																																									
AE / SAE reporting	AE/SAE Reporting																																																									
STUDY TREATMENT																																																									
AMG 176 dosing			X									X											X									X										X				X											
Azacitidine dosing			X									X								X	X																																				
LABORATORY ASSESSMENTS																																																									
Local Labs																																																									
Safety lab tests	X	X									X											X									X										X				X					X				X				
TLS monitoring test	X	X		X		X			X	X	X		X		X			X	X	X	X	X		X		X			X	X	X		X		X			X	X	X	X								X	X								X
Cardiac monitoring tests	X	X							X		X							X		X	X	X							X		X							X		X	X			X	X			X	X	X			X	X			X	X
Pregnancy test	X	X																																																							
Hepatitis serology	X																																																									
Central Labs																																																									
AMG 176 PK		X		X	X		X	X			X		X			X	X			X	X	X		X	X		X	X	X	X	X		X	X		X	X	X	X	X	X		X		X		X		X	X		X		X		X		X
Azacitidine PK		X		X		X			X																																																
Biomarker - Whole blood NaHep	X	X		X	X						X											X		X	X						X																										
Biomarker - Whole blood immune cell subsets		X					X				X									X	X	X					X				X									X	X								X	X								X
Biomarker - PBMC		X																																						X																	
Biomarker - Plasma	X																																																									
Biomarker - Serum	X																																																									
Biomarker - Pharmacogenetics (saliva sample)	X																																																									
Bone marrow aspirate/biospy	X																																																									
DISEASE AND IMAGING ASSESSMENTS																																																									
Bone marrow aspirate/biopsy	X																																																									
Peripheral blood count	X	X																				X																			X									X								

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See Table 1-9 for assessment notes and abbreviation definitions.

Table 1-6. Schedule of Activities: Parts 4 (Cohorts 5a and 5b Only) and 5A (AML) AMG 176 BIW in Combination With Azacitidine

	TREATMENT																																
Cycles (every 28 days)	Cycle 2-4														≥ Cycle 5																		
Weeks	W5-16														Q4W																		
Days	D1			D2			D3	D4-7	D8&15			D9&16			D10&17	D1			D2			D3	D4-7	D8&15			D9&16			D10&17	EOT	SFU	LTFU/EOS
Hours (relative to start of dosing)	pre-dose	0	EOI	pre-dose	0	EOI	24h after D2		pre-dose	0	EOI	pre-dose	0	EOI	24h after D9 & D16	pre-dose	0	EOI	pre-dose	0	EOI	24h after D2		pre-dose	0	EOI	pre-dose	0	EOI	24h after D9 & D16			
GENERAL ASSESSMENTS																																	
Clinical evaluation	X			X					X			X				X			X					X			X				X	X	
Vital signs	X		X	X		X	X		X		X	X		X		X		X	X		X	X		X		X	X		X		X	X	
12-lead ECG	X		X	X		X	X		X		X	X		X	X	X		X	X		X	X		X		X	X		X	X	X	X	
ECHO/MUGA																															X		X
Conmed reporting	Concomitant Medication Reporting																																
AE / SAE reporting	AE & SAE Reporting																																X
Subsequent anti-cancer therapy & Survival																																	X
STUDY TREATMENT																																	
AMG 176 dosing		X			X					X			X				X			X				X			X						
Azacitidine dosing		X			X		X	X									X			X		X	X										
LABORATORY ASSESSMENTS																																	
Local Labs																																	
Safety lab tests	X			X					X			X				X			X					X			X				X	X	
Cardiac monitoring test	X			X			X		X			X			X	X			X			X		X			X			X	X	X	
Pregnancy test	X															X															X	X	
Central Labs																																	
AMG 176 PK	X		X	X		X			X		X	X		X																			
Biomarker PBMC	X																														X		
Bone marrow/aspirate	C2D1, C3D1, and thereafter prior to every other cycle or when clinically indicated until disease progression and to confirm CR and MRD status																																
DISEASE AND IMAGING ASSESSMENTS																																	
AML SUBJECTS ONLY																																	
Bone marrow aspirate/biopsy	C2D1, C3D1, and thereafter prior to every other cycle or when clinically indicated until disease progression and to confirm CR and MRD status																																
Peripheral blood count	X								X							X								X							X		
Overall disease response	Assessed and documented at every cycle and at time of PD																																

See Table 1-9 for assessment notes and abbreviation definitions.

Table 1-7. Schedule of Activities: Part 5B (AML) Conventional Dosing – Regimen 1 (Days 1 Through 3 In Week 1 And BIW In Weeks 2 And 3 Only)

	Screen	Treatment Cycle 1																																																										
Weeks in Cycle		W1																						W2																			W3										W4								
Days	D-14 to D0	D1									D2-3									D4-7				D8									D9									D10	D15				D16				D17	D22				D23				D24
Hours (relative to start of dosing)		pre-dose	0	EOI	3	4	5	7	8	12	24h after D1/ pre-dose	0	EOI	3	4	5	7	8	12	24h after previous doing	48h after previous doing	72h after previous doing	96h after previous doing	pre-dose	0	EOI	3	4	5	7	8	12	24h after D8/ pre-dose	0	EOI	3	4	5	7	8	12	24h after D9	pre-dose	0	EOI	8	pre-dose	0	EOI	8	24h after D16	pre-dose	0	EOI	8	pre-dose	0	EOI	8	24h after D23
GENERAL AND SAFETY ASSESSMENT																																																												
Informed consent	X																																																											
Clinical evaluation	X	X									X													X									X										X				X					X				X				
Vital signs	X	X		X							X		X											X		X							X		X								X		X		X		X			X		X		X		X		
12-lead ECG	X	X		X	X		X	X	X		X		X			X	X	X		X				X		X	X		X	X	X	X	X		X	X		X	X	X	X	X	X		X	X	X		X	X	X	X		X	X	X		X	X	X
ECHO/MUGA	X																																													X									X					
Hospitalization		Hospitalization days																																																										
TLS prophylaxis		X									X													X									X																											
Prior / Conmed reporting		Prior & Concomitant Medications Reporting																																																								
AE / SAE reporting		AE & SAE Reporting																																																								
Subsequent anti-cancer therapy & Survival																																																												
STUDY TREATMENT																																																												
AMG 176 dosing			X									X													X									X										X				X												
Azacitidine dosing			X									X								**D4-5**					X									X																										
LABORATORY ASSESSMENTS																																																												
Local Labs																																																												
Safety lab tests	X	X									X													X									X										X				X					X				X				
TLS monitoring test	X	X		X		X			X	X	X		X		X			X	X	X	X	X	X	X		X		X			X	X	X		X		X			X	X	X	X								X	X								X
Cardiac monitoring tests	X	X							X		X							X		X				X							X		X							X		X	X			X	X			X	X	X			X	X			X	X
Pregnancy test	X	X																																																										
Hepatitis serology	X																																																											
Central Labs																																																												
AMG 176 PK		X		X	X		X	X			X		X	X		X	X			X	X	X	X	X		X	X		X	X			X		X	X		X	X			X	X		X		X		X		X									
Azacitidine PK		X		X		X			X		X		X											X		X							X		X																									
Biomarker - Whole blood NaHep	X	X		X	X						X													X		X	X						X																											
Biomarker - Whole blood immune cell subsets		X					X				X									X	X	X	X	X					X				X									X	X								X	X								X
Biomarker - PBMC		X																																								X																		
Biomarker - Plasma	X																																																											
Biomarker - Serum	X																																																											
Biomarker - Pharmacogenetics (saliva sample)	X																																																											
Bone marrow aspirate/biospy	X																																																											
DISEASE AND IMAGING ASSESSMENTS																																																												
Bone marrow aspirate/biopsy	X																																																											
Peripheral blood count	X	X																						X																			X									X								
Overall disease response	Assessed and documented at every cycle and at time of PD																																																											

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See Table 1-9 for assessment notes and abbreviation definitions.

Table 1-7. Schedule of Activities: Part 5B (AML) Conventional Dosing – Regimen 1 (Days 1 Through 3 In Week 1 And BIW In Weeks 2 And 3 Only)

	Treatment Cycles 2-4																														
Weeks in Cycle	W5-16																														
Days	D1			D2-3			D4-7	D8			D9			D10	D15				D16				D17	D22				D23				D24
Hours (relative to start of dosing)	pre-dose	0	EOI	24h after D1/ pre-dose	0	EOI	24h after previous doing	pre-dose	0	EOI	24h after D8/ pre-dose	0	EOI	24h after D9	pre-dose	0	EOI	8	pre-dose	0	EOI	8	24h after D16	pre-dose	0	EOI	8	pre-dose	0	EOI	8	24h after D23
GENERAL AND SAFETY ASSESSMENT																															
Informed consent																															
Clinical evaluation	X			X				X			X				X				X					X				X			
Vital signs	X		X	X		X		X		X	X		X		X		X		X		X			X		X		X			
12-lead ECG	X		X	X		X	X	X		X	X		X	X	X		X	X	X		X	X	X	X		X	X	X	X	X	X
ECHO/MUGA																		X									X					
TLS prophylaxis	X			X				X			X																				
Prior / Conmed reporting	Prior & Concomitant Medications Reporting																														
AE / SAE reporting	AE & SAE Reporting																														
Subsequent anti-cancer therapy & Survival																															
STUDY TREATMENT																															
AMG 176 dosing		X			X				X			X				X				X											
Azacitidine dosing		X			X		D4-5		X			X																			
LABORATORY ASSESSMENTS																															
Local Labs																															
Safety lab tests	X			X				X			X				X				X					X				X			
TLS monitoring test	X		X	X		X	X	X		X	X		X	X	X								X	X							X
Cardiac monitoring tests	X			X			X	X			X			X	X			X	X			X	X	X			X	X		X	X
Pregnancy test	X																														
Hepatitis serology																															
Central Labs																															
AMG 176 PK	X		X	X		X	X	X		X	X		X		X		X		X		X		X								
Biomarker - PBMC	X																														
Bone marrow aspirate/biospy	C2D1, C3D1, and thereafter prior to every other cycle or when clinically indicated until disease progression and to confirm CR and MRD status																														
DISEASE AND IMAGING ASSESSMENTS																															
Bone marrow aspirate/biopsy	C2D1, C3D1, and thereafter prior to every other cycle or when clinically indicated until disease progression and to confirm CR and MRD status																														
Peripheral blood count	X							X							X									X							
Overall disease response	Assessed and documented at every cycle and at time of PD																														

See Table 1-9Table 1-9 for assessment notes and abbreviation definitions.

Table 1-7. Schedule of Activities: Part 5B (AML) Conventional Dosing – Regimen 1 (Days 1 Through 3 In Week 1 And BIW In Weeks 2 And 3 Only)

	Treatment Cycles 5+																																		
Weeks in Cycle	Q4W																																		
Days	D1			D2-3			D4-7	D8			D9			D10	D15				D16				D17	D22				D23				D24			
Hours (relative to start of dosing)	pre-dose	0	EOI	24h after D1/ pre-dose	0	EOI	24h after previous doing	pre-dose	0	EOI	24h after D8/ pre-dose	0	EOI	24h after D9	pre-dose	0	EOI	8	pre-dose	0	EOI	8	24h after D16	pre-dose	0	EOI	8	pre-dose	0	EOI	8	24h after D23	EOT	SFU	LTFU/EOS
GENERAL AND SAFETY ASSESSMENT																																			
Informed consent																																			
Clinical evaluation	X			X				X			X				X				X					X				X					X	X	
Vital signs	X		X	X		X		X		X	X		X		X		X		X		X			X		X		X		X			X	X	
12-lead ECG	X		X	X		X	X	X		X	X		X	X	X		X	X	X		X	X	X	X		X	X	X		X	X	X	X		
ECHO/MUGA																		X									X						X		X
TLS prophylaxis	X			X				X			X																								
Prior / Conmed reporting	Prior & Concomitant Medications Reporting																																		X
AE / SAE reporting	AE & SAE Reporting																																		X
Subsequent anti-cancer therapy & Survival																																			X
STUDY TREATMENT																																			
AMG 176 dosing		X			X				X			X				X				X															
Azacitidine dosing		X			X		D4-5		X			X																							
LABORATORY ASSESSMENTS																																			
Local Labs																																			
Safety lab tests	X			X				X			X				X				X					X				X					X	X	
TLS monitoring test	X		X	X		X	X	X		X	X		X	X	X								X	X								X			
Cardiac monitoring tests	X			X			X	X			X			X	X			X	X			X	X	X			X	X			X	X	X	X	
Pregnancy test	X																																X	X	
Hepatitis serology																																			
Central Labs																																			
Biomarker - PBMC																																	X		
Bone marrow aspirate/biospy	C2D1, C3D1, and thereafter prior to every other cycle or when clinically indicated until disease progression and to confirm CR and MRD status																																		
DISEASE AND IMAGING ASSESSMENTS																																			
Bone marrow aspirate/biospy																																			
Peripheral blood count	X							X							X									X									X		
Overall disease response	Assessed and documented at every cycle and at time of PD																																		

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See Table 1-9 for assessment notes and abbreviation definitions.

Table 1-8. Schedule of Activities: Part 5B (AML) Conventional Dosing – Regimen 2 (Days 1 Through 5 In Week 1 and BIW In Week 2 Only)

	Screen	Treatment Cycle 1																																																						
Weeks in Cycle		W1																				W2																			W3									W4								
Days	D-14 to D0	D1									D2-5									D6-7		D8									D9									D10	D15				D16				D17	D22				D23				D24
Hours (relative to start of dosing)		pre-dose	0	EOI	3	4	5	7	8	12	24h after D1/pre-dose	0	EOI	3	4	5	7	8	12	24h after D5 doing	48h after D5 doing	pre-dose	0	EOI	3	4	5	7	8	12	24h after D8/pre-dose	0	EOI	3	4	5	7	8	12	24h after D9	pre-dose	0	EOI	8	pre-dose	0	EOI	8	24h after D16	pre-dose	0	EOI	8	pre-dose	0	EOI	8	24h after D23
GENERAL AND SAFETY ASSESSMENT																																																										
Informed consent	X																																																									
Clinical evaluation	X	X									X											X									X										X				X					X				X				
Vital signs	X	X		X							X		X									X		X							X		X								X		X		X		X			X		X		X		X		
12-lead ECG	X	X		X	X		X	X	X		X		X			X	X	X		X		X		X	X		X	X	X	X	X		X	X		X	X	X	X	X	X		X	X	X		X	X	X	X		X	X	X		X	X	X
ECHO/MUGA	X																																											X									X					
Hospitalization		Hospitalization days (Days 1 through 4)																																																								
TLS prophylaxis		X									X											X									X																											
Prior / Conmed reporting		Prior & Concomitant Medications Reporting																																																							
AE / SAE reporting		AE & SAE Reporting																																																							
Subsequent anti-cancer therapy & Survival																																																										
STUDY TREATMENT																																																										
AMG 176 dosing			X									X											X									X																									
Azacitidine dosing			X									X											X									X																									
LABORATORY ASSESSMENTS																																																										
Local Labs																																																										
Safety lab tests	X	X									X											X									X										X				X					X				X				
TLS monitoring test	X	X		X		X			X	X	X		X		X			X	X	X	X	X		X		X			X	X	X		X		X			X	X	X	X								X	X								X
Cardiac monitoring tests	X	X							X		X							X		X		X							X		X							X		X	X			X	X			X	X	X			X	X			X	X
Pregnancy test	X	X																																																								
Hepatitis serology	X																																																									
Central Labs																																																										
AMG 176 PK		X		X	X		X	X			X		X	X		X	X			X	X	X		X	X		X	X			X		X	X		X	X			X																	
Azacitidine PK		X		X		X			X		X		X									X		X							X		X																								
[redacted]	[redacted]	[redacted]		[redacted]	[redacted]		[redacted]				[redacted]									[redacted]	[redacted]	[redacted]		[redacted]	[redacted]		[redacted]				[redacted]									[redacted]	[redacted]								[redacted]	[redacted]								[redacted]
DISEASE AND IMAGING ASSESSMENTS																																																										
Bone marrow aspirate/biopsy	X																																																									
Peripheral blood count	X	X																				X																			X									X								
Overall disease response	Assessed and documented at every cycle and at time of PD																																																									

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See Table 1-9 for assessment notes and abbreviation definitions.

Table 1-8. Schedule of Activities: Part 5B (AML) Conventional Dosing – Regimen 2 (Days 1 Through 5 In Week 1 and BIW In Week 2 Only)

	Treatment Cycle 2-4																																																						
Weeks in Cycle	W5-16																																																						
Days	D1									D2-5									D6-7	D8									D9									D10	D15				D16				D17	D22				D23				D24
Hours (relative to start of dosing)	pre-dose	0	EOI	3	4	5	7	8	12	24h after D1/pre-dose	0	EOI	3	4	5	7	8	12	24h after D5 doing	pre-dose	0	EOI	3	4	5	7	8	12	24h after D8/pre-dose	0	EOI	3	4	5	7	8	12	24h after D9	pre-dose	0	EOI	8	pre-dose	0	EOI	8	24h after D16	pre-dose	0	EOI	8	pre-dose	0	EOI	8	24h after D23
GENERAL AND SAFETY ASSESSMENT																																																							
Informed consent																																																								
Clinical evaluation	X									X										X									X										X				X					X				X				
Vital signs	X		X							X		X								X		X							X		X								X		X		X		X			X		X		X		X		
12-lead ECG	X		X	X		X	X	X		X		X			X	X	X		X	X		X	X		X	X	X	X	X		X	X		X	X	X	X	X	X		X	X	X		X	X	X	X		X	X	X		X	X	X
ECHO/MUGA																																									X									X					
TLS prophylaxis	X									X										X									X																										
Prior / Conmed reporting	Prior & Concomitant Medications Reporting																																																						
AE / SAE reporting	AE & SAE Reporting																																																						
Subsequent anti-cancer therapy & Survival																																																							
STUDY TREATMENT																																																							
AMG 176 dosing		X									X										X									X																									
Azacitidine dosing		X									X										X									X																									
LABORATORY ASSESSMENTS																																																							
Local Labs																																																							
Safety lab tests	X									X										X									X										X				X					X				X				
TLS monitoring test	X		X		X			X	X	X		X		X			X	X	X	X		X		X			X	X	X		X		X			X	X	X	X								X	X								X
Cardiac monitoring tests	X							X		X							X		X	X							X		X							X		X	X			X	X			X	X	X			X	X			X	X
Pregnancy test	X																																																							
Hepatitis serology																																																								
Central Labs																																																								
AMG 176 PK	X		X	X		X	X			X		X	X		X	X			X	X		X	X		X	X			X		X	X		X	X			X																		
[redacted]	[redacted]																																																							
Bone marrow aspirate/biopsy	C2D1, C3D1, and thereafter prior to every other cycle or when clinically indicated until disease progression and to confirm CR and MRD status																																																							
DISEASE AND IMAGING ASSESSMENTS																																																								
Bone marrow aspirate/biopsy	C2D1, C3D1, and thereafter prior to every other cycle or when clinically indicated until disease progression and to confirm CR and MRD status																																																							
Peripheral blood count	X																			X																			X									X								
Overall disease response	Assessed and documented at every cycle and at time of PD																																																						

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See Table 1-9 for assessment notes and abbreviation definitions.

Table 1-8. Schedule of Activities: Part 5B (AML) Conventional Dosing – Regimen 2 (Days 1 Through 5 In Week 1 and BIW In Week 2 Only)

	Treatment Cycle 2-4																																																							
Weeks in Cycle	W5-16																																																						
Days	D1									D2-5									D6-7	D8									D9									D10	D15				D16				D17	D22				D23				D24
Hours (relative to start of dosing)	pre-dose	0	EOI	3	4	5	7	8	12	24h after D1/pre-dose	0	EOI	3	4	5	7	8	12	24h after D5 doing	pre-dose	0	EOI	3	4	5	7	8	12	24h after D8/pre-dose	0	EOI	3	4	5	7	8	12	24h after D9	pre-dose	0	EOI	8	pre-dose	0	EOI	8	24h after D16	pre-dose	0	EOI	8	pre-dose	0	EOI	8	24h after D23
GENERAL AND SAFETY ASSESSMENT																																																							
Informed consent																																																							
Clinical evaluation	X									X										X									X										X				X					X				X				
Vital signs	X		X							X		X								X		X							X		X								X		X		X		X			X		X		X		X		
12-lead ECG	X		X	X		X	X	X		X		X			X	X	X		X	X		X	X		X	X	X	X	X		X	X		X	X	X	X	X	X		X	X	X		X	X	X	X		X	X	X		X	X	X
ECHO/MUGA																																										X									X					
TLS prophylaxis	X									X										X									X																											
Prior / Conmed reporting	Prior & Concomitant Medications Reporting																																																						
AE / SAE reporting	AE & SAE Reporting																																																						
Subsequent anti-cancer therapy & Survival																																																							
STUDY TREATMENT																																																							
AMG 176 dosing		X									X										X									X																									
Azacitidine dosing		X									X										X									X																									
LABORATORY ASSESSMENTS																																																							
Local Labs																																																							
Safety lab tests	X									X										X									X										X				X					X				X				
TLS monitoring test	X		X		X			X	X	X		X		X			X	X	X	X		X		X			X	X	X		X		X			X	X	X	X								X	X								X
Cardiac monitoring tests	X							X		X							X		X	X							X		X							X		X	X			X	X			X	X	X			X	X			X	X
Pregnancy test	X																																																						
Hepatitis serology																																																							
Central Labs																																																							
AMG 176 PK	X		X	X		X	X			X		X	X		X	X			X	X		X	X		X	X			X		X	X		X	X			X																		
[redacted]	[redacted]																																																						
Bone marrow aspirate/biopsy	C2D1, C3D1, and thereafter prior to every other cycle or when clinically indicated until disease progression and to confirm CR and MRD status																																																						
DISEASE AND IMAGING ASSESSMENTS																																																							
Bone marrow aspirate/biopsy	C2D1, C3D1, and thereafter prior to every other cycle or when clinically indicated until disease progression and to confirm CR and MRD status																																																						
Peripheral blood count	X																			X																			X									X								
Overall disease response	Assessed and documented at every cycle and at time of PD																																																						

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See Table 1-9 for assessment notes and abbreviation definitions.

Table 1-9. Schedule of Activities Notes and Abbreviation Definitions

Clinical evaluations: Physical exam, ECOG status, and weight will be collected pre-dose on dosing days. Medical and surgical history, height and neuropathy assessment (for MM subjects only) need only be collected at the screening visit. Prior to dosing on day 1 of every cycle, BSA must be calculated.
ECG: ECGs will be performed at the timepoints in the SOA as follows: Screening ECGs: Single ECG Baseline (pre-dose cycle 1 day 1): Three baseline ECGs will be collected approximately 15 minutes apart (± 5 minutes), with each baseline ECG in triplicate run consecutively (ie, all 3 ECGs should be completed within a total of 5 minutes from the start of the first to the completion of the third) for a total of 9 ECGs Cycles 1 through 4: Triplicate ECGs run consecutively (ie, all 3 ECGs should be started with ± 5 minutes of infusion and be completed within a total of 5 minutes from the start of the first to the completion of the third) Cycle 5 and all subsequent cycles: Single ECG For Part 4 Cohorts 5a and 5b as well as Part 5**A**, 12-lead ECG assessments for C1D4 through D7 are optional based on investigator discretion.
ECHO or MUGA: Additional ECHO/MUGA, cardiac imaging and cardiac assessments are to be conducted if any clinical signs or symptoms of cardiomyopathy or other cardiac compromise are noted. If an ECHO or MUGA was performed within 4 weeks of C1D1 as part of standard of care, then it does not have to be repeated during screening as long as the same modality is used throughout the study. During LTFU and ECHO/MUGA is only required at the first LTFU visit.
Hospitalization for TLS monitoring and prophylaxis: All subjects will be hospitalized to monitor for TLS. Hospitalization will begin within 24 hours before the first dose of AMG 176 and continue until 24 hours post first AMG 176 dose for subjects on the AMG 176 QW schedule (Parts 1b, 3b, and 4) or post second dose of AMG 176 for subjects on the BIW schedule (Parts 1a and 3a). Hospitalization period can be increased per institutional standards or investigators discretion.
TLS Prophylaxis: See Section 6.1.4.1 for prophylaxis requirements including additional serum chemistry and hematology laboratory samples that must be collected within 24 hours prior to the first dose, and electrolyte values must be within normal range prior to AMG 176 dosing. Hospitalization for the purpose of TLS prophylaxis will not be captured as a Serious Adverse Event (SAE).
Peripheral Neuropathy Assessment: For MM subjects a peripheral neuropathy assessment will be performed at screening, on treatment if clinically indicated and then at the SFU visit. A neurological examination does not need to be performed by a neurologist, but should be performed by a qualified professional with knowledge and experience performing a neurological exam.
Patient Interview Substudy – Parts 3b, 4, and 5: Approximately 10 AML subjects from Parts 3b, 4, and 5 at select sites in countries where English is the primary language will be asked to participate in a Patient Interview Substudy (one 60-minute interview). The interview will take place as soon as possible after the completion of cycle 1, excluding days on which AMG 176 is administered and days on which subjects are hospitalized.

Table 1-9. Schedule of Activities Notes and Abbreviation Definitions (continued)

AMG 176 dosing: AMG 176 will be administered IV BIW (day 1 and 2, Weeks 1, 2, and 3) or QW (day 1, Weeks 1, 2, 3, [and 4]) depending on the Part and cohort the subject is enrolled in. A ramp-up dose of 120 mg/m^2 will be required if the target dose is ≥ 180 mg/m^2. AMG 176 will be infused for 2 hours (± 5 minutes). For Part 3d: After week 3 subjects may crossover to Part 3b or Part 4 for continued treatment if approved by the investigator and Amgen medical monitor. Subjects from Part 3d who crossover to Part 3b will not crossover (for a second time) to Part 4.
For Part 5**B** (conventional dosing): Dosing will be AMG 176 on 3 consecutive days the first week, and BIW on weeks 2 and 3 each cycle in the first 6 subjects (regimen 1). If this schedule is deemed safe by the DLRT, the next 6 subjects will receive AMG 176 on 5 consecutive days the first week, and BIW dosing week 2 for each cycle (**R**egimen 2).
Azacitidine: Azacitidine will be co-administered with AMG 176 to subjects enrolled in Parts 4 and 5. Azacitidine will be administered at a dose of 75 mg/m^2 IV or SC daily for the first 7 days of a 28-day cycle.
Oral itraconazole capsules (200 mg) will be given once daily (QD) for 7 days, starting at 8 am (± 1 hour) on day -3 through day 4 (last dose of itraconazole will be on day 4). Itraconazole dosing on day 1 should be at approximately the same time (± 5 minutes) as the start of infusion of AMG 176.
Safety Labs: Safety labs include chemistry, hematology, urinalysis, and coagulation analytes. See Table 11-1 for the list of analytes. Pre-dose safety labs are to be collected per the SOA and can be collected up to approximately 24 hours before treatment begins unless otherwise indicated (eg, TLS monitoring test).
TLS monitoring test: TLS monitoring tests consists of the chemistry analytes serum potassium, phosphorous, calcium, uric acid, and creatinine and will be performed at the timepoints in the SOA. The pre-dose samples must be collected within 4 hours before AMG 176 administration to ensure electrolytes are within normal range. Note: The pre-dose safety chemistry and TLS monitoring tests can be drawn at the same time provided they are collected within 4 hours before AMG 176 administration. For the BIW schedule, the D1 24-hour post-dose and the D2 pre-dose TLS monitoring test can be drawn at the same time. For Part 4 Cohorts 5a and 5b as well as Part 5**A**, TLS monitoring test for C1D4 through D7 are optional based on investigator discretion.
Cardiac monitoring tests: Cardiac monitoring tests include the following analytes: troponin (I or T), creatine kinase-muscle/brain (CK-MB), and N-terminal prohormone of brain natriuretic peptide (NT-pro-BNP). These cardiac monitoring tests will be collected at the time points specified in the SOA and analyzed locally. In addition, samples will need to be submitted to the central lab. Refer to the central lab manual. For Part 4 Cohorts 5a and 5b as well as Part 5**A**, cardiac monitoring tests for C1D4 through D7 are optional based on investigator discretion.

Table 1-9. Schedule of Activities Notes and Abbreviation Definitions (continued)

Pregnancy test (serum or urine). Applies to females of childbearing potential and will be performed locally at screening, prior to each treatment cycle (pre-dose), end of treatment, and at the safety follow-up visit.
PK: PK samples should be collected at the exact nominal time point as noted. Timepoints shown in the schedule of activities are relative to start of dosing of the corresponding treatment: AMG 176 or azacitidine. For pre-dose PK sample, the sample should be collected within 1 hour before the dose. For all other timepoints, PK samples should be collected within ± 15 min of the designated time points. If unable to collect a PK sample at the specified nominal time point, then collect the sample as close as possible and record the actual collection time. Note: It is important to document the exact date and time of investigational product administration and PK sample collection. AMG 176 PK: Samples collected and analyzed for AMG 176 at the timepoints indicated for cycle 1. Note: In the event that one or more additional step-doses are administered, PK should be collected at the following time points for the first two doses at the target dose: pre-dose, EOI, hour 3, hour 5, hour 7, hour 8, and hour 12 relative to the start of the target doses. All AMG 176 timepoints are relative to start of infusion. Azacitidine PK: Samples collected and analyzed for azacitidine at pre-dose, EOI (10-40 min for IV or 30 min for SC), and 4 and 8 h after the start of IV infusion or following the SC dose of azacitidine. For Part 4 Cohorts 5a and 5b as well as Part 5**A**, AMG 176 PK assessments for C1D4 through D7 are optional based on investigator discretion.
Optional Pharmacogenetics - saliva: For subjects who consent to the pharmacogenomics portion of the study, a saliva sample will be collected for extraction of DNA. These collections will not be requested for subjects in Japan.
Multiple myeloma Disease Assessments: Refer to Section 8.2.2.1
AML Disease Assessments: Refer to Section 8.2.2.2
EOT and SFU: In any case of premature treatment discontinuation, the investigator should make every effort to perform all examinations scheduled for the EOT and SFU visits. These data should be recorded, as they comprise an essential evaluation that should be performed prior to removing any subject from treatment and to allow for the evaluation of the study endpoints. The EOT visit will occur upon the decision to end the treatment (eg, due to intolerable adverse event [AE], disease progression). The SFU visit will occur 30 days (+3 days) after last dose of protocol-required therapies. Note: If a subject withdraws consent, it is important to distinguish between withdrawal of consent from treatment (partial withdrawal of consent) which will allow for continued follow-up in LTFU (eg, for survival) or withdrawal of consent from study (full consent withdrawal). These discussions should be thoroughly documented in the subjects medical records.

Table 1-9. Schedule of Activities Notes and Abbreviation Definitions (continued)

LTFU/EOS: Long-term follow-up (LTFU) visits will occur every 3 months (± 14 days) for up to 1 year after EOT. The EOS for a subject will occur when the subject completes the LTFU or dies, whichever occurs first. During LTFU, all SAEs that the investigator becomes aware of, regardless of whether they are or are not suspected to be related to the investigational product, will be reported to Amgen. All serious adverse events (regardless of causality) shall be reported to Amgen immediately and no later than 24 hours after the investigator first becomes aware of the event. Note: If a subject withdraws consent, it is important to distinguish between withdrawal of consent from treatment which will allow for continued follow-up in LTFU (eg, for survival) or withdrawal of consent from study. These discussions should be thoroughly documented in the subjects' medical records.
AE = adverse event; ALT = alanine aminotransferase; AML = acute myeloid leukemia; ANC = absolute neutrophil count; AST = aspartate aminotransferase; BIW = twice weekly; BNP = B-type natriuretic protein; BSA = body surface area; CBC = complete blood count; CR = complete response; CT = computed tomography; CXDX = cycle X day X; D = day; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; EOI = end of infusion; EOS = end of study; EOT = end of treatment; FDG = fluorodeoxyglucose; [redacted]; G-CSF = granulocyte-colony stimulating factor; GGT = gamma-glutamyl transferase; h = hour; HBcAb = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCVAb = hepatitis C virus antibody; Ig = immunoglobulin; INR = international normalized ratio; LDH = lactate dehydrogenase; LFT = liver function test; LTFU = long-term follow-up; MCH = mean cell hemoglobin; MCHC = mean cell hemoglobin concentration; MCV = mean cell volume; min = minute; MM = multiple myeloma; MRD = minimal residual disease; MUGA = multigated acquisition scan; NaHep = sodium heparin; PBMC = peripheral blood mononuclear cell; PD = pharmacodynamics; PET = positron emission tomography; PK = pharmacokinetics; PT = prothrombin time; PTT = partial thromboplastin time; Q4W = every 4 weeks; Q8W = every 8 weeks; QTc = QT interval corrected; RBC = red blood cell; SAE = serious adverse event; SC = subcutaneous; Screen = Screening; SFLC = serum-free light chain; SFU = safety follow-up; SOA = schedule of activities; SPEP = serum protein electrophoresis; TBA = total bile acid; TLS = tumor lysis syndrome; UPEP = urine protein electrophoresis; W = week

2. Introduction

2.1 Study Rationale

Acute Myeloid Leukemia (AML) is a clonal disorder characterized by ineffective hematopoiesis and an accumulation of abnormal blasts in the bone marrow (Albitar et al, 2002; Doll and List, 1989). The combination of azacitidine and venetoclax represents the current standard frontline therapy for newly diagnosed patients considered unfit for intensive chemotherapy due to either age or medical comorbidity (DiNardo et al, 2020). While remission rates and median overall survival (OS) represent a significant improvement compared to prior therapy, the regimen is not curative. Primary resistance may occur, with a mean OS of less than 3 months observed for patients upon relapse (Fenaux et al, 2009; Prebet et al, 2011; Jabbour et al, 2010). Recent studies demonstrate that the myeloid cell leukemia sequence 1 (MCL1) protein, an intrinsic anti-apoptotic protein within the B-cell lymphoma/leukemia 2 (BCL2) family, may drive the resistance to BCL2 inhibition by venetoclax.

The upregulation of MCL1 has been described in many human malignant subtypes, including AML and myelodysplastic syndrome**s** (MDS) (Fischer et al, 202**3**; Caenepeel et al, 2018), highlighting MCL1 as a promising target for the next generation of therapy for these malignancies. MCL1-dependency was observed in AML mouse models as well as in human AML derived cell lines (Glaser et al, 2012), and inhibition of MCL1 induced leukemic cell death in these models. Preclinical investigations have also demonstrated that MCL1 inhibition synergizes with standard of care (SOC) therapy and increases antileukemic activity by sensitizing leukemic cells towards apoptosis (Kelly et al, 2014; Phillips et al, 2015; Caenepeel et al, 2018). As evidence of this, combination of MCL1 inhibition with venetoclax overcomes BCL2 inhibitor resistance and is active in venetoclax-resistant cell lines and patient samples (Zhang et al, 2020). In the current study, AMG 176, an MCL1 inhibitor, is combined with azacitidine to overcome treatment resistance in subjects with relapsed or refractory AML. In support of this expectation, preliminary results demonstrate clinical responses in subject previously treated and refractory to azacitidine and venetoclax therapy (see Table 2-1).

Patients with AML are susceptible to invasive fungal infections and often require prophylaxis and treatment with azole antifungal agents such as voriconazole and posaconazole (Halpern et al, 2015; Lat and Thompson, 2011), which are known to inhibit cytochrome P450 3A4 (CYP3A4) and P-glycoprotein (P-gp). Since AMG 176 may be metabolized by CYP3A4 and is a P-gp substrate, co-administration with inhibitors of

CYP3A4/P-gp may lead to increases in AMG 176 exposure. As a result, clinical trials with AMG 176 prohibited the use of azole antifungal therapy and other medications that are strong CYP3A4/P-gp inhibitors.

To answer the question of whether a drug-drug interaction (DDI) exists between azole and AMG 176 therapy, an assessment is planned in a separate cohort of AML subjects (Part 3d) to evaluate the effect of itraconazole, a strong CYP3A4 and P-gp inhibitor, on the pharmacokinetics of AMG 176. Itraconazole was selected for this assessment as an index inhibitor of CYP3A that will allow extrapolation of results to other azole antifungal therapies (Chen et al, 2016; Liu et al, 2016; US FDA, 2016). Analysis to date of this itraconazole interaction cohort (Part 3d) has thus far shown no prohibitive interaction between azoles antifungals and AMG 176, allowing for clinical use of azole antifungal therapy in subjects receiving AMG 176 (see Section 4.3.1.2.3).

In this study, Part 1 and Part 2 were initially designed to investigate AMG 176 as monotherapy and combinational therapy in subjects with multiple myeloma (MM). As of December 2019, 48 subjects were enrolled in Part 1 where clinical responses were observed at dose levels > 240 mg/m². However, AMG 176 associated elevations of troponin were observed at dose levels of 360 and 480 mg/m² in MM subjects. In contrast, clinical responses in AML were observed at the lower dose levels, indicating that AML may be more susceptible to MCL1 inhibition and can be treated with lower doses compared to subjects with MM. The combination of these observations led to further development in AML and a pause in MM development for now. Part 1 will remain closed to enrollment and Part 2 was removed from the protocol during Amendment 10. To avoid the potential for troponin elevations, only doses ≤ 240 mg/m² will be further investigated. Additionally, preclinical data demonstrates that MCL1 inhibition is more efficacious in combination with other antileukemic therapies. Consequently, combinational therapy will be prioritized in this study (Parts 4 and 5) to optimize the clinical benefit to subjects, and monotherapy dose escalation will be performed only to inform the combinational study, and not to confirm the likely monotherapy maximum tolerated dose (MTD) of 240 mg/m². As of November 2022, 33 subjects have been enrolled in monotherapy (Part 3b: 11 subjects) and combination therapy (Part 4: 22 subjects) cohorts at dose levels of ≤ 240 mg/m²; no concerning safety events (including elevations of troponin) and no Dose-Limiting Toxicities (DLTs) were observed.

2.2 Background

2.2.1 Disease

2.2.1.1 Multiple Myeloma Background

Multiple myeloma is a plasma cell neoplasia characterized by clonal proliferation of malignant plasma cells in the bone marrow microenvironment, production of a monoclonal protein present in the blood or urine and associated organ dysfunction (Palumbo and Anderson 2011).

Multiple myeloma is the second most common (10-15% of all) hematological cancer. It is responsible for 15-20% of deaths from hematological cancer and about 2% cancer deaths. Recent improved understanding of the pathogenesis of myeloma has led to the development of new treatments. Survival is improving, with median OS in the range of 7-10 years after initial diagnosis. Nevertheless, myeloma remains an incurable cancer and with subsequent relapses the disease becomes refractory to current treatments. Therefore, relapsed or refractory MM is still an unmet medical need (Smith and Yong 2013).

Myeloma arises from an asymptomatic premalignant proliferation of monoclonal plasma cells that are derived from post–germinal-center B cells. Multistep genetic and micro-environmental changes lead to the transformation of these cells into a malignant neoplasm. Myeloma is thought to evolve most commonly from a monoclonal gammopathy of undetermined clinical significance (usually known as MGUS) that progresses to smoldering myeloma and, finally, to symptomatic myeloma. Several genetic abnormalities that occur in tumor plasma cells play major roles in the pathogenesis of myeloma (Palumbo and Anderson, 2011).

The uncontrolled growth of myeloma cells has many consequences, including skeletal destruction, bone marrow failure, increased plasma volume and viscosity, suppression of normal immunoglobulin (Ig) production, and renal insufficiency (Durie, 2011).

Symptomatic (active) disease should be treated immediately, whereas asymptomatic (smoldering) myeloma requires only clinical observation, since early treatment with conventional chemotherapy has shown no benefit. Investigational trials are currently evaluating the ability of novel therapies to delay the progression from asymptomatic to symptomatic myeloma. The treatment strategy is mainly related to age. Current data would support the initiation of induction therapy with thalidomide, lenalidomide, or bortezomib-based regimens plus hematopoietic stem-cell transplantation for patients under the age of 65 years who do not have substantial heart, lung, renal, or liver

dysfunction. Autologous stem-cell transplantation with a reduced-intensity conditioning regimen should be considered for older patients or those with coexisting conditions. Conventional therapy combined with thalidomide, lenalidomide, or bortezomib should be administered in patients older than 65 years of age. Less intensive approaches that limit toxic effects or prevent treatment interruption that would reduce the intended treatment effect should be considered in patients over 75 years of age or in younger patients with coexisting conditions. Biologic age, which may differ from chronologic age, and the presence of coexisting conditions should determine treatment choice and drug dose (Palumbo and Anderson, 2011; NCT03301220). There are ongoing studies evaluating the additive effects of newer agents in first line therapy, including monoclonal antibodies and next generation proteasome inhibitors (Mateos et al, 2018; NCT02541383; NCT01335399; NCT0185052; NCT02252172; NCT02579863).

Treatment of relapsed or refractory MM presents a special therapeutic challenge, due to the heterogeneity of disease at relapse and the absence of clear biological based recommendations regarding the choice of salvage therapies at various time points of disease progression. With increasing recognition of the inherent clonal heterogeneity and genomic instability of the plasma cells influencing both inherent and acquired therapeutic resistance, the identification of the optimal choice and sequence of therapies has become critical. Several new agents and targets are currently under development and show considerable promise. Besides carfilzomib (proteasome inhibitor) and pomalidomide (immunomodulatory drug [IMiD]) that were granted approval by the United States (US) Food and Drug Administration (FDA) in 2012 and 2013, respectively, for relapsed or refractory MM, the proteasome inhibitor ixazomib received approval in 2015. Other newer treatment approaches also received approval in 2015, including monoclonal antibodies targeting SLAMF7 (ie, elotuzumab) or CD38 (ie, daratuzumab) (O'Donnell and Raje, 2017). Despite advances in the management of MM as described, relapse is inevitable in almost all patients. Recurrence of myeloma is typically more aggressive with each relapse, leading to the development of treatment-refractory disease, which is associated with a shorter survival (Dimopoulos et al, 2014). As the approved agents move to earlier lines of therapy and in combination regimens, more treatment options are still warranted.

2.2.1.2 Acute Myeloid Leukemia Background

Acute myeloid leukemia is characterized by accumulation of abnormal blasts in bone marrow. These cells disrupt normal hematopoiesis, thus contributing to the bone marrow failure that is the most common underlying cause of death. The abnormal blasts can escape into the peripheral blood and may infiltrate organs. Diagnosis is based on demonstration that the marrow or blood has > 20% blasts of myeloid origin (Estey, 2016).

Acute myeloid leukemia represents approximately 90% of all acute leukemias in adults, and accounts for about 25% of all cases of leukemia diagnosed in the Western hemisphere (Hayat et al, 2007; Döhner et al, 2017). In the United States (US), AML represents the most common form of acute leukemia in adults and causes approximately 1.2% of all cancer deaths with an annual incidence rate of 2.2 per 100 000, or approximately 20 000 new cases per year. Age adjusted incidence ranges from 1 per 100 000 in people < 20 years to > 10 per 100 000 in the elderly. Current induction chemotherapy protocols combining cytarabine and an anthracycline administered as first-line treatment induce remissions in a majority (55% to 75%) of patients. Standard consolidation therapy with high doses of cytarabine leads to improved survival in younger patients. However, up to 70% of patients relapse, and only 20% to 30% of patients attain a long-term disease-free survival (Döhner et al, 2017). Azacitidine combined with venetoclax has become the standard frontline therapy for newly diagnosed patients who are older or unfit for intensive chemotherapy. The ongoing phase 3 randomized control trial (VIALEA) of azacitidine with or without venetoclax in newly diagnosed AML subjects recently confirmed a significant survival benefit for the combination and solidified its status as the SOC (DiNardo et al, 2020). While the remission rates and median OS all represent a significant improvement compared to prior therapy, the regimen is not curative. Primary resistance does occur, and relapses are not infrequent. Patients who progress despite venetoclax therapy have extremely poor outcomes, with no defined SOC and a median survival of 2.9 months with treatment and 1.4 months without treatment (Maiti et al, 2021). Consequently, there is a high unmet need for new therapies in this population. Preliminary data from this study as of 06 September 2022 has shown responses in heavily treated refractory subjects, including in those previously exposed to BCL2 inhibitor venetoclax.

2.2.1.3 Combination Therapy in Multiple Myeloma and Acute Myeloid Leukemia

Both indications targeted in this study have well described genomic instability and clonal heterogeneity (Bianchi and Ghobrial, 2014; Ding et al, 2012). In relapsed MM, the combination of three novel agents have proven to be superior to doublets in at least 5 different randomized clinical trials (Dimopoulos et al, 2016; Moreau et al, 2016; Palumbo et al, 2016; Lonial et al, 2015; Stewart et al, 2015). Similarly, it is expected that combination strategies in AML will allow for superior results than monotherapy approaches despite targeting dominant mutations (Wouters, 2017). Because of these observations and with the desire to allow for expedient development of effective therapies for these grievous diseases, the proposed study will include evaluation of AMG 176 in monotherapy and selected combination therapies.

2.2.2 Amgen Investigational Product Background: AMG 176

AMG 176 is a potent and selective inhibitor of protein-protein interactions between MCL1 (myeloid cell leukemia sequence 1) and pro-apoptotic members of the BCL2 family. Programmed cell death or apoptosis is regulated via a complex network of protein-protein interactions between the pro- and anti-apoptotic sub-groups that make-up the BCL2 protein family (Czabotar et al, 2014; Strasser et al, 2011; Kozopas et al, 1993). Myeloid cell leukemia sequence 1 is an anti-apoptotic member of this family and promotes cell survival. In contrast, pro-apoptotic family members such as B-cell receptor associated kinases (BAK), B-cell lymphoma/leukemia 2 associated X-protein (BAX), or the BCL2 homology 3 (BH3)-only protein family members, such as Bcl-2-interacting mediator of cell death (BIM) and p53 up-regulated modulator of apoptosis (PUMA), are critical effectors for the induction of apoptosis. Upon the induction of apoptotic stimuli, pro-apoptotic BH-3 only proteins bind MCL1 and other pro-survival BCL2 family members, disrupting interactions between MCL1 and the pro-apoptotic effector proteins, BAK and BAX. This leads to activation and oligomerization of BAK and BAX, mitochondrial outer membrane permeabilization (MOMP), and the release of cytochrome C, caspase activation and cell death (Czabotar et al, 2014; Strasser et al, 2011).

Malignant transformation results in cellular stress from a variety of pro-apoptotic insults, including hypoxia and gain-of-function mutations in oncogenes, suggesting there is a strong selective advantage for tumors to evolve mechanisms that culminate in the evasion of apoptosis. The over-expression of anti-apoptotic BCL2 family members, such as MCL1 and BCL2, has emerged as a central mechanism by which cancers buffer

pro-apoptotic stress. There is now considerable data suggesting that MCL1 is integral to the resistance of apoptosis in a substantial number of solid and hematopoietic cancers. Genetic ablation of MCL1 has been shown to protect mice from the development of AML (Glaser et al, 2012). Additional mouse knockout studies have implicated MCL1 in the maintenance of plasma cells, an observation that suggests MCL1 may be a critical pro-survival factor in MM (Peperzak et al, 2013). Myeloid cell leukemia sequence 1 is highly expressed in a variety of human tumors, and over-expression of MCL1 has been implicated in resistance to chemotherapy and to BCL2/B-cell lymphoma extra large (BCL-XL) inhibitors (Wertz et al, 2011; van Delft et al, 2006). Finally, focal amplification of the MCL1 gene has been observed in up to 10% of cancers derived from multiple tissue types, including lung and breast (Beroukhim et al, 2010). These data suggest that the inhibition of MCL1 represents a novel and compelling therapeutic strategy for the treatment of cancer. A promising strategy for targeting MCL1 takes advantage of specific small molecules that selectively bind to MCL1 and disrupt its interactions with the BH3 domain of pro-apoptotic partner proteins such as BAK, and BIM, leading to the activation of the intrinsic apoptotic cascade and death in cells dependent on MCL1 for survival.

2.2.2.1 AMG 176 Preclinical Pharmacodynamic and Antitumor Studies

AMG 176 selectively disrupts the human MCL1 – BIM interaction in a cell-free time resolved fluorescence resonance energy transfer-based assay with a mean half maximal inhibitory concentration (IC_{50}) of 0.241 nM. Furthermore, AMG 176 is highly selective for MCL1, demonstrating > 4000-fold selectivity over the pro-survival BCL2 family members, BCL2 and BCL-XL in a BIM binding assay. In cellular assays, AMG 176 disrupts the interaction between MCL1 and BAK with IC_{50} of 30.8 nM. In cell viability studies performed in a panel of tumor cell lines derived from MM, AML and non-Hodgkin's lymphoma AMG 176 exhibited IC_{50} values ranging from 14 nM to greater than 20 μM, with IC_{50} values of less than 1 μM observed in 13 of the 23 tested cell lines.

In-vivo, AMG 176 treatment resulted in a dose-dependent inhibition of the interaction between MCL1 and BAK. In pharmacodynamic (PD) studies, treatment with a single dose of AMG 176 resulted in a dose-dependent induction of multiple markers of apoptosis including activation of BAK, and the cleavage of caspase 3 and PARP in an OPM2-Luc MM tumor xenograft model. In an OPM2-Luc tumor xenograft efficacy model, AMG 176 significantly inhibited the growth of established tumors, with tumor regression observed at 2 doses 30 and 60 mg/kg administered orally once daily **(QD)**.

Additional studies were performed examining AMG 176 efficacy in an OPM2-Luc tumor xenograft model following an intermittent dosing schedule. AMG 176 significantly inhibited the growth of established tumors at doses of 30 mg/kg on a 2-day on/5-day off (QD × 2) schedule or a 5-day on/2-day off schedule (QD × 5). At doses of 60 mg/kg, regression of established tumors was observed with a 2 day on/5-day off (QD × 2) and a 5-day on/2-day off (QD × 5) schedule. Once weekly (QW) oral administration of AMG 176 significantly inhibited the growth of established OPM-2 MM tumor xenografts at doses of 50 mg/kg and 100 mg/kg, with 97% tumor growth inhibition observed at 50 mg/kg and 70% tumor regression observed at 100 mg/kg respectively.

Although single agent activity was observed in the preclinical experiments described above, the mechanism of action of AMG 176 is expected to allow for additive or synergistic effects when combined with agents that lead the malignant cell towards apoptosis. With this hypothesis, combination studies with well-established therapeutic agents for MM and AML were conducted.

In a cell viability study performed using OPM-2 cell line, the addition of different concentrations of dexamethasone to AM-8621 (an analog of AMG 176) led to a 1- to 2.5-fold change in the IC_{50} values.

The combination of AMG 176 and carfilzomib was tested in an orthotopic OPM-2 model of MM in which tumor cells were engrafted in the bone marrow of mice. Daily administration of AMG 176 (20 mg/kg) combined with twice-weekly treatment with carfilzomib (3 mg/kg), achieved significant inhibition of tumor burden (99% reduction in bioluminescence imaging [BLI]), exceeding the effect achieved with either single agent alone (85% and 82% reduction in BLI with AMG 176 and carfilzomib, respectively).

The combination of AM-8621 and the hypomethylating agent decitabine was tested across a panel of 4 AML cell lines (EOL1, GDM1, MOLM13 and MV-4-11) in a 72-hour viability assay. A synergistic interaction was detected in each of the 4 cell lines with this combination. Additionally, the combination of AM-8621 and decitabine was tested in primary AML patient samples where improvements in both potency and efficacy were observed over either single agent alone.

In vivo, treatment with AMG 176 significantly inhibited the growth of established orthotopic MOLM13-Luc AML tumors, at doses of 60 and 30 mg/kg on a 2-day on/5-day off (Q2W) off schedule (Caenepeel et al, 2018). The combination of AMG 176 and the hypomethylating agent decitabine was also tested in the MOLM13 orthotopic AML

xenograft model. Mice were treated with the combination of AMG 176 at 30 mg/kg (Q2W) and decitabine administered 3 times a week at a dose of 1 mg/kg and activity compared against the single agent treatment. A significant reduction in tumor burden was observed with the combination of AMG 176 plus decitabine (98% tumor growth inhibition) compared to single agent AMG 176 (81% tumor growth inhibition) and single agent decitabine (64% tumor growth inhibition) (Caenepeel et al, 2019).

2.2.2.2 AMG 176 Pharmacokinetics

AMG 176 was characterized in vitro and in vivo preclinical studies. In animal species AMG 176 had low clearance (CL) relative to hepatic blood flow. In vitro, the metabolism of AMG 176 was catalyzed primarily by cytochrome P450 (CYP) 3A4 and CYP2C8. In vitro, AMG 176 was highly bound to plasma proteins in all species including human (mean fraction unbound of 0.024), and did not partition into red blood cells (RBCs), which makes plasma concentrations suitable for PK.

In vitro, AMG 176 was a non-selective CYP inhibitor in human liver microsomes (Ki ranged from 2.6 to 9.4 μM, with the most potent effect against CYP2C9), a time-dependent inhibitor of CYP3A4 (Ki of 80 to 178 μM and kinact of 0.044 to 0.75 min^{-1}), an inducer of CYP2B6 and CYP3A4 in primary human hepatocytes, and an inhibitor of organic anion polypeptide transporters (OATP)1B1, breast cancer resistance protein (BCRP), and OATP1B3 (IC_{50} of 1.2, 1.5, and 3.9 μM, respectively). Subject to its administered dose and regimen, AMG 176 has the potential to cause CYP mediated DDIs by inhibition (eg, inhibition of CYP3A4 substrates), CYP3A4 induction and transporter mediated DDIs.

2.2.2.3 AMG 176 Nonclinical Toxicology

AMG 176 has been evaluated in a comprehensive series of toxicology studies in laboratory animals and in vitro test systems. The design of the nonclinical safety assessment program was in accordance with International Council for Harmonisation (ICH) Harmonised Tripartite Guideline S9, “Nonclinical Evaluation for Anticancer Pharmaceuticals” (ICH S9, 2010). The goal of this program was to adequately characterize the toxicity of AMG 176 for clinical use.

Potency of AMG 176 vs MCL1 interaction in the dog is nearly identical to that seen in the human. The potency of AMG 176 vs the rodent MCL1 protein is 177-fold lower than in the dog (AMG 176 Investigator’s Brochure). AMG 176 nonclinical safety studies consisted of an exploratory 14-day dog intravenous (IV) toxicology study, Good

Laboratory Practices (GLP) 28-day rat and dog IV toxicology studies, in vitro and in vivo phototoxicity assay, an in vitro hemolysis assay, and in vitro safety pharmacology studies (human ether-à-go-go-related gene [hERG] and isolated rabbit heart) to characterize potential cardiovascular effects (AMG 176 Investigator's Brochure).

The doses selected for the 28-day IV dog and rat toxicology studies were intended to characterize the toxicity of AMG 176 and provide data to support a starting dose for the first in human (FIH) study. An IV route of administration and a dosing schedule of 2 days of dosing followed by 5 days of non-dosing was used to support the anticipated clinical route and dosing schedule (see Section 4.3.2). While no preclinical safety data exist for QW dosing, the **BIW** dosing data provide a conservative case and no additional safety concerns are anticipated with QW dosing. In a 28-day rat IV infusion toxicology study the severely toxic dose in 10% of the animals (STD10) was 60 mg/kg based on mortality at 120 mg/kg and in a 28-day IV toxicology study in dogs, the highest-non-severely-toxic dose (HNSTD) was 10 mg/kg based on early deaths at 20 mg/kg. In both the rat and dog, morbidity and mortality were related to mucosal epithelial degeneration in the small and large intestines. AMG 176 was phototoxic in an in vitro assay but not in an in vivo study, the latter of which is considered definitive. AMG 176 in vehicles containing hydroxypropyl-β-cyclodextrin caused hemolysis of whole blood at concentrations of 0.048, 0.12, 0.24, 1.2, and 2.4 mg/mL in rat blood and at 0.1 and 1.0 mg/mL dog blood.

2.2.2.4 AMG 176 Clinical Experience

AMG 176 is currently being investigated in a phase 1, FIH, multicenter, open-label, dose-expansion study (Study 20150161) in subjects with relapsed or refractory (R/R) AML. For efficacy data in AML subjects, see Table 2-1.

A detailed description of the chemistry, pharmacology, PK, efficacy, and safety of AMG 176 is provided in the Investigator's Brochure.

Table 2-1. Study 20150161 Best Overall Response – Acute Myeloid Leukemia

	Part 3a AMG 176 60 mg/m^2 BIW monotherapy (N = 6)	Part 3a AMG 176 120 mg/m^2 BIW monotherapy (N = 5)	Part 3b AMG 176 60 mg/m^2 QW + azacitidine (N = 5)	Part 3b AMG 176 120 mg/m^2 QW monotherapy (N = 5)	Part 4 AMG 176 120 mg/m^2 QW + azacitidine (N = 4)	Part 3b AMG 176 180 mg/m^2 QW monotherapy (N = 5)	Part 4 AMG 176 180 mg/m^2 QW + azacitidine (N = 4)	Part 3b AMG 176 240 mg/m^2 QW monotherapy (N = 4)	Part 4 AMG 176 240 mg/m^2 QW + azacitidine (N = 6)
Best overall response – n (%)									
CR without minimal residual disease (CR_{MRD}-)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Complete remission (CR)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
CR with incomplete hematologic recovery (CRi)	1 (17)	1 (20)	0 (0.0)	0 (0.0)	1 (25)[a]	0 (0.0)	0 (0.0)	1 (25)	2 (33)[a]
Morphologic leukemia-free state (MLFS)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (20)	0 (0.0)	0 (0.0)	0 (0.0)
Partial remission (PR)	1 (17)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (25)	0 (0.0)	0 (0.0)
Stable disease (SD)[b]	0 (0.0)	0 (0.0)	0 (0.0)	1 (20)	2 (50)	2 (40)	1 (25)	0 (0.0)	1 (17)[a]
Progressive disease (PD)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

BIW = twice weekly; CRi = complete response/remission with incomplete recovery of peripheral blood counts; QW = once weekly;
For AML = Best overall response is defined as the first response category achieved in the following order: CR_{MRD}-, CR, CRi, MLFS, PR, SD, PD. Response criteria for AML are European LeukemiaNet Response Criteria.
[a] Active subjects with days on Study 160 to 448.
[b] Only SD > 100 days is included in this table.
Data snapshot date: September 2022.

2.3 Benefit/Risk Assessment

Based on nonclinical toxicity studies in AMG 176, early evidence of clinical activity, and clinical safety experience in the current study, the overall benefit/risk profile supports the further clinical development of AMG 176 in combination therapy for subjects with R/R AML. Clinical signs and symptoms, along with other safety laboratory parameters, will be monitored during the study and at the appropriate time points to ensure subjects' safety. As of 01 August 2022, this study enrolled 44 subjects with relapsed or refractory AML. Reference should be made to the Investigator's Brochure (IB) for further data on AMG 176.

The following benefit/risk assessment supports the conduct of this clinical trial. Reference should be made to the Investigator's Brochure for further data on AMG 176.

2.3.1 Key Benefits

As AMG 176 is in early development and clinical experience is limited, key benefits are still being evaluated.

Nearly all subjects have had prior exposure to venetoclax and azacitidine, with majority confirmed as refractory. This population has a median OS of less than 3 months (Maiti et al, 2021). These clinical responses documented in a heavily pretreated population demonstrate the synergistic capability of AMG 176 to overcome treatment resistance (Table 2-1). These results support the potential of more robust clinical responses and improved outcomes with the addition of AMG 176 to other AML therapies.

2.3.2 Key Risks

Based on biological plausibility, nonclinical toxicity studies of AMG 176, and clinical safety experience, tumor lysis syndrome (TLS) and increased troponins have been determined to be identified risks.

Refer to Section 6.2 for dose modification guidelines for AMG 176 and azacitidine.

2.3.2.1 Tumor Lysis Syndrome

Administration of AMG 176 has been associated with TLS including 1 subject with a fatal outcome out of 109 safety-evaluable subjects. The BCL2 inhibitor venetoclax also carries an associated risk of TLS, suggesting this may represent a feature of antiapoptotic therapy. Subjects with a high tumor burden or compromised renal function (eg, ISS Stage II/III) may be at elevated risk for TLS, which may further increase in the setting of combinational therapy with azacitidine due to the anticipated increase in

antileukemic activity. To mitigate the risk of TLS, blood chemistry (potassium, uric acid, phosphorus, calcium, and creatinine) must be assessed in all subjects and any pre-existing abnormalities must be corrected prior to starting treatment with AMG 176. In addition, subjects must be appropriately hydrated prior to each dose of AMG 176. Refer to Section 11.9 for specific recommendations regarding the mitigation and management of TLS.

2.3.2.2 Increased Troponin

Increased troponin elevations may occur with MCL-1 inhibition (Guo et al, 2018). Clinical experience to date from the FIH study of AMG 176 (Study 20150161) in subjects with R/R MM and in subjects with R/R AML demonstrated troponin elevations primarily at higher dose levels of 360 mg/m² and 480 mg/m² when administered as monotherapy, but neither cardiac toxicity nor concerning elevations were observed at doses of AMG 176 of 240 mg/m² or less when administered as monotherapy or in combination with azacitidine. Mitigation measures for this study include monitoring troponin cardiac enzymes and electrocardiograms (ECGs).

A cardiac monitoring plan has been implemented to mitigate the risk of cardiac toxicity. Refer to Section 11.2 (Appendix 2), Section 8.2.5.3, and Section 6.2 for specific information regarding the cardiac monitoring plan and dose modification guidelines, respectively.

2.3.2.3 Other Risk

In addition to the 2 identified risks, potential risks for AMG 176 based on nonclinical findings include:

- gastrointestinal toxicity
- bone marrow toxicity
- male reproductive toxicity
- drug-drug interactions
- hepatobiliary toxicity
- cardiovascular toxicity (for details, see Section 2.2.2.3).

Enrolled subjects will be advised on the risk associated with AMG 176 administration and signs and symptoms of the risks, along with other safety labs, will be monitored during the study and at the appropriate time points to ensure subjects' safety. Please refer to the AMG 176 IB for further description of potential risks.

3. Objectives and Endpoints

Objectives	Endpoints
Primary	
Multiple Myeloma Part 1a (BIW)	
• Evaluate the safety and tolerability of AMG 176 monotherapy in subjects with relapsed or refractory multiple myeloma (MM) and determine the maximum tolerated dose (MTD) for twice weekly (BIW) dosing schedule	• Incidence of Dose-Limiting Toxicities (DLTs), treatment-related and treatment-emergent adverse events, and clinically significant changes in vital signs, electrocardiograms (ECGs), and clinical laboratory tests
• Evaluate the pharmacokinetics (PK) of AMG 176 when administered as monotherapy (BIW)	• PK parameters for AMG 176, including, but not limited to, maximum observed concentration (C_{max}), area under the concentration-time curve (AUC), clearance (CL), and half-life ($t_{½}$)
Multiple Myeloma Part 1b (QW)	
• Evaluate the safety and tolerability of AMG 176 monotherapy in subjects with relapsed or refractory MM and determine the MTD for a once weekly (QW) dosing schedule	• Incidence of DLTs, treatment-related, treatment-emergent adverse events and clinically significant changes in vital signs, ECGs, and clinical laboratory tests
• Evaluate the PK of AMG 176 when administered as monotherapy (QW)	• PK parameters for AMG 176 including, but not limited to C_{max}, AUC, CL, and $t_{½}$
Acute Myeloid Leukemia Part 3a (BIW)	
• Evaluate the safety and tolerability of AMG 176 monotherapy in subjects with relapsed or refractory acute myeloid leukemia (AML) and determine the MTD for BIW dosing as a monotherapy in subjects with relapsed or refractory AML	• Incidence of DLTs, treatment-related, treatment-emergent adverse events and clinically significant changes in vital signs, ECGs, and clinical laboratory tests
• Evaluate the PK of AMG 176 when administered as monotherapy (BIW)	• PK parameters for AMG 176 including, but not limited to C_{max}, AUC, CL, and $t_{½}$
Acute Myeloid Leukemia Part 3b (QW)	
• Evaluate the safety and tolerability of AMG 176 QW monotherapy in subjects with relapsed or refractory AML	• Incidence of DLTs, treatment-related, treatment-emergent adverse events and clinically significant changes in vital signs, ECGs, and clinical laboratory tests
• Evaluate the PK of AMG 176 when administered as monotherapy (QW)	• PK parameters for AMG 176 including, but not limited to C_{max}, AUC, CL, and $t_{½}$
Acute Myeloid Leukemia Part 3c (QW) in Japan	
• Evaluate the safety and tolerability of AMG 176 QW monotherapy in subjects in Japan with relapsed or refractory AML	• Incidence of DLTs, treatment-related, treatment-emergent adverse events and clinically significant changes in vital signs, ECGs, and clinical laboratory tests

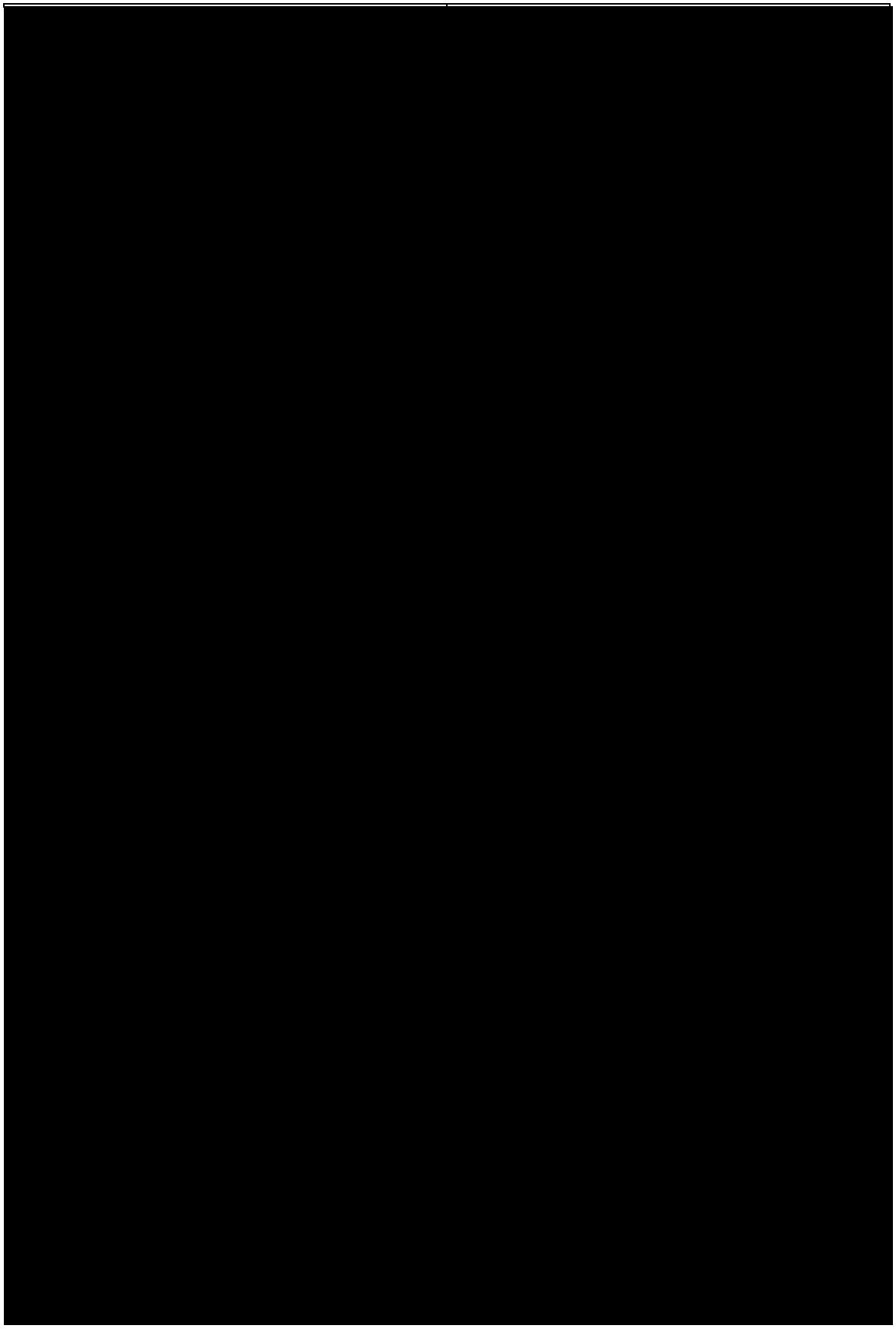
• Evaluate the PK of AMG 176 when administered as monotherapy (QW) in Japan	• PK parameters for AMG 176 including, but not limited to C_{max}, AUC, CL, and $t_{½}$
Acute Myeloid Leukemia Part 3d - Drug-drug Interaction (DDI) Assessment with Itraconazole in United States (US)	
• Evaluate the PK of AMG 176 when given alone and in combination with itraconazole in subjects with AML	• PK parameters for AMG 176 including, but not limited to C_{max}, AUC, CL, and $t_{½}$
Acute Myeloid Leukemia Parts 4 and 5 (QW, BIW, and conventional AML dosing) in combination with azacitidine	
• Evaluate the safety and tolerability of AMG 176 in combination with azacitidine in subjects with relapsed or refractory AML and in Part 4 only, determine the maximum tolerated combination dose (MTCD) of AMG 176 in combination with azacitidine	• Incidence of DLTs (Part 4 only), treatment-related, treatment-emergent adverse events and clinically significant changes in vital signs, ECGs, and clinical laboratory tests
• Evaluate the PK of AMG 176 and azacitidine when administered in combination	• PK parameters for AMG 176 and azacitidine including, but not limited to, C_{max}, AUC, CL, and $t_{½}$
Secondary	
Multiple Myeloma Part 1a (BIW)	
• Demonstrate inactivation of myeloid cell leukemia sequence 1 (MCL1) by the increase of active B-cell lymphoma/leukemia 2 associated X protein (BAX) and caspase 3 in circulating monocytes and/or the decrease of circulating monocytes in AMG 176 BIW treated subjects	• BAX and caspase 3 expression in circulating monocytes and/or circulating monocyte counts
• Evaluate preliminary efficacy of AMG 176 BIW when given as monotherapy in relapsed or refractory MM	• Overall response (OR) according to International Myeloma Working Group uniform response criteria (IMWG-URC) for MM subjects, progression-free survival (PFS), time to response, and duration of response (DOR)
Multiple Myeloma Part 1b (QW)	
• Demonstrate inactivation of MCL1 by the increase of active BAX and caspase 3 in circulating monocytes and /or the decrease of circulating monocytes in AMG 176 QW treated subjects	• BAX and caspase 3 expression in circulating monocytes and /or circulating monocyte counts
• Evaluate preliminary efficacy of AMG 176 QW when given as monotherapy in relapsed or refractory MM	• Overall response according to IMWG-URC for MM subjects, PFS, time to response, and DOR

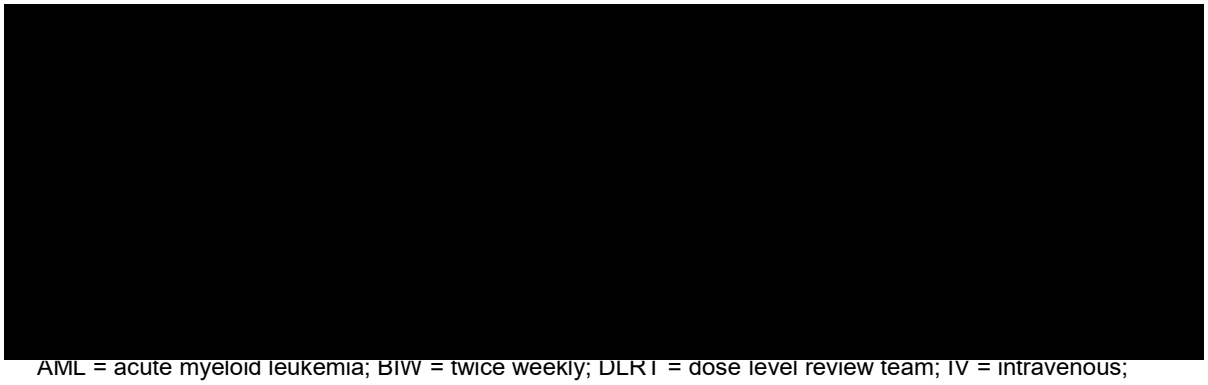
Acute Myeloid Leukemia Part 3a (BIW), Part 3b (QW), and Part 3c (QW)	
• Evaluate preliminary efficacy of AMG 176 when given as monotherapy in relapsed or refractory AML (For Part 3c: Japan subjects only)	• Overall response according to the 2017 European LeukemiaNet (ELN) criteria (Döhner et al, 2017) in AML subjects, event-free survival (EFS), time to response, and DOR (see Section 11.15)
Acute Myeloid Leukemia Part 3d - DDI Assessment with Itraconazole in US	
• Evaluate the safety and tolerability of AMG 176 when given alone and in combination with itraconazole in subjects with AML	• Treatment-emergent adverse events and changes in vital signs, ECGs, and clinical laboratory tests
Acute Myeloid Leukemia Parts 4 and 5 (QW and BIW)	
• Evaluate preliminary efficacy of AMG 176 when given in combination with azacitidine in relapsed or refractory AML	• Overall response according to the 2017 ELN criteria in AML subjects, EFS, time to response, and DOR (see Section 11.15)

Exploratory	
*Multiple Myeloma Part 1a (**BIW**)*	
[redacted]	[redacted]

*Acute Myeloid Leukemia Part 3a (**BIW**) and 3b (QW)*

[redacted]





AML = acute myeloid leukemia; BIW = twice weekly; DLRT = dose level review team; IV = intravenous; MM = multiple myeloma; MTCD = maximum tolerated combination dose; MTD = maximum tolerated dose; mTPI = modified toxicity probability interval; PD = pharmacodynamics; PK = pharmacokinetics; QW = once weekly; RP2D = recommended phase 2 dose; SC = subcutaneous; US = United States

4. Study Design

4.1 Overall Design

This is a phase 1, multicenter, open-label dose-escalation study to define the MTD or recommended dose and **maximum tolerated combination dose (**MTCD**)** as well as the safety, tolerability, PK, PD, and efficacy of AMG 176 administered as monotherapy or in combination with SOC.

A dose-level review team (DLRT) will be responsible for dosing recommendations, which may include escalation to the next nominal or intermediate dose, de-escalation to a lower nominal or intermediate dose; modifications of the ramp-up dosing, alternative dose frequencies, continuation, delay or termination of dosing; or repetition or expansion of a cohort; or determination of recommended dose. For definition of the DLT-evaluation period and DLT-evaluable subject refer to Section 6.2.1.2.1.

Cycles of AMG 176 treatment may continue until confirmed progressive disease (PD) (defined by 2017 European LeukemiaNet [ELN] criteria for AML subjects [Section 11.15]), the subject becomes intolerant to the study medication, signs and symptoms of clinical progression are evident as determined by the principal investigator, or the subject withdraws consent. Evaluation of disease response will be performed every 28 days (± 7 days) until PD irrespective of cycle duration including dose delays or treatment discontinuation. The disease assessment schedule is independent of treatment schedules.

Ramp-up dosing in cycle 1 will be utilized whenever the AMG 176 target dose level is at 180 mg/m² or higher to mitigate the risk of TLS (see Section 6.1.1).

A safety follow-up (SFU) visit must be performed 30 days (+3 days) after the last dose of protocol-required therapies. Long-term follow-up assessments will occur every 3 months (± 14 days) after end of treatment (EOT) for 1 year and include survival, subsequent anti-cancer therapy, and any cardiac associated serious adverse event or studies performed.

The overall study design is described by a study schema in Section 1.2. An overview of the study design is presented in Table 4-1. The endpoints are defined in Section 3.

Table 4-1. Overview of Study Design

Part	Indication	Cohort/Treatment Group	AMG 176 Dose Levels[a, b]	Number of Subjects	Design
CLOSED TO ENROLLMENT					
1a	*Multiple Myeloma*	*AMG 176 BIW monotherapy*	*AMG 176 BIW IV 30, 40, 50, 60, 120, 240 mg/m^2* *Ramp-up Dosing implemented: 180, 240, 360, and 480 mg/m^2*	*36 subjects enrolled*	*A standard 3+3 design was used to identify the MTD (or recommended dose), as well as the safety, tolerability, PK, and PD of AMG 176 administered BIW.*
1b	*Multiple Myeloma*	*AMG 176 QW monotherapy*	*AMG 176 QW IV 180, 240, 360, and 480 mg/m^2*	*12 subjects enrolled*	*A standard 3+3 design was used to identify the MTD (or recommended dose), as well as the safety, tolerability, PK, and PD of AMG 176 administered QW.*
3a	*AML*	*AMG 176 BIW monotherapy*	*AMG 176 BIW IV 60, 120, and 180 mg/m^2*	*17 subjects enrolled*	*A standard 3+3 design was used to identify the MTD, as well as the safety, tolerability, PK, and PD of AMG 176 administered BIW.*
3b	*AML*	*AMG 176 QW monotherapy*	*AMG 176 QW IV 120, 180, and 240 mg/m^2*	*11 subjects enrolled*	*An mTPI design was used to evaluate the safety, tolerability, PK, and PD of AMG 176 administered.*
3c	*AML*	*AMG 176 QW monotherapy Japan-only cohort*	*AMG 176 QW IV 120 mg/m^2*	*4 subjects enrolled in Japan*	*A standard 3+3 design without dose escalation was used to evaluate the safety, tolerability, PK, and PD of AMG 176 administered QW in subjects with AML in Japan.*

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Footnotes defined on last page of the table.

Table 4-1. Overview of Study Design (continued)

Part	Indication	Cohort/Treatment Group	AMG 176 Dose Levels[a, b]	Number of Subjects	Design
OPEN TO ENROLLMENT					
3d	AML	AMG 176 in combination with itraconazole; US-only cohort	AMG 176 QW IV 60 mg/m^2 in combination with itraconazole (200 mg) QD starting on day -3 through day 4 (total of 7 days) only in cycle 1.	**Approximately** 11 subjects	A fixed sequence design (itraconazole plus AMG 176 in week 1, followed by AMG 176 in subsequent weeks) will be used to evaluate the effect of itraconazole (strong CYP3A4 inhibitor) on the PK of AMG 176.
4	AML	AMG 176 in combination with azacitidine	Cohorts 1-4[c]: AMG 176 QW IV (60, 120, 180, and 240 mg/m^2) in combination with azacitidine Cohort 5a[c]: AMG 176 BIW IV (120 mg/m^2) in combination with azacitidine Cohort 5b[c]: AMG 176 BIW IV (240 mg/m^2) in combination with azacitidine	Approximately 60 subjects	An mTPI design will be used to define the combination RP2D. Safety, tolerability, PK, and PD of AMG 176 in combination with azacitidine will also be established. Part 4 enrollment will begin once 120 mg/m^2 of Part 3b is cleared as safe and tolerable by the DLRT. Azacitidine will be administered at a dose of 75 mg/m^2 either IV or SC, as recommended in the prescribing information, daily for the first 7 days of a 28-day cycle.
5**A**	AML	AMG 176 (QW or BIW) in combination with azacitidine	Cohort 1-2: RP2D in combination with azacitidine	Approximately **48** subjects[d]	Part 5 (dose expansion) will begin once the combination RP2D has been determined from Part 4. **Simon's two-stage minimax design (Simon, 1989) will be used for conducting trial in each cohort of Part 5A. The null hypothesis is that the true response rate (CR or CRi) is 0.1 and the alternative hypothesis is that the true response rate (CR or CRi) is 0.32. The design controls the two-sided type I error rate at 0.05 and yields the power of 0.8. The total estimated sample size is 48, with 24 subjects in each cohort.**

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Footnotes defined on last page of the table

Table 4-1. Overview of Study Design (continued)

Part	Indication	Cohort/Treatment Group	AMG 176 Dose Levels[a, b]	Number of Subjects	Design
OPEN TO ENROLLMENT					
5**B**	AML	AMG 176 conventional dosing	AMG 176 on 3 consecutive days the first week, and BIW on weeks 2 and 3 each cycle (Regimen 1) and on 5 consecutive days the first week, and BIW on week 2 for each cycle (Regimen 2)	Approximately 20 subjects[d,e]	Two regimens will be tested, both utilizing a 28-day cycle. Regimen 1 consists of receiving AMG 176 at 240 mg/m² QD for 3 days + 4 days off followed by BIW dosing on weeks 2 and 3. If this schedule is deemed safe by the DLRT after 6 subjects have enrolled on Regimen 1, Regimen 2 subjects will receive AMG 176 at 240 mg/m² QD for 5 consecutive days, and then BIW on week 2. **The enrollment of Part 5B will start after Part 5A is complete.**

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AML = acute myeloid leukemia; BIW = twice weekly; **CR = complete response; CRI = complete response/remission with incomplete recovery of peripheral blood counts;** DLRT = dose-level review team; IV = intravenous; MM = multiple myeloma; MTCD= maximum tolerated combination dose; MTD = maximum tolerated dose; mTPI = modified Toxicity Probability Interval; OBD = optimal biological dose; PD = pharmacodynamic; PK = pharmacokinetics; **QD = once daily;** QW = once weekly; RP2D = recommended phase 2 dose; SC = subcutaneous; US = United States.

[a] Ramp-up dosing in cycle 1 will be utilized whenever the target dose level is at 180 mg/m^2 or higher. Ramp-up dosing consists of an initial dose at cycle 1 week 1 of 120 mg/m^2 followed by an increase to the target dose level for subsequent doses.

[b] AMG 176 will be administered in monthly cycles of treatment. Each cycle AMG 176 BIW is defined as an IV infusion once daily for two consecutive days followed by a 5-day break and repeated each week for 3 weeks followed by one week with no treatment. Intravenous BIW begins at study day 1. Each cycle of AMG 176 QW is defined as an IV infusion once weekly followed by a 6-day break and repeated each week either for 3 weeks followed by one week with no treatment, or for 4 consecutive weeks. Intravenous QW begins at study day 1.

[c] Twice weekly AMG 176 dosing schedule may be investigated at the same time, in the same dose, or at a lower dose as the QW AMG 176 dosing schedule. Note: Part 2 was designed to be a combination treatment for MM in a previous amendment. It was removed due to a change in AMG 176 clinical development.

[d] Study team may modify the actual number of subjects enrolled at a given dose level/frequency based on emerging data, but the total number of all subjects in Part 5 will remain approximately 68.

[e] If Regimen 2 is deemed safe by the DLRT, then further enrollment to Part 5**B** may proceed at either Regimen 1 or Regimen 2, as determined by the study team.

4.1.1 AMG 176 Monotherapy (Part 3b) and Combination with Azacitidine (Parts 4 and 5) for AML

Part 3b (AML) will include weekly doses of AMG 176 monotherapy at 120, 180, and 240 mg/m^2 to inform the combinational therapy cohorts in Parts 4 and 5. Clinical trial results from Part 1a and Part 1b demonstrated that dose levels of AMG 176 of less than or equal to 240 mg/m^2 (Part 1a BIW; Part 1b QW) were not associated with increased troponin in contrast to the 360 mg/m^2 dose level where 2 of 8 subjects experienced a DLT (troponin elevation). Additionally, clinical responses in AML were observed at doses ≤ 240 mg/m^2. To avoid the potential for cardiac toxicity with the MTD of 360 mg/m^2, only doses ≤ 240 mg/m^2 will be further investigated on this study, with this dose representing the monotherapy RP2D. Additionally, preclinical data demonstrates that MCL1 inhibition is more efficacious in combination with other antileukemic therapies. Consequently, combinational therapy will be prioritized in this study to optimize the clinical benefit to subjects (Parts 4 and 5).

Part 4 will start with AMG 176 60 mg/m^2 in combination with azacitidine and will begin after completion of the 120 mg/m^2 AMG 176 monotherapy cohort in Part 3b. The decision to initiate enrollment in Part 4 will be made by the DLRT after the review of all available safety and tolerability data from the 120 mg/m^2 AMG 176 monotherapy cohort. Following Part 4 (combination dose exploration), a dose expansion phase (Part 5) will be conducted in approximately 6**8** subjects to confirm safety, PK, and PD at the MTCD and to obtain additional safety and efficacy data.

Additionally, dose levels lower than 30 mg/m^2 may also be explored if required or supported by emerging data. Intermediate doses and alternative dose frequencies may also be used if required or supported by emerging data. For each part, DLTs will be assessed during DLT evaluation period. See Section 6.2.1.2.2 for defined DLTs for MM and AML. Subjects who complete the DLT evaluation period (see Section 6.2.1.1) without experiencing a DLT may proceed to a higher dose level within Part 3b or crossover to Part 4 combinational therapy for the following treatment cycle once the target cohort has been deemed safe by the DLRT and after consultation with the sponsor. Dose-limiting toxicities experienced by subjects who proceeded to a higher dose or combination treatment as described above will not be considered for dose level decisions. However, the DLRT will take this information into account to inform dose escalation recommendations.

For AML Part 3b and Part 4, each dose cohort will initially enroll 3-4 subjects and up to 10 subjects per cohort may be enrolled. After reviewing all available safety and tolerability data, dose level decisions (eg, escalation/de-escalation/expansion) will be made by the DLRT using a modified Toxicity Probability Interval (mTPI) model (Ji et al, 2010) based on all subjects that have been enrolled at current dose. Dose escalation is considered to be complete if one of the following rules is met:

- The highest planned dose level is evaluated, MTD/MTCD has not been defined and no DLTs occur at any dose level. In this case the maximum administrated dose (MAD) may be used for phase 2.
- An MTD/MTCD is identified.

Guidelines for dose level decisions can be found in Table 4-2. Details regarding the mTPI model and dose finding are described in Section 11.16. Please note one exception to the guidelines provided in Table 4-2, a single grade 3 treatment-related troponin elevation will result in dose de-escalation regardless of number of subjects treated at current dose.

Table 4-2. Guidelines for Dose-level Decisions for Part 3b and Part 4

No. of DLT-evaluable[a] subjects treated at current dose	Number of DLTs		
	Escalate	Stay at current dose	De-escalate[b]
3	0	1	≥ 2
6	0-1	-	≥ 2
9	0-1	2	≥ 3
10[c]	0-1	2-3	≥ 4

DLT = dose-limiting toxicity
[a] A subject is considered DLT-evaluable if he/she experienced a DLT during the DLT evaluation period or if he/she received 75% of the planned doses of AMG 176 and completed the DLT evaluation period.
[b] De-escalate guideline applies only when current dose level and enrollment is allowed to a lower dose level.
[c] The maximum number of evaluable subjects at one dose level is 10.

The MTD/MTCD is defined as the highest dose with a probability of DLT lower than or close to a targeted toxicity probability of 0.2.

For the first dose level and at each new higher dose level, the first enrolled subject will be treated, and then after a period of 72 hours, subsequent subjects will be treated, provided that there are no significant toxicities relating to the treatment of the first subject.

In addition to safety, efficacy of complete remission per ELN in Part 4 will be evaluated. At MTCD or optimal biological dose (OBD), 1 complete remission out of 6 subjects, or 2 complete remissions out of 10 subjects are expected.

Upon completion of Part 4, enrollment will commence in Part 5A to confirm the safety and tolerability of the two selected doses along with the dosing schedule (QW or BIW) and to further evaluate the preliminary efficacy of AMG 176 in combination with azacitidine. In Part 5A, approximately 48 subjects will be enrolled, with 24 subjects randomized to the cohort of AMG 176 120 mg/m² in combination with azacitidine and 24 subjects randomized to the cohort of AMG 176 240 mg/m² in combination with azacitidine, where the same dosing schedule (QW or BIW) will be used for both cohorts. Simon's two-stage minimax design (Simon, 1989) will be used for conducting the trial in each cohort of Part 5A. Details about Simon's two-stage minimax design are provided in Section 9.4.1.1.

In Part 5B, 20 subjects will be enrolled to test 2 regimens. The enrollment of Part 5B will start after Part 5A is complete. Regimen 1 consists of administering AMG 176 at 240 mg/m² QD for 3 days + 4 days off followed by BIW dosing on weeks 2 and 3. If this schedule is deemed safe by the DLRT after 6 subjects have enrolled on Regimen 1 cohort, the next 6 subjects in Regimen 2 cohort will receive AMG 176 at 240 mg/m² QD for 5 consecutive days, and then BIW on week 2. Safety data will be monitored continually.

4.1.2 AMG 176 Tolerability in Subjects with AML in Japan (Part 3c)

AML subjects will be confirmed according to a standard 3+3 design without dose escalation. Three subjects with relapsed or refractory AML will be enrolled into Part 3c and treated with AMG 176 using the QW dosing schedule (see Part 1b for description). Three additional subjects will be enrolled if 1 of initial 3 subjects experience a DLT. A dose with > 33% subjects experiencing a DLT is defined as not tolerable. The tolerable dose of investigational drug is defined as a dose at which fewer than one-third of subjects experience a DLT. If 2 or more of 6 subjects experience a DLT, appropriate action will be discussed by DLRT.

4.1.3 Drug-drug interaction Assessments with Itraconazole in the United States (Part 3d)

A separate cohort of **about** 11 subjects with AML will be enrolled for this DDI assessment using a fixed sequence design (Figure 1-7), where AMG 176 will be

co-administered with itraconazole during week 1 followed by dosing of AMG 176 alone in subsequent weeks. Since subjects are hospitalized during the first week of AMG 176 dosing, itraconazole administration will be limited to the first week to ensure proper monitoring and oversight of subjects in the event of increased exposure to AMG 176. A 7-day sentinel dosing will be utilized between the first and second subject enrolled in this cohort. All safety data available will be evaluated in the first subject prior to enrolling all subsequent subjects.

Subjects will receive:

- Oral itraconazole capsules (200 mg) QD starting at 8 am on day -3 through day 4 (total of 7 days) to achieve adequate CYP3A4 inhibition prior to, and following, AMG 176 administration.
- Intravenous AMG 176 (60 mg/m^2) on day 1 at approximately the same time as itraconazole dosing (± 5 minutes).

Serial PK sampling will be conducted at specified time points after the AMG 176 dose on day 1 to characterize the plasma concentrations of AMG 176 when given in combination with itraconazole. Subjects will receive AMG 176 (60 mg/m^2) alone on day 8 and day 15. Serial PK sampling will be conducted at specified time points after the AMG 176 dose on day 15 to characterize the plasma concentrations of AMG 176 without itraconazole. AMG 176 pharmacokinetics will be compared from day 1 (with itraconazole) relative to day 15 (without itraconazole). After day 15, subjects will be eligible to receive the highest cleared monotherapy or combination therapy dose if deemed safe by the investigator and Amgen medical monitor.

4.2 Number of Subjects

Subjects with relapsed or refractory MM and subjects with relapsed or refractory AML are eligible for this study (see Section 5). It is anticipated that **approximately** 21**9** subjects will be enrolled in the different parts of this study.

CLOSED TO ENROLLMENT: Multiple myeloma Part 1a enrolled 36 subjects for dose escalation. Multiple myeloma Part 1b enrolled 12 subjects for dose escalation. Acute myeloid leukemia Part 3a enrolled 17 subjects for dose escalation. Acute myeloid leukemia Part 3c enrolled 4 subjects in Japan. Part 3b enrolled 11 subjects.

OPEN TO ENROLLMENT: Part 3d will enroll **about** 11 subjects in the US. Part 4 will enroll approximately 60 subjects. Part 5 will enroll approximately 6**8** subjects.

The rationale for the number of subjects required is detailed in Section 9.2.

Subjects in this clinical investigation shall be referred to as “subjects”. For the sample size justification, see Section 9.2.

4.2.1 Replacement of Subjects

During dose escalation, subjects who are not DLT-evaluable will be replaced (see Section 6.2.1.1). Subjects in Part 3d who are unable to complete the 3-week period will be replaced. Subjects will not be replaced for any other reason.

4.2.2 Number of Sites

The study will be conducted at approximately 7 to 23 sites in North America, Australia, Asia, and Europe.

4.3 Justification for Investigational Product Dose

AMG 176 is administered as an IV infusion once daily twice weekly (BIW) followed by 5 days break in Part 1a, Part 3a, and cohorts 5a and 5b of Part 4. AMG 176 is administered as an IV infusion for one day followed by 6 days break (QW); in Part 1b, 3b, 3c, 3d, and 4 (cohorts 1-4). This schedule was repeated for a total of 3 consecutive weeks followed by 1 week off in the earlier parts of the study, which are now closed to enrollment (ie, Parts 1a, 1b, and 3a). AMG 176 was administered QW in Part 3c, which is now closed to enrollment, for a total of 4 consecutive weeks. AMG 176 **was** administered QW in Parts 3b, 3d, and 4 (cohorts 1-4) for a total of 4 consecutive weeks and BIW in Part 4 (cohorts 5a and 5b) for the first 3 weeks of each 28-day cycle. Additionally, AMG 176 will be administered in Part 5 either QW for a total of 4 consecutive weeks or BIW for the first 3 weeks of each 28-day cycle. This 28-day duration is considered 1 cycle. Ramp-up dosing of 120 mg/m^2 will be utilized whenever the target dose level is at 180 mg/m^2 or higher, applicable to all indications (AML or MM) and all dosing schedules (BIW or QW) to mitigate the risk of TLS (see Section 4.1).

The AMG 176 doses proposed in this study are:

<u>Multiple Myeloma</u>

- For MM Part 1a BIW potential dose levels are: 30, 40, 50, 60, 120, 180, 240, 360, and 480 mg/m^2 of AMG 176 (IV; BIW).
- For MM Part 1b QW potential dose levels are: 180, 240, 360, and 480 mg/m^2 of AMG 176 (IV; QW). The starting dose level will be 180 mg/m^2 tested with BIW dosing in MM subjects but dosing will be only one day per week instead of day 1 and day 2.

Acute Myeloid Leukemia

- For AML Part 3a of the study, potential dose levels are: 60, 120, and 180 mg/m^2 of AMG 176 (IV; BIW). The starting dose level will be the latest dose tested in MM subjects and cleared as safe and tolerable by the DLRT up to a maximum starting dose of 60 mg/m^2. Part 3a doses will be given once daily twice weekly (BIW) followed by a 5-day break and repeated each week for 3 weeks followed by 1 week with no treatment.
- For AML Part 3b, potential dose levels are: 120, 180, and 240 mg/m^2 of AMG 176 (IV; QW). For AML Part 3c, the potential dose level is 120 mg/m^2 (IV; QW). For AML Part 3d, the dose selected is 60 mg/m^2 (IV; QW).
- For AML Part 4 of the study, potential dose levels are: 60, 120, 180, and 240 mg/m^2 of AMG 176 (IV; QW or BIW). Investigations of QW and BIW dosing schedule may run in parallel. Part 4 will start after 120 mg/m^2 dose cohort(s) of Part 3b is cleared as safe and tolerable by the DLRT. Subjects in Japan will be enrolled in Part 4 after safety and tolerability is confirmed in Part 3c by the DLRT.
- For AML Part 5**A**, 2 cohorts will be enrolled: Cohorts 1 and 2 will evaluate 2 different dose levels to determine the optimal biological dose (OBD) on either a QW or BIW dosing schedule.
- AML Part 5**B**, will evaluate AMG 176 first under Regimen 1 dosing (3 consecutive days on week 1, BIW on weeks 2 and 3) for 6 subjects. If this schedule is deemed safe by the DLRT, the next 6 subjects will proceed under Regimen 2 dosing (days 1 - 5 on week 1, BIW on week 2). If Regimen 2 is deemed safe by the DLRT, then the remaining enrollment to Part 5**B** will employ the Regimen 2 dosing schedule.

4.3.1 Starting and Maximum Planned Doses

The proposed clinical starting dose of 30 mg/m^2 was based on the HNSTD noted in GLP toxicology study in Beagle dogs and the STD10 in GLP toxicology study in rats, which were found to be 10 mg/kg and 60 mg/kg administered daily, respectively. This corresponds, per ICH S9 Guidance, to a human daily equivalent dose of 33 mg/m^2 and 36 mg/m^2. AMG 176 human PK parameters were predicted from a combination of in vitro and in vivo nonclinical data. It was assumed that AMG 176 PK parameters remained constant and did not depend on doses or time. At the starting dose of 30 mg/m^2 BIW, the predicted exposure margins of maximum observed concentration (C_{max}) and area under concentration-time curve (AUC) to the rat STD10 were 174-fold and 400-fold, respectively. The predicted exposure margins of C_{max} and AUC to the dog HNSTD were estimated at 64-fold and 180-fold, respectively, for BIW (see Table 4-1). While no preclinical data exist for QW dosing, it is anticipated that the C_{max} for a QW dose regimen would be roughly equivalent to the respective dose level BIW (ie, the C_{max} for a 60 mg/m^2 dose QW would be similar to that following a 60 mg/m^2 dose given BIW). Meanwhile, the AUC is expected to be significantly less for QW dosing compared to BIW. For this reason, the exposure margins for C_{max} and AUC for the QW arm are

predicted to be about the same and greater, respectively, for the rat STD10 and the dog HNSTD.

4.3.1.1 Multiple Myeloma

The highest planned dose in MM subjects was 480 mg/m^2 for MM subjects BIW. Safety and tolerability data from prior dose levels will guide the dose escalations and the planned top dose for AMG 176 in the dose escalation phase (see Section 4.1).

The AMG 176 PK-tumor dynamic relationships were characterized by the tumor dynamic models with data collected from athymic nude mice bearing OPM-2 tumors after multiple doses of AMG 176 following BIW or QW regimens. The tumor dynamic model described tumor growth, drug inhibitory effect and tumor volume change over the treatment period in control- and AMG 176-treated mice. To project human efficacious dose, it was assumed that it required at least the same AMG 176 plasma concentration in human as that in mice for inhibiting tumor growth. The predicted ED_{50} for monotherapy in humans was therefore 360 mg/m^2 or 480 mg/m^2, following BIW or QW dosing regimens, respectively.

4.3.1.2 Acute Myeloid Leukemia

4.3.1.2.1 Part 1a

As described above in Section 4.3.1.

4.3.1.2.2 Part 3b and 3c

For AML Part 3b and 3c, the starting dose is 120 mg/m^2 QW, which is based on prior clinical experience that demonstrated significant clinical efficacy in subjects with AML (Section 2.3.1) and a lower risk of troponin elevation. Increased troponin has been designated as an identified risk (Section 2.3.2); however, no troponin elevations were observed at total weekly doses of 120 mg/m^2 or 180 mg/m^2. Together, these data suggest that a dose of 120 mg/m^2 administered QW will be safe and efficacious in subjects with AML. Dose levels of 180 mg/m^2 and 240 mg/m^2 of AMG 176 administered QW as monotherapy may also be investigated in Part 3b based on review of safety data by the DLRT. For safety data at levels exceeding 240 mg/m^2 of AMG 176, see Section 2.2.2.4.

4.3.1.2.3 Part 3d

For AML Part 3d, the dose selected is 60 mg/m^2 (IV, QW), which was selected based on considerations of the predicted magnitude of the DDI during co-administration with itraconazole and available safety and efficacy data.

Itraconazole is widely used as a strong index inhibitor of CYP3A4 in clinical DDI studies based on potency and specificity of CYP3A4 inhibition and is also a clinical inhibitor for P-gp (Chen et al, 2019; Liu et al, 2016; US FDA, 2016). Patients with AML are susceptible to invasive fungal infections and often require prophylaxis and treatment with antifungal agents such as voriconazole and posaconazole (Halpern et al, 2015; Lat and Thompson, 2011), which are known to inhibit CYP3A4 and P-gp. AMG 176 is metabolized, in part, by CYP3A4, and is a P-gp substrate; hence, co-administration with inhibitors of CYP3A4/P-gp may lead to increases in AMG 176 exposure. As a result, clinical trials with AMG 176 previously prohibited the use of medications that are strong CYP3A4/P-gp inhibitors, including voriconazole and posaconazole.

A DDI assessment is planned in a separate cohort of AML subjects (Part 3d) in the FIH study 20150161 to evaluate the effect of itraconazole, a strong CYP3A4 and P-gp inhibitor, on the pharmacokinetics of AMG 176. In Part 3d, subjects receive oral itraconazole capsules (200 mg) QD starting at 8 am on day -3 through day 4 (total of 7 days) to achieve adequate CYP3A4/P-gp inhibition prior to, and following, AMG 176 administration. AMG 176 is dosed QW on day 1 of week 1 through 3. Data analysis is conducted to assess AMG 176 exposure changes with or without co-administration of itraconazole (exposures on week 1 vs week 3).

As of November 2022, preliminary data were available for 5 subjects from Part 3d AMG 176 60 mg/m² in combination with itraconazole. Preliminary analyses indicate no trend for increases in AMG 176 exposure with concomitant administration of itraconazole, although a trend towards decreases in AMG 176 exposure was observed: point estimates for C_{max} and area under the concentration time curve from 0 to 168 hours ($AUC_{0\text{-}168\ hr}$) ratios for AMG 176 with and without itraconazole were 0.62 (90% CI 0.15, 1.10) and 0.79 (90% CI 0.24, 1.33), respectively. Based on the current understanding of the DDI mechanism between AMG 176 and itraconazole, a decrease in exposure is not expected; the trend for decrease is likely due to the large PK variability and 1 outlier subject. Further analyses will be conducted as more subject data (up to 11 subjects) become available.

A less than 1.4-fold increase in exposure is expected for AMG 176 when co-administered with itraconazole indicating a weak to no DDI, based on the analyses of preliminary clinical data from Part 3d and physiologically-based pharmacokinetic (PBPK) modeling and simulation (Section 4.3.1.2.3.1). Consequently, in Protocol

Amendment 15 the exclusion criterion for co-administration of AMG 176 with azole antifungal therapies that are strong CYP3A4/P-gp inhibitors was removed.

4.3.1.2.3.1 Predicted Magnitude of DDI

A preliminary PBPK model was developed in the Simcyp Simulator (version 20) and was used to predict the magnitude of DDI with itraconazole, a strong CYP3A4 and P-gp inhibitor. Briefly, a compound file for AMG 176 was developed and verified based on in vitro and available clinical data of AMG 176 monotherapy across multiple dosing regimens. Simcyp library model files for itraconazole and the primary metabolite OH-itraconazole were used as inhibitors of CYP3A4. The preliminary PBPK model was used to simulate the effect of itraconazole (200 mg × 7 days from day -3 through day 4) on AMG 176 given concurrently as a 60, 120, 180, and 240 mg/m² QW **IV** infusion over 2 hours on day 1 using population representative or virtual population simulation. The predicted AUC ratio was 1.2 to 1.4. Based on this preliminary PBPK modeling analysis, a weak to no DDI is predicted when AMG 176 is co-administered with itraconazole.

4.3.1.2.3.2 Safety

Increased troponin is an identified risk for AMG 176 based on available safety data from the first trial that evaluated a range of doses from 30 to 480 mg/m^2 given QW or twice weekly (BIW) to subjects with AML and MM. Troponin elevations in AML and MM subjects studied to date were observed primarily at higher dose levels of 360 and 480 mg/m^2 (BIW); troponin elevations were not reported for dose levels of 120 mg/m^2 (QW and BIW), 180 mg/m^2 (QW and BIW), and 240 mg/m^2 (QW and BIW). Based on existing data, the 60 mg/m^2 dose selected for this DDI assessment provides an estimated 6-fold safety margin in the event of increased exposures with itraconazole with respect to doses associated with troponin elevations in AML and MM subjects studied to date.

4.3.1.2.3.3 Efficacy

In AML subjects in the FIH study, 2 subjects achieved complete response with incomplete cell recovery (CRi) (1 subject each at 60 and 120 mg/m^2 BIW) and 1 subject achieved a PR (at 60 mg/m^2 BIW) (Section 2.3.1). The 60 mg/m^2 dose selected for this DDI assessment may provide therapeutic benefit for subjects based on the clinical responses observed to date.

In summary, the AMG 176 dose selected (60 mg/m^2 QW) for Part 3d has an estimated 6-fold safety margin with respect to doses associated with troponin elevations. This dose is expected to be safe and tolerated during co-administration with itraconazole in

the event of an increase in AMG 176 plasma concentrations. The AMG 176 dose selected is additionally expected to provide potential therapeutic benefit to subjects. For Part 3d, after week 3, subjects may crossover to Part 3b or Part 4 for continued treatment if approved by the investigator and Amgen medical monitor.

4.3.2 Justification for the AML Conventional Dosing Schedule (5 Consecutive Days)

Amgen's preclinical humanized mouse modeling supports a conventional AML dosing schedule of AMG 176 (5 consecutive days) as more efficacious compared with QW or BIW dosing. The model did not demonstrate any increased or prolonged hematotoxicity with conventional AML dosing. However, markedly greater tumor growth inhibition was observed.

Preliminary population PK modeling of the conventional AML dosing regimen (240 mg/m² QD for 5 days on, followed by 2 days off) demonstrated no concerning PK accumulation (< 2-fold) after multiple QD dosing of AMG 176. Compared to BIW (240 mg/m²) dosing, the conventional dosing regimen (240 mg/m² QD for 5 days on, followed by 2 days off) achieved C_{max} and $AUC_{0\text{-}168\ hr}$ within a 2-fold range (median C_{max} increased 1.1-fold and median $AUC_{0\text{-}168\ hr}$ increased 1.9-fold at the relevant target dose).

Preliminary dose-exposure-response analyses were conducted for troponin elevations in R/R MM and R/R AML subjects for AMG 176 (QW or BIW) administered as monotherapy or in combination with azacitidine, including subjects with troponin elevation as primary or secondary event due to other safety events (such as sepsis) or progression of disease. Based on data from the conventional troponin assay (ADVIA Centaur®, cut-off upper reference limit of 0.04 or 0.1 ng/ml), preliminary exposure-response analyses for potential AMG 176 induced cardiac troponin elevation indicated no clear exposure-response correlation. Based on data from an exploratory high sensitivity troponin assay (Abbott Architect HS TnI), preliminary dose-response analyses indicated correlation of troponin elevation with increasing AMG 176 dose levels, but no concerning troponin elevation have been observed at dose levels less than or equal to 240 mg/m² QW or BIW.

Considering no significant PK accumulation and < 2-fold increase in exposures for the conventional dosing regimen compared to the BIW dosing regimen at 240 mg/m² dose level, concerning troponin elevation is not expected for the conventional dosing regimens.

Consequently, preclinical data and PK modeling supports the clinical investigation of the conventional AML dosing schedules. With preclinical animal studies showing greater efficacy with conventional AML dosing, Amgen explores here the safety of a more conventional AML dosing regimen (ie, 5 consecutive days of AMG 176 administration during week 1 of a cycle).

4.3.3 Justification of the Monotherapy Recommended Phase 2 Dose (RP2D)

In the current study, **P**art 1 and **P**art 2 were initially designed to investigate tapotoclax as monotherapy and combinational therapy in subjects with multiple myeloma (MM). As of December 2019, 48 subjects were enrolled in **P**art 1 where clinical responses were observed at dose levels > 240 mg/m². At that time, tapotoclax-associated elevations of troponin were observed at dose levels of 360 mg/m² and 480 mg/m². Consequently, to avoid the potential for troponin elevations, only doses less than equal to 240 mg/m² are currently under investigation. Additionally, monotherapy efficacy of tapotoclax in AML has been limited, with an overall response rate (ORR = CR + incomplete hematologic recovery [CRi]) of 9.4% (3 out of 32 subjects) in monotherapy **P**arts 3a, 3b, and 3c (all responses were CRi). In contrast, increased antileukemic activity has been observed in combination with azacitidine. Consequently, combination therapy has been prioritized in the current study (**P**arts 4 and 5) to optimize the clinical benefit to subjects, and monotherapy investigations were completed to support the combination therapy studies.

As of November 2022, in AML subjects, 2 out of 17 subjects in **P**art 3a (ORR = 11.8%), 1 out of 11 subjects in **P**art 3b (ORR = 9.1%), 0 out of 4 subjects in **P**art 3c (ORR = 0%), and 3 out of 21 subjects in **P**art 4 (ORR = 14.3%) have achieved the best overall response of CR or CRi. With the 21 AML subjects who received combination tapotoclax plus azacitidine in **P**art 4, 12 subjects had at least 1 evaluable disease response; 2 subject (9.6%) had CR; 1 subject (4.8%) had CRi; 8 subjects (38.1%) had stable disease (SD); 1 subject (4.8%) had PD (9 subjects [42.9%] did not have an evaluable disease response) (see Table 2-1 for details). Three out of 21 subjects (14.3%) achieved CRi or better in all cohorts in **P**art 4, and 2 out of 6 subjects (33%) achieved CR in tapotoclax 240 mg/m² QW plus azacitidine cohort, demonstrating a better response at the 240 mg/m² dose compared with lower doses when administered in combination with azacitidine.

Preliminary PK/PD modeling for tapotoclax (monotherapy or in combination with azacitidine) to date have shown subtherapeutic exposures with regard to the estimated minimum efficacious exposures for tapotoclax at doses below 240 mg/m².

The observed dose-exposure ($AUC_{0\text{-}168\ hr}$)-efficacy relationship for tapotoclax in combination with azacitidine demonstrated better response with increased tapotoclax dose and exposure, indicating a preliminary dose-exposure-response relationship for efficacy in the combination therapy setting.

As a result of these data, tapotoclax 240 mg/m² is the monotherapy recommended phase 2 dose (RP2D).

4.3.4 Dose Optimization Plan to Inform Combination Recommended Phase 2 Dose (RP2D)

The recommended combinational phase 2 dose (RP2D) will be estimated using the totality of data from across the FIH study, including the PK, safety, efficacy, PD [redacted] for efficacy, and other results from the dose escalation and dose expansion. Dose-exposure-response analyses for safety and efficacy will be conducted to inform the RP2D.

Two dose levels will be selected for the expansion phase based on the preliminary dose–exposure–response analyses and PK/PD modeling using available data from preclinical and dose escalation phase. In order to minimize bias, assignments will be randomized to each dose level **in Part 5A**. Pharmacokinetic exposure separation, minimal dose expected to achieve efficacy, highest dose with acceptable safety profile and other aspects will be considered for dose selection of the expansion phase.

AMG 176 has exhibited a predictable PK/PD profile. Based on the available data from the dose escalation part of Study 20150161, preliminary dose-exposure analyses indicated dose-related increases in exposure with mean terminal elimination $t_{½}$ of approximately 4 to 23 hours in AML subjects. Preliminary dose-exposure-response analyses in subjects with relapsed or refractory (R/R) MM and in subjects with R/R AML demonstrated no concerning safety signals, including troponin elevations, at AMG 176 doses of 240 mg/m² or less (QW or BIW) when administered as monotherapy or in combination with azacitidine. Preliminary efficacy is observed at a range of dose levels from 60 to 240 mg/m² for AMG 176 monotherapy and in combination with azacitidine in AML subjects.

Further dose exposure response analyses and PK/PD modeling based on the totality of data (PK, safety, efficacy, PD [redacted] for efficacy), using all data from dose escalation and dose expansion, will be conducted to develop robust doseexposureresponse relationships to guide the selection of the combination RP2D, designated as the dose that achieves maximum efficacy with acceptable toxicity in the target AML population.

4.4 Justification for Non-investigational Product Dose

4.4.1 Azacitidine

For Parts 4 and 5**A**, the dose of azacitidine for the first treatment cycle, for all subjects regardless of baseline hematology laboratory values, is 75 mg/m^2 subcutaneously **(SC)** or **IV**, daily for the first 7 days of a 28 day cycle (as per local prescribing information).

For Part 5B, all subjects will receive 7 days of azacitidine IV or SC daily at 75 mg/m² on days 1 - 5, 8 - 9 of each 28-day cycle. Prophylactic treatment to mitigate nausea and vomiting will be administered.

4.4.2 Itraconazole

Itraconazole is widely used as a strong index inhibitor of CYP3A4 in clinical DDI studies based on potency and specificity of CYP3A4 inhibition (Chen et al, 2019; Liu et al, 2016; US FDA, 2016). For Part 3d, the itraconazole dose selected is oral capsules 200 mg QD starting on day -3 through day 4 (total of 7 days). This dose level and duration is consistent with recommendations outlined by the Innovation and Quality of Pharmaceutical Development's Clinical Pharmacology Leadership Group (IQ-CPLG) that were based on an extensive literature review of clinical DDI studies with itraconazole (Liu et al, 2016) and verified using mechanistic PBPK modeling approaches (Chen et al, 2019). The current assessment will continue to require itraconazole dosing to cover 4 to 5 half-lives of AMG 176 in order to ensure adequate CYP3A4 inhibition during the elimination phase of AMG 176. The estimated $t_{½}$ of AMG 176 ranges from approximately 4 to 25 hours across the range of doses evaluated, with most subjects exhibiting a $t_{½}$ of approximately 8 to 12 hours. Hence, an additional 3 days of itraconazole dosing after the AMG 176 dose on day 1 is considered adequate.

4.5 End of Study

4.5.1 End of Study Definition

Primary Completion: The primary completion date is defined as the date when the last subject is assessed or receives an intervention for the final collection of data for the primary endpoint(s).

The primary completion date is the date when data for the primary endpoint are last collected for the purposes of conducting the last primary analysis (see Section 9.4.1.2).

If the study concludes prior to the primary completion date originally planned in the protocol (ie, early termination of the study), then the primary completion will be the date when the last subject is assessed or receives an intervention for evaluation in the study (ie, last subject last visit).

End of Study: The end of study date is defined as the date when the last subject across all sites is assessed or receives an intervention for evaluation in the study (ie, last subject last visit), following any additional parts in the study (eg, long-term follow-up, additional antibody testing), as applicable.

4.5.2 Study Duration for Subjects

It is anticipated that each subject will be on study for approximately 2 weeks for screening, 6 months for the treatment period plus a 30-day (+3 days) safety follow-up visit after the last dose of protocol-required therapies. The estimated study duration for **subjects** from screening through the safety follow-up visit is 7.5 months but this may be longer or shorter depending on the subject's disease, ability to tolerate AMG 176, and/or willingness to participate in the study. In addition, long-term follow-up assessments will occur every 3 months (± 14 days) after EOT for up to 1 year.

5. Study Population

Investigators will be expected to maintain a screening log of all potential study candidates that includes limited information about the potential candidate (eg, date of screening).

Eligibility criteria will be evaluated during screening.

Before any study-specific activities/procedures, the appropriate written informed consent must be obtained (see Section 11.3).

5.1 Inclusion Criteria

Subjects are eligible to be included in the study only if all of the following criteria apply:

All subjects:

101 Subject has provided informed consent prior to initiation of any study-specific activities/procedures.

103 Must be willing and able to undergo a core bone marrow biopsy (MM and AML subjects) and bone marrow aspirate (MM and AML subjects) at screening. Core bone marrow biopsy or bone marrow aspirate performed as prior SOC can be used to meet screening requirements if performed within 4 weeks from enrollment

and no curative anti-cancer therapy was administered during the time from biopsy to enrollment.

105 Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2

106 Age ≥ 18 years old

- For subjects in Japan only: if a subject is younger than 20 years at the time of signing the informed consent form, informed consent must be obtained from both the subject and his/her legal representative

107 Life expectancy of > 3 months, in the opinion of the investigator

109 Hepatic function, as follows; total bile acid (TBA) < 5 × upper limit of normal (ULN), aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 3 × ULN, total bilirubin ≤ 1.5 × ULN (except subjects with Gilbert's syndrome).

110 Cardiac function, as follows; left ventricular ejection fraction (LVEF) greater than or equal to 50%. 2-D transthoracic echocardiogram (ECHO) is the preferred method of evaluation. Multigated Acquisition Scan (MUGA) is acceptable if ECHO is not available.

111 Calculated or measured creatinine clearance (CrCl) of ≥ 30 mL/minute calculated using the formula of Cockcroft and Gault [(140 – Age) × Mass (kg) / (72 × Creatinine mg/dL)]. Multiply result by 0.85 if female.

112 Female subjects of childbearing potential must have a negative serum or urine pregnancy test within 3 days of the first dose (see Section 11.5 for definition of females of childbearing potential).

Multiple myeloma subjects only:

102 Pathologically documented, definitively diagnosed, MM relapse or refractory PD and have received at least 2 therapeutic treatments or regimens for MM. The investigator must be of the opinion that no other treatment option will result in a durable response.

104 Measurable disease per the International Myeloma Working Group (IMWG) response criteria (assessed within 28 days prior to enrollment), as indicated by one or more of the following:

- Serum M-protein ≥ 0.5 g/dL
- Urine M-protein ≥ 200 mg/24 hours
- Subjects who do not meet 1 of the 2 prior criteria: serum free light chain (SFLC) > 10 mg/dL (≥ 100 mg/L) and an abnormal SFLC ratio (< 0.26 or > 1.65) as per the IMWG response criteria

108 Hematological function, as follows without transfusion or growth factor support:

- Absolute neutrophil count (ANC) ≥ 1.0 × 10^9/L
- Platelet count ≥ 50X 10^9/L (in subjects where < 50% of bone marrow nucleated cells were plasma cells) or ≥ 30 × 10^9/L (in subjects where ≥ 50% of bone marrow nucleated cells were plasma cells) without transfusion or growth factor support
- Subjects should not have received platelet transfusions for at least 1 week prior to screening

- Hemoglobin ≥ 8 g/dL
- Screening ANC should be independent of granulocyte- and granulocyte/macrophage colony stimulating factor (G-CSF and GM-CSF) support for at least 1 week and of pegylated G-CSF for ≥ 2 weeks

Acute myeloid leukemia subjects only:

113 AML as defined by the World Health Organization (WHO) Classification (Section 11.14) persisting or recurring following one or more treatment courses, and for subjects in Japan, determined by the investigator to be not eligible for approved anticancer drug therapy in Japan; EXCEPT acute promyelocytic leukemia (APL). The investigator must be of the opinion that no other treatment option will result in a durable response. In Part 5**A** cohorts 1 and 2, enrollment will be restricted to subjects with persisting or recurring AML after 1 to 2 lines of prior therapy.

114 Greater than or equal to 5% blasts (or blast equivalents) in bone marrow.

115 Circulating white blood cells (WBCs) < 25 000/μL.

5.2 Exclusion Criteria

Subjects are excluded from the study if any of the following criteria apply:

All subjects:

201 Previously received an allogeneic stem cell transplant within 6 months OR having received immunosuppressive therapy within the last 3 months OR having signs or symptoms of acute or chronic graft-versus-host disease.

202 Autologous stem cell transplant less than 90 days prior to enrollment.

209 Currently receiving treatment in another investigational device or drug study. Other investigational procedures while participating in this study will be allowed if approved by Amgen medical monitor.

210 History of other malignancy within the past 2 years prior to enrollment, with the following exceptions:

- Malignancy treated with curative intent and with no known active disease present for ≥ 2 years before enrollment and felt to be at low risk for recurrence by the treating physician
- Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease
- Adequately treated cervical carcinoma in situ without evidence of disease
- Adequately treated breast ductal carcinoma in situ without evidence of disease
- Prostatic intraepithelial neoplasia without evidence of prostate cancer
- Adequately treated urothelial papillary noninvasive carcinoma or carcinoma in situ

211 Known sensitivity to any of the products or component to be administered during dosing.

212 Myocardial infarction within 6 months of enrollment, symptomatic congestive heart failure (New York Heart Association > class II).

213 History of arterial thrombosis (eg, stroke or transient ischemic attack) in the past 6 months prior to enrollment.

214 Active infection requiring IV anti-infective treatments within 1 week of enrollment

215 Known or suspected human immunodeficiency virus (HIV) infection or subjects who are HIV seropositive. Testing will be performed if required by local regulatory authorities.

216 Exclusion of hepatitis B and C infection based on the following results:

- Positive for hepatitis B surface antigen (HbsAg) (indicative of chronic hepatitis B or recent acute hepatitis B)
- Negative HbsAg and positive for hepatitis B core antibody (HbcAb) and/or hepatitis B surface antibody (HBsAb; Japan only): hepatitis B virus DNA by polymerase chain reaction (PCR) is necessary. Detectable hepatitis B virus DNA suggests occult hepatitis B. Negative for PCR test can be enrolled in the study
- Positive Hepatitis C virus antibody (HCVAb): hepatitis C virus RNA by PCR is necessary. Detectable hepatitis C virus RNA suggests chronic hepatitis C. Negative for PCR test can be enrolled in the study

217 Unresolved toxicities from prior anti-tumor therapy, defined as not having resolved to Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 grade 1, or to levels dictated in the eligibility criteria with the exception of grade 2 peripheral neuropathy, alopecia or toxicities from prior anti-tumor therapy that are considered irreversible (defined as having been present and stable for > 4 weeks may be allowed if they are not otherwise described in the exclusion criteria AND there is agreement to allow by both the investigator and sponsor).

218 Treatment with medications known to cause QT interval corrected (QTc) interval prolongation within 1 week prior to enrollment unless approved by the Amgen Medical Team.

219 Anti-tumor therapy: chemotherapy, antibody therapy, molecular targeted therapy, or investigational agent within 5 times the $t_{½}$ of the drug, or until the relevant biological effect has resolved (whichever is longer). Exceptions: hydroxyurea to control peripheral blood leukemic cell counts is allowed until prior to receiving the first dose of AMG 176. Hydroxyurea is unapproved for AML in Japan.

220 Prior systemic radiation therapy must have been completed at least 28 days prior to enrollment. Prior focal radiotherapy completed at 14 days prior to enrollment.

221 Major surgery within 28 days of enrollment.

235 Women of reproductive potential who are unwilling to practice an acceptable method of highly effective birth control while on study through 3 months after receiving the last dose of study drug. Men who are unwilling to practice sexual abstinence (refrain from heterosexual intercourse) or use a condom with spermicide during treatment and for an additional 4 months following the last dose of study drug if sexually active with a female of childbearing potential. For acceptable methods of highly effective birth control, and definition of females of childbearing potential see Section 11.5.

223 Women planning to become pregnant or breastfeed while on study through 3 months after receiving the last dose of study drug. Subjects who suspend breastfeeding prior to starting treatment with study drug and do not intend to resume breastfeeding before 3 months after receiving the last dose of study drug can be enrolled

236 Male subjects who are unwilling to abstain from donating sperm during treatment and for an additional 4 months following the last study drug administration

224 History or evidence of any other clinically significant disorder, condition or disease that, in the opinion of the investigator or Amgen physician, if consulted, would pose a risk to subject safety or interfere with the study evaluation, procedures or completion.

225 Use of any medications (except anti-tumor medications), including herbal medicines (eg, St. John's wort), vitamins, or supplements consumed by the subject within 5 times the $t_{½}$ of the drug, or until the relevant biological effect has resolved (whichever is longer), and continuing use if applicable, that was not reviewed and approved by the principal investigator and the Amgen medical monitor prior to enrollment. Written documentation of this review and Amgen acknowledgment is required for subject participation.

226 Use of known strong inhibitors of CYP3A4 within 5 times the $t_{½}$ or until the relevant biological effect has resolved (whichever is longer), prior to enrollment unless reviewed and approved by the principal investigator and the Amgen medical monitor prior to enrollment. Written documentation of this review is required for subject participation. Exception: use of azole antifungal therapies falling into this category based on the current data from Part 3d subjects.

228 Use of known CYP3A4 sensitive substrates with a narrow therapeutic window within 5 times the $t_{½}$ of the drug or its major active metabolite or until the relevant biological effect has resolved (whichever is longer), following the last dose of the drug prior to receiving the first dose of AMG 176 unless reviewed and approved by the principal investigator and the Amgen medical monitor prior to enrollment. Written documentation of this review and Amgen acknowledgment is required for subject participation. Refer to prescribing information for any concomitant medications

229 Use of known OATP1B1 and/or OATP1B3 or BCRP substrates with a narrow therapeutic window within 5 times the $t_{½}$ of the drug or its major active metabolite or until the relevant biological effect has resolved (whichever is longer), following the last dose of the drug prior to enrollment unless reviewed and approved by the principal investigator and the Amgen medical monitor prior to enrollment. Written documentation of this review and Amgen acknowledgment is required for subject participation. Refer to prescribing information for any concomitant medications.

230 Subject likely to not be available to complete all protocol required study visits or procedures, and/or to comply with all required study procedures (eg, Patient Reported Outcomes) to the best of the subject and investigator's knowledge.

231 Subjects with elevated cardiac troponin above the manufacturer's 99th percentile upper reference limit (URL) for ADVIA Centaur XP assay (0.04 ng/mL for females and 0.059 ng/mL for males) at screening confirmed by the central laboratory.

232 Subjects with evidence of recent cardiac injury at screening based on creatine kinase-muscle/brain (CK-MB), N-terminal prohormone of brain natriuretic peptide (NT-pro-BNP), and electrocardiogram (ECG) assessments at screening.

239 DDI assessment cohort with itraconazole only: History of QT prolongation, torsades de pointes, ventricular tachycardia, and cardiac arrest

240 History or evidence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection unless agreed upon with medical monitor and meeting the following criteria:

- negative test for SARS-CoV-2 RNA by real time polymerase chain reaction (RT-PCR) within 72 hours prior to first dose of AMG 176; and
- no acute symptoms of coronavirus disease 2019 (COVID-19) within 10 days prior to first dose of AMG 176 (counted from day of positive test for asymptomatic subjects)

241 Prior treatment with an MCL1 inhibitor.

Multiple myeloma subjects only:

203 Multiple myeloma with IgM subtype.

204 POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes).

205 Existing plasma cell leukemia or rapidly proliferating extra medullary disease unless discussed and approved by Amgen medical monitor prior to enrollment.

206 Waldenstrom's macroglobulinemia.

207 Amyloidosis.

208 Glucocorticoid therapy (prednisone > 30 mg/day or equivalent) within 7 days prior to enrollment. Topical or inhaled corticosteroids are permitted.

5.3 Subject Enrollment

Before subjects begin participation in any study-specific activities/procedures, Amgen requires a copy of the site's written institutional review board/independent ethics committee (IRB/IEC) approval of the protocol, informed consent form, and all other subject information and/or recruitment material, if applicable (see Section 11.3).

The subject must personally sign and date the IRB/IEC and Amgen approved informed consent before commencement of study-specific procedures. For Part 3c only: If a subject is younger than 20 years at the time of signing the informed consent, informed consent must be obtained both from the subject and his/her legal representative.

Each subject who enters into the screening period for the study receives a unique subject identification number before any study-related activities/procedures are performed. The subject identification number will be assigned manually **or automatically**. This number will be used to identify the subject throughout the clinical study and must be used on all study documentation related to that subject.

The unique study identification number will consist of 11 digits. The first 3 digits will represent the last 3 digits of the protocol number (eg, 161). The next 5 digits will

represent the country code and site number (eg, 66001) and will be identical for all subjects at the site. The next 3 digits will be assigned in sequential order as subjects are screened (eg, 001, 002, 003). For example, the first subject to enter screening at US site 66001 will receive the number 16166001001, and the second subject at the same site will be 16166001002. The subject identification number must remain constant throughout the entire clinical study; it must not be changed after initial assignment, including if a subject is rescreened.

All screening tests and procedures should be performed within 14 days of administration of the first dose of AMG 176 (day 1), or itraconazole (ie, day -17 to day -3) for Part 3d, unless otherwise indicated. Subjects may be re-screened up to 2 additional times at the discretion of the investigator. The subject must be re-consented if a re-screening attempt occurs outside of the 14-day screening period. Subjects who are deemed ineligible will be documented as screen failures (see Section 5.4).

Subjects may be eligible to enroll once all screening tests and procedures are completed and results indicate that all eligibility criteria are met. A site representative will complete and send the subject registration form and/or enrollment eligibility worksheet to the sponsor or designee. The Amgen representative will acknowledge receipt and return confirmation of dose cohort (dose exploration part) or group (dose expansion part), respectively, to the site.

A subject is considered enrolled when the investigator decides that the subject has met all eligibility criteria. The investigator is to document this decision and date, in the subject's medical record and in/on the enrollment case report form (CRF).

The subject identification number must remain constant throughout the entire clinical study; it must not be changed after initial assignment, including if a subject is rescreened.

5.4 Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently dosed with AMG 176. A minimal set of screen failure information will be collected that includes demography, screen failure details, eligibility criteria, and any serious adverse events.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. Refer to Section 8.1.1.

6. Treatments

Study treatment is defined as any investigational product(s), non-investigational product(s), placebo, or medical device(s) intended to be administered to a study subject according to the study protocol.

Note that in several countries, investigational product and non-investigational product are referred to as investigational medicinal product and non-investigational medicinal product, respectively.

The Investigational Product Instruction Manual (IPIM), a document external to this protocol, contains detailed information regarding the storage, preparation, destruction, and administration of each treatment.

6.1 Treatment(s) Administered

The Amgen Investigational Product used in this study is AMG 176. The non-investigational products used in this study (azacitidine) may be considered investigational in some countries.

The Investigational Product Instruction Manual (IPIM), a document external to this protocol, contains detailed information regarding the storage, preparation, destruction, and administration of AMG 176.

6.1.1 Investigational Product: AMG 176

All investigational products will be administered at the research facility by a qualified staff member. A physician must be available at the time of administration of Investigational Product.

Description

AMG 176 is an anhydrous crystalline material that is a white to light brown powder, which is formulated as a sterile concentrate for solution for infusion. The solution is administered IV after dilution into an IV bag containing normal saline (0.9% sodium chloride).

Dosage Form

The AMG 176 investigational product is formulated as a sterile concentrate for solution for infusion at a concentration of 25 mg/mL in 10% w/w 2-hydroxypropyl beta-cyclodextrin, and buffered with 100 mM glycine to pH 9.0. AMG 176 is supplied as a sterile, preservative-free solution for IV infusion.

Drug Supply and Storage

AMG 176 will be supplied as either a 10 mL liquid deliverable volume in a single use **(**20**R)** glass vial or a 14.4 mL liquid deliverable volume in a single use **(**30**R)** glass vial.

The primary container closure system for the 10 mL presentation consists of a 20**R** borosilicate glass vial with a 20 mm elastomeric stopper, and an aluminum seal with flip-off dust cover. A single use vial containing 14.4 mL fill of 25 mg/mL AMG 176 has also been developed for use in the clinic. Additional details are provided in the IPIM.

It is recommended that AMG 176 be stored at or below 25°C, protected from light, and according to the storage and expiration information (where required) provided on the label that is affixed to the package containing the investigational product.

Dosage, Administration, and Schedule

AMG 176 will be administered on a 28-day cycle. The dosing schemes include BIW administration for 3 weeks of 4 in a cycle (6 doses per cycle, see below), QW administration every week of the cycle (4 doses per cycle, see below), or a conventional AML dosing scheme administering azacitidine in combination with AMG 176 (7 doses per cycle). Prior to dosing on day 1 of every cycle, body surface area (BSA) must be calculated. Each cycle of AMG 176 BIW is defined as an IV infusion once daily for 2 consecutive days followed by a 5-day break and repeated each week for 3 weeks (Part 1a, 3a, 4 [cohorts 5a and 5b]) followed by 1 week with no treatment. Intravenous BIW begins at study day 1. Each cycle of AMG 176 QW is defined as an IV infusion QW followed by a 6-day break and repeated each week either for 3 weeks followed by 1 week with no treatment (Part 1b), or for 4 consecutive weeks (Parts 3b, 3c, and 4 [cohorts 1-4]). Dosing begins at study day 1. Part 5 dosing will be based on MTCD determined in Part 4.

Ramp-up dosing will be utilized whenever the target dose level is at 180 mg/m^2 or higher to mitigate the risk of TLS. Ramp-up dosing consists of an initial dose at cycle 1 week 1 of 120 mg/m^2 followed by an increase to the target dose level for subsequent doses. Decisions regarding the AMG 176 ramp-up dosing period regimen, ramp-up period starting dose, dosing increments, will be made by DLRT and communicated to the IRB/IEC, as appropriate (see Section 11.3).

Tumor lysis syndrome prophylaxis must be initiated in all subjects prior to all ramp-up dosing of AMG 176 and prior to all subsequent dose escalations (ie, first dose on the targeted cohort dose level). Hospitalization and monitoring should begin the night before

AMG 176 administration and must continue until at least the 24-hour post-dose (QW schedule) or until 48 hours post the first dose in the BIW dosing schedule. Refer to Section 6.1.4.1 for additional details on prophylaxis and management of TLS.

The AMG 176 dose, start date/time, stop date/time and lot number is to be recorded for each subject in the electronic CRF (eCRF).

The AMG 176 infusion time will be 120 (± 5) minutes.

If a subject develops a reaction during or after the AMG 176 infusion, immediate treatment should be initiated according to best clinical practice. Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. All medication and symptoms should be documented in the eCRF.

Intra-subject Dose Escalation

For each part, DLTs will be assessed during the DLT evaluation period. Subjects who complete the DLT-observation period without experiencing a DLT may proceed to a higher dose level or different dosing schedule cohort once the target cohort has been deemed safe by the DLRT and after consultation with the sponsor. Dose-limiting toxicities experienced by subjects who proceeded to a higher dose or different schedule will not be considered for dose level decisions. However, the DLRT will take this information into account to inform dose escalation recommendations.

6.1.2 Non-investigational Products: Azacitidine and Itraconazole

In some countries, the non-investigational products used in this study (azacitidine and itraconazole) may be considered investigational based on regional requirements.

Refer to regional prescribing information for full details regarding azacitidine and itraconazole, respectively.

6.1.2.1 Azacitidine (Parts 4 and 5)

Description

Azacitidine is a pyrimidine nucleoside analog of cytidine. The empirical formula is $C_8H_{12}N_4O_5$. The molecular weight is 244 g/mol.

The mechanism of action is through hypomethylation of DNA and direct cytotoxicity. Hypomethylation may restore normal function to genes that are critical for differentiation and proliferation. The concentration of azacitidine required for maximum inhibition of DNA methylation in vitro does not cause major suppression of DNA synthesis.

Formulation

Azacitidine is a white to off-white solid. Azacitidine was found to be insoluble in acetone, ethanol, and methyl ethyl ketone; slightly soluble in ethanol/water (50/50), propylene glycol, and polyethylene glycol; sparingly soluble in water, water-saturated octanol, 5% dextrose in water, N-methyl-2-pyrrolidone, normal saline, and 5% Tween 80 in water; and soluble in dimethylsulfoxide (DMSO).

The finished product is supplied in a sterile form for reconstitution as a suspension for **SC** injection or reconstitution as a solution with further dilution for IV infusion.

Storage

Store unreconstituted vials at 25°C; excursions permitted to 15°C to 30°C (5°F to 86°F).

Accountability

Sites will be required to record and document subject compliance regarding azacitidine dosing. The quantity administered, route, start date/time, stop date/time, and lot number of azacitidine are to be recorded on each subject's CRF(s). Stop date/time is required to be recorded on each subject's CRF(s) only for IV administrations.

Azacitidine will not be supplied by Amgen for this study unless required by local regulation or in response to a regional supply shortage. In Japan, azacitidine will be supplied by Amgen for this study.

Packaging

Azacitidine is supplied as a lyophilized powder in 100 mg single use vials packaged in cartons of 1 or 2 vial(s). Vials contain 100 mg of azacitidine and 100 mg of mannitol as a sterile lyophilized powder.

Dosage, Administration, and Schedule

For Parts 4 and 5A, azacitidine will be administered at a dose of 75 mg/m^2 either IV or SC, as recommended in the prescribing information, daily for the first 7 days of a 28day cycle. The dose may be increased to 100 mg/m^2 if no beneficial effect is seen after 2 cycles and if no toxicity other than manageable nausea and vomiting has occurred.
For Part 5B, all subjects will receive 7 days of azacitidine IV or SC daily at 75 mg/m² on days 1 - 5, 8 - 9 of each 28-day cycle.

On days where azacitidine is co-administered with AMG 176, azacitidine will be given before AMG 176. A minimum of a 30-minute gap between the administration of azacitidine and AMG 176 is recommended.

6.1.2.2 Itraconazole (Part 3d)

Description

Itraconazole is a synthetic triazole antifungal agent. Itraconazole is a 1:1:1:1 racemic mixture of 4 diastereomers (2 enantiomeric pairs), each possessing 3 chiral centers. Itraconazole has a molecular formula of $C_{35}H_{38}Cl_2N_8O_4$ and a molecular weight of 705.64.

The mechanism of action is through inhibition of the cytochrome P450-dependent synthesis of ergosterol, which is a vital component of fungal cell membranes.

Formulation

Itraconazole is a white to slightly yellowish powder. It is insoluble in water, very slightly soluble in alcohols, and freely soluble in dichloromethane. It has a pKa of 3.70 (based on extrapolation of values obtained from methanolic solutions) and a log (n-octanol/water) partition coefficient of 5.66 at pH 8.1.

Itraconazole capsules contain 100 mg of itraconazole coated on sugar spheres (composed of sucrose, maize starch, and purified water). Inactive ingredients are hard gelatin capsule, hypromellose, polyethylene glycol 20 000, titanium dioxide, FD&C Blue No. 1, FD&C Blue No. 2, D&C Red No. 22, and D&C Red No. 28.

Storage

Store at 15°C to 25°C. Protect from light and moisture.

Accountability

Oral itraconazole capsules should be taken with a full meal. Sites will be required to record and document subject compliance regarding itraconazole dosing.

Itraconazole will not be supplied by Amgen for this study unless required by local regulation.

Packaging

Itraconazole is supplied as a commercially available oral capsule containing 100 mg of itraconazole, with a blue opaque cap and pink transparent body. The capsules are supplied in unit-dose blister packs of 3 × 10 capsules, bottles of 30 capsules, and in the PulsePak® containing 7 blister packs × 4 capsules each.

Dosage, Administration, and Schedule

Subjects will receive oral itraconazole capsules (200 mg) QD starting at approximately 8 am on day -3 through day 4 (total of 7 days) to achieve adequate CYP3A4 inhibition prior to, and following, AMG 176 administration.

6.1.3 Medical Devices

There are no investigational devices in this study.

Other non-investigational medical devices may be used in the conduct of this study as part of standard care.

Non-investigational medical devices (eg, syringes, sterile needles), that are commercially available are not usually provided or reimbursed by Amgen (except, for example, if required by local regulation). The investigator will be responsible for obtaining supplies of these devices.

6.1.4 Other Protocol-required Therapies

All other protocol-required therapies including, allopurinol, that are commercially available are not provided or reimbursed by Amgen (except if required by local regulation). The investigator will be responsible for obtaining supplies of these protocol-required therapies.

6.1.4.1 Tumor Lysis Prophylaxis (All Subjects)

There is a potential for TLS in subjects affected by hematologic malignancies especially in those with bulky disease, elevated pretreatment lactate dehydrogenase (LDH) levels, elevated leukocyte count, renal dysfunction, and dehydration. To mitigate the risk of TLS, AMG 176 ramp-up dosing (see Section 6.1.1) will be used and TLS prophylaxis must be initiated in all subjects prior to all ramp-up dosing of AMG 176 and prior to all subsequent dose escalations (ie, first dose on the targeted cohort dose level). In Part 5**B**, subjects will receive ramp-up dosing on days 1 and 2 of week 1 in cycle 1 followed by the target dose starting on day 3. Prior to administering these doses, all electrolyte values (including potassium, uric acid, phosphorous, calcium, and creatinine) should be reviewed and must be within normal range. However, LDH is not mandatory.

All subjects will be hospitalized to monitor for TLS and all TLS monitoring assessments will be performed as outlined in the Schedule of Assessments (see Section 1.3).

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 conducted per institutional protocols (Coiffier et al, 2008; Cairo et al, 2004).

Tumor lysis syndrome prophylaxis includes:

- Allopurinol or equivalent should be used to reduce uric acid level. This should be initiated at least 72 hours prior to dosing. Treatment may need to be continued for up to 5 weeks. Other agents to reduce uric acid level, such as rasburicase, may be used per principal investigator discretion and the institutional guidelines. Dosing per institutional guidelines.
- NOTE: Allopurinol is unapproved for TLS prophylaxis in Japan.
- Hospitalization and monitoring, should begin the night before AMG 176 administration and must continue until at least 24 hours post-dose (QW schedule) or until 48 hours post the first dose in the BIW dosing schedule
- NOTE: Subjects in Part 3c will be hospitalized for a minimum of 29 days beginning from the night before AMG 176 administration in the first cycle.
- IV hydration must be started the night before AMG 176 administration and to be continued until at least 24 hours post–dose (QW schedule) during hospitalization as clinically tolerated (refer to Section 11.8.1 for more details about the level of IV hydration required)
- Monitoring of electrolyte values is required prior to dosing anytime a dose is higher than one previously given to the subject. This will include at the following times:
  - Prior to the week 1, day 1 dose
  - Prior to each dose during the ramp-up period
  - Prior to the initial dosing at the target dose level
- Prior to administering these doses, all electrolyte values (including LDH, potassium, uric acid, phosphorus, calcium and creatinine) must be reviewed and within normal range (samples must be drawn within 24 hours prior to dosing of AMG 176). The investigator's decision to proceed with AMG 176 treatment initiation will be based on these laboratory values.

Within the first 24 hours after either the first dose or dose escalation, if any laboratory criteria for TLS are met, no additional AMG 176 doses should be administered until resolution. A rapidly rising serum potassium is a medical emergency.

Prophylactic dose reductions for potassium, phosphorus and/or uric acid values at the high end of normal range should be considered.

If the potassium, uric acid, inorganic phosphate and/or creatinine values are higher than the normal range or the calcium is lower or higher than the normal range, this (these) value(s) can be approved following a discussion between the Amgen medical monitor and investigator.

On the AMG 176 dosing days chemistry labs must be performed pre-dose (within 4 hours before AMG 176 administration), 2, 4, 8, 12 and 24 hours after the start of AMG 176 infusion. Pre-dose labs will be used as baseline to assess potential

electrolytes abnormalities occurring post AMG 176 administration. These labs must be reviewed in real time by the investigator.

Day 2 dosing of AMG 176 (BIW schedule) should not be administered until the 24 hours post dose laboratory values are reviewed by the investigator.

All 24-hour laboratory assessments may be taken ± 2 hours, if necessary.

Monitor for signs and symptoms of TLS (eg, fever, chills, tachycardia, nausea, vomiting, diarrhea, diaphoresis, hypotension, muscle aches, weakness, paresthesias, mental status changes, confusion, and seizures). If any clinical features are observed, recheck potassium, phosphorus, uric acid, calcium and creatinine within 1 hour.

Additional information on the management recommendations of laboratory abnormalities can be found in Section 11.2.

- Nephrology (or acute dialysis service) consultation should be considered on admission (based on investigator discretion) for hospitalized subjects per institutional guidelines to ensure emergency dialysis is available and the appropriate staff is aware and prepared.

6.1.5 Other Treatment Procedures

There are no other treatment procedures in this protocol.

6.1.6 Product Complaints

A product complaint is any written, electronic or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a drug(s), combination product, or device(s) after it is released for distribution to market or clinic by either (1) Amgen or (2) distributors or partners for whom Amgen manufactures the material. This includes all components distributed with the drug, such as packaging drug containers, delivery systems, labeling, and inserts.

This includes any investigational or non-investigational product(s) provisioned and/or repackaged/modified by Amgen.

Any product complaint(s) associated with an investigational product(s) or non-investigational products supplied by Amgen are to be reported according to the instructions provided in the IPIM.

6.1.7 Excluded Treatments, Medical Devices, and/or Procedures During Study Period

The following medications and/or therapies should not be administered within the timeframes specified prior to enrollment or during the study (unless otherwise specified below):

- Allogenic stem cell transplant

- Autologous stem cell transplant
- Anti-tumor therapy (chemotherapy, antibody therapy, molecular targeted therapy, retinoid therapy, or investigational agent or procedures); concurrent use of bisphosphonates or denosumab for bone loss are permitted. In subjects with AML hydroxyurea is allowed to control blasts as described in Section 6.7.2.
- NOTE: Hydroxyurea is unapproved for AML in Japan.
- Treatment with medications known to cause QTc interval prolongation unless approved by the Amgen Medical Team
- Any live vaccine therapies used for the prevention of infectious disease
- Any major surgery or radiotherapy unless agreed upon by Amgen and investigator
- Over the counter medication(s) that was not reviewed and approved by the principal investigator and the Amgen medical monitor
- Herbal medicines (eg, St. John's wort) that were not reviewed and approved by the principal investigator and the Amgen medical monitor

The use of certain medications and illicit drugs within 5 half-lives or 28 days, whichever is shorter prior to the first dose of study drug and for the duration of the trial will not be allowed. If a prohibited medication is required for single use (such as for a procedure) while study drug is held, the Amgen medical monitor can approve such use.

The following medications or non-drug therapies are prohibited:

- Use of known strong inhibitors of CYP3A4/P-gp such as ketoconazole, itraconazole, HIV protease inhibitors, nefazodone, cyclosporine, erythromycin, clindamycin, tetracycline, and clarithromycin within the 14 days or 5 times the $t_{½}$ of the drug, or until the relevant biological effect has resolved (whichever is longer); or products containing grapefruit, Seville oranges, or St. John's wort within 7 days, prior to enrollment. Exception: use of azole antifungal therapies.
- Use of known CYP3A4 sensitive substrates with a narrow therapeutic window (such as pimozide, and sirolimus) within 5 half-lives of the drug or its major active metabolite, whichever is longer, following the last dose of the drug prior to receiving the first dose of AMG 176. Refer to prescribing information for concomitant medications.
- Use of known OATP1B1 and/or OATP1B3 substrates with a narrow therapeutic window within 5 half-lives of the drug or its major active metabolite, whichever is longer, following the last dose of the drug prior to enrollment. Refer to prescribing information for concomitant medications.
- Use of known BCRP substrates with a narrow therapeutic window within 5 half-lives of the drug or its major active metabolite, whichever is longer, following the last dose of the drug prior to enrollment. Refer to prescribing information for concomitant medications.

- Use of oral contraceptives (either combined or progesterone only), estrogenic vaginal ring/percutaneous contraceptive patches, or implants of levonorgestrel/Injectable progesterone for the purpose of pregnancy prevention is prohibited in this study as it is not known if there is the potential of inhibition/induction of enzymes that affect the metabolism of estrogens and/or progestins. However, oral contraceptives may be used for the treatment of menorrhagia or other abnormal menstrual bleeding at the discretion of the investigator.

If use of any other prior or concomitant medication or procedure is in question, please refer to prescribing information and/or consult with the Amgen medical monitor.

There are no prohibited therapies and procedures during the 30-day safety follow-up or the long-term follow-up.

6.1.8 Concomitant Medications with Itraconazole (Part 3d only)

Itraconazole has the potential to interact with many concomitant drugs. Please refer to the current itraconazole US Prescribing Information (USPI) for additional information including:

- Medications which are contraindicated and prohibited during and after the last dose of itraconazole administration
- Medications which are not recommended during and after the last dose of itraconazole administration
- The following medications are contraindicated with itraconzale and should not be administered during concomitant administration with itraconazole: cisapride, oral midazolam, nisoldipine, pimozide, quinidine, dofetilide, triazolam, levacetylmethadol (levomethadyl), and ergot alkaloids such as dihydroergotamine, ergometrine (ergonovine), ergotamine, and methylergometrine (methylergonovine). This is not an exhaustive list; please refer to itraconazole USPI for additional details.

6.2 Dose Modification

6.2.1 Dose-cohort Study Escalation/De-escalation and Stopping Rules

Dose Level Determination

The DLRT will be responsible for dosing recommendations, which may include escalation to the next nominal or intermediate dose, de-escalation to a lower nominal or intermediate dose; modifications of the ramp-up dosing, alternative dose frequencies, continuation, delay or termination of dosing; or repetition or expansion of a cohort; or determination of recommended dose. Refer to Section 11.3 for additional details regarding the DLRT.

6.2.1.1 Dose-Limiting Toxicity Evaluation Period

The minimum DLT evaluation period is defined as 4 weeks of treatment in cycle 1.

The DLT evaluation period may also be extended to assess events starting within the evaluation period in case the DLT definition is time dependent (neutropenia or thrombocytopenia, see below).

Subjects are considered DLT-evaluable if they experienced a DLT during the DLT evaluation period or if they received 75% of the planned doses of AMG 176 (and 100% of the planned doses of azacitidine in Part 4) and completed the DLT evaluation period.

Subjects who did not complete 75% of the planned doses of AMG 176 (and 100% of the planned doses of azacitidine in Part 4) or discontinue from the study prior to completing the DLT evaluation period for reasons other than a DLT will be considered non DLT-evaluable for dose escalation decisions and MTD/MTCD determination and will be replaced by an additional subject at that same dose level. Subjects who receive supportive care during the DLT evaluation period that confounds the evaluation of DLTs (not including supportive care described in Section 6.2.1.2 as part of the DLT definition) may be considered non-evaluable for dose escalation decisions and MTD determination and replaced at the discretion of the Medical Monitor.

6.2.1.2 Definition of Dosage Limiting Toxicities

A DLT will be defined as any of the events described below occurring in a subject during the DLT evaluation period and regarded by the investigators and/or Amgen medical monitor to be related to AMG 176.

Any adverse event occurring outside the DLT evaluation period that is determined by the investigator to be possibly related to the investigational product, which is seen more frequently or is more severe than expected or is persistent despite appropriate management, can be determined to be a DLT upon unanimous decision by the DLRT after review of the adverse event and all available safety data. The grading of adverse events will be based on the guidelines provided in the CTCAE version 4.0 (available online at http://evs.nci.nih.gov/ftp1/CTCAE/About.html). For troponin elevation, refer to Section 6.2.1.2.2 for CTCAE grading interpretation. Determination of the severity of adverse events will be consistent with CTCAE version 4.0. The relationship of an adverse event to investigational product will be determined by the investigator. An event should be considered related to treatment if, in the investigator's medical judgment, there is a reasonable possibility that the event may have been caused by AMG 176.

6.2.1.2.1 Dose-Limiting Toxicities

A DLT is defined as a grade 3 or higher non-hematological or a grade 4 hematologic adverse event that occurs during the DLT observation period (day 1 through day 28 after the administration of the first dose of AMG 176) in Parts 1 BIW and QW Dose Escalation unless clearly attributable to causes other than AMG 176 treatment.

If a DLT of TLS is observed during the ramp-up period, it will be attributed to the ramp-up period and a modification may be made to the ramp-up period regimen for subsequent groups. Any other DLTs observed during the ramp-up and/or designated group dosing period may require a modification of the designated cohort dose (and/or ramp-up period regimen, if appropriate) as directed per the Dose Escalation Guidelines.

Available study data, including data collected after the initial DLT-observation period along with demographics, investigational product administration, medical history, concomitant medications, adverse events, ECG, vital signs, laboratory results, and PK/PD information will be reviewed. In addition to DLTs, all ≥ grade 3 toxicities not meeting DLT criteria will be reviewed and may be considered in DLRT decisions. Modeling of available potential safety risk data (eg, for thrombocytopenia) to predict safety risk for dose escalation decisions may also be considered.

Table 6-1. DLT Criteria

	Multiple Myeloma Subjects	Acute Myeloid Leukemia Subjects	All Subjects
DLT Criteria	• Non-hematologic adverse events: - grade 3 nausea, vomiting, or diarrhea persisting more than 3 days despite optimal medical support. ≥ grade 4 nausea, vomiting, or diarrhea of any duration would be considered as a DLT - grade 3 fatigue lasting > 7 days - ≥ grade 3 acute kidney injury (creatinine > 3 × baseline or > 4.0 mg/dL) lasting > 3 days - any treatment-related death	• Non-hematologic adverse events: - ≥ grade 3 non-hematologic adverse event that is not clearly resulting from the underlying leukemia - recurrence within the DLT window of any adverse events listed under the non-hematologic adverse event exception (not including nausea and vomiting) - any grade 2 non-hematologic adverse event lasting > 7 days that causes significant symptoms, dangerous medical repercussions, or warranting treatment interruption or dose reduction - ≥ grade 3 nausea, vomiting or diarrhea persisting more than 3 days despite optimal medical support - ≥ grade 3 fatigue persisting > 7 days - any other ≥ grade 3 adverse event - failure to recover from AMG 176 related toxicities to grade ≤ 1 or baseline severity after delaying next cycle up to 14 days	• any clinical TLS per Cairo-Bishop criteria (see Section 11.8.3) despite the use of prophylaxis • DILI meeting Hy's Law criteria (ie, AST or ALT ≥ 3 × ULN and serum bilirubin > 2 × ULN measured on the same day, without signs of cholestasis and in absence of any other explanation for the DILI). See Section 6.2.3 for hepatotoxicity management • grade 3 elevation of troponin-I (see grading criteria in Section 6.2.1.2.2)[a]

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Footnotes defined on last page of the table

Table 6-1. DLT Criteria (continued)

	Multiple Myeloma Subjects	Acute Myeloid Leukemia Subjects	All Subjects
DLT Criteria	• hematologic adverse events: - grade 3 or 4 neutropenia with fever > 38.5°C - grade 4 neutropenia lasting > 7 days - grade 3 thrombocytopenia with ≥ grade 2 hemorrhage - grade 4 thrombocytopenia lasting > 7 days - grade 3 anemia with symptoms or requiring intervention (eg, transfusion) - grade 4 anemia - ≥ grade 4 hematologic adverse events • any grade 5 adverse event that is not clearly due to disease progression	• hematological adverse events: - grade 4 neutropenia or thrombocytopenia lasting ≥ 42 days from start of cycle in absence of evidence of active AML • any treatment-related death	• Symptoms of clinically significant cardiac dysfunction, ECG changes, or diagnostic evidence of decreased cardiac function or cardiac injury irrespective of any cardiac troponin-I level (central or locally obtained)

Footnotes defined on last page of the table

Table 6-1. DLT Criteria (continued)

	Multiple Myeloma Subjects	Acute Myeloid Leukemia Subjects	All Subjects
Exceptions	The following adverse events are not DLTs unless the specific criteria above are met: • Fatigue • Nausea • Diarrhea • Vomiting • Neutropenia • anemia • thrombocytopenia • lymphopenia • increased serum creatinine or electrolyte abnormalities Non-hematological adverse events: • grade 3 or 4 elevation of serum lipase in absence of clinical pancreatitis that last < 72 hours	• Infections and most hematologic adverse events • Non-hematologic adverse events: - grade 3 weight gain or loss - grade 3 diarrhea despite optimal anti-diarrheal therapy that resolves to ≤ grade 2 within < 72 hours with or without clinical intervention - grade 3 or 4 isolated electrolyte abnormalities that is not clinically significant and resolves to ≤ grade 2 within 72 hours with or without clinical intervention - grade 3 nausea and vomiting that does not require tube feeding, total parenteral nutrition, or prolonged hospitalization and resolves to ≤ grade 2 within < 72 hours with or without clinical intervention - grade 3 or 4 serum lipase without clinical signs or symptoms of pancreatitis that returns to baseline within 72 hours of interrupting study drug - infection grade 3 (with concurrent neutropenia grade 3 or 4) that resolves to ≤ grade 2 within 7 days with or without clinical intervention - grade 3 fatigue or asthenia - grade 3 constipation that resolves to ≤ grade 2 within 7 days with or without clinical intervention	N/A

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AML = acute myeloid leukemia; ALT = alanine aminotransferase; AST = aspartate aminotransferase; DILI = drug-induced liver injury; DLT = dose-limiting toxicity; ECG = electrocardiogram; N/A = not applicable; TLS = tumor lysis syndrome; ULN = upper limit of normal; URL = upper reference limit

[a] Further treatment with AMG 176 may be considered for grade 1 elevations of troponin-I (ie, isolated elevation of troponin > 99th percentile URL of 0.04 ng/mL for females and 0.059 ng/mL for males) after a cardiology evaluation is completed and results are discussed with the Amgen medical monitor.

6.2.1.2.2 Grading of Troponin-I Elevation

Central testing of cardiac troponin-I will be performed for eligibility **confirmation**, grading, and withholding decisions. The following criteria is developed based on CTCAE 4.0 to determine the grade of troponin-I elevation with ADVIA Centaur XP TnI assay performed by central lab:

- grade 1: isolated elevation of troponin > 99th percentile URL of 0.04 ng/mL for females and 0.059 ng/mL for males
- grade 3: troponin elevation greater than or equal to manufacturer's defined cut-off for MI of 0.78 ng/mL

6.2.2 Dosage Adjustments, Delays, Rules for Withholding or Restarting, Permanent Discontinuation

6.2.2.1 Amgen Investigational Product: AMG 176

The reason for dose change of AMG 176 is to be recorded on each subject's CRF(s).

Dosage Adjustments

Upon completion of the ramp-up dosing if applicable, the subject should continue on the same target dose of AMG 176 throughout the study unless the following events occur:

- For subjects experiencing an adverse event meeting the DLT definition or intolerable related adverse events BUT showing evidence of response, there will be an option to reduce the dose to the immediate next lower dose level shown to be safe and tolerable in the dose escalation part of the study.
    - The study drug can be resumed once the adverse events recover to baseline or grade 1 and the reintroduction of AMG 176 is deemed safe by the site investigator and Amgen's Medical Monitor.
    - Subjects must be informed of the risk of continuing on therapy. Each subject is only allowed a single dose reduction. Subjects showing evidence of response or subjects who in the opinion of the investigator may be responding to AMG 176, may have the option to have more than single dose reduction if deemed safe by the site investigator and Amgen's medical monitor.
- Subjects who experience grade 3 arrhythmia possibly associated with AMG 176, AMG 176 dosing must be resumed at the immediate next lower dose level if the requirements mentioned below in Rules for Restarting are met.
- For subjects meeting the withholding criteria for elevation of cardiac troponin (> 0.1 ng/mL), AMG 176 dosing can be resumed at the immediate next lower dose level if the requirements mentioned below in Rules for Dose Withholding are met.

Subjects should not be re-challenged with AMG 176 if the following AMG 176-related adverse events occur:

- Any life-threatening adverse events
- Drug-induced liver injury (DILI) meeting Hy's law
- Persistent grade 3 adverse events that do not recover to baseline or grade 1 within 4 weeks.
- Any AMG 176 related adverse event meeting DLT-criteria that recurs despite 2 dose level reductions

Dosage Delays

During the DLT evaluation period, if the dosing is delayed for more than 2 weeks the subject will be removed from the study and will be replaced. After DLT evaluation period, if the dosing is delayed for < 4 weeks, the subject should resume the treatment as soon as possible if deemed safe by the investigator. The investigator should inform the Amgen Clinical team as soon as the unexpected dosing interruption occurs. If the dosing of AMG 176 is delayed > 4 weeks (missing 1 cycle) due to AMG 176 related adverse events, the subject will be permanently removed from AMG 176 treatment. If the dosing delay occurred under conditions other than those associated with AMG 176 related toxicities, the case will be reviewed by Amgen medical monitor to determine whether the subject will be allowed to resume AMG 176 treatment.

Rules for Dose Withholding

AMG 176 should be withheld for any of the following:

- Suspected DLT (including adverse events that meet DLT definition outside DLT observation period).
- Aspartate aminotransferase or ALT greater than 3 × ULN or total bilirubin greater than 1.5 × ULN.
- Any grade 3 arrhythmia deemed possibly related to AMG 176. Should dosing be resumed, AMG 176 should be given at the next lower dose level.
- Any central lab elevation of cardiac troponin $>$ 0.1 ng/mL (ADVIA Centaur XP manufacturer's prognostic cut-off) OR any change in the clinical status, above lab analytes (central or locally obtained), echocardiogram, or ECG deemed significant by the investigator or study subjects' care team.

– Upon meeting withholding criteria for AMG 176, investigator/site physician should evaluate appropriateness of apparent benefit vs risk of re-initiating AMG 176. Based on the assessment, a subject may be continued drug at a reduced dose or permanently discontinue therapy.

  - Low elevations from 0.04 ng/mL for females or 0.059 ng/mL for males to $\leq$ 0.1 ng/mL do not require withholding or dose reductions, though troponins should be monitored with subsequent doses.

- Elevations > 0.1 ng/mL should result in a dose withholding, and if further treatment is considered, should be restarted at one dose level below the dose where elevated troponins were observed

- Any consideration for continued treatment of AMG 176 after troponin elevations will require discussion between the investigator, subject, and Amgen medical monitor, and following normalization of all abnormalities.
- Study subjects that meet withholding criteria require continuous cardiac monitoring (telemetry) for at least 24 hours, and a cardiologist's evaluation that includes transthoracic echocardiography to assess the study subject and provide recommendations for further cardiac care. Monitoring should continue according to local SOC.

Rules for Restarting

AMG 176 dosing can be resumed:

- If the adverse event resolves to grade ≤ 1 or return to subjects' baseline values.
- For subjects meeting the withholding criteria for elevation of cardiac troponin (> 0.1 ng/mL), AMG 176 dosing can be resumed at the immediate next lower dose level if the requirements mentioned above in Rules for Dose Withholding are met.
- If the restarting of therapy should be deemed safe by the site investigator and Amgen's medical monitor.

Rules for Permanent Discontinuation

Subjects will permanently discontinue from the investigational product if the following are observed:

- Subjects experience adverse events meeting the DLT criteria at any time. Subjects will be followed until the DLT is resolved, returns to baseline value or is considered stable. Subjects will be withdrawn from AMG 176 treatment and will be treated as deemed appropriate by the investigator or treating physician. Except for:
- Subjects showing evidence of response or subjects who in the opinion of the investigator may be responding to AMG 176, may have the option to continue therapy once the adverse events recover to baseline or grade 1 and the re-introduction of AMG 176 is deemed safe by the investigator, and Amgen's medical monitor. The subject should restart at a reduced dose.
- Intolerability of AMG 176
- Grade 3 central laboratory elevations of troponin
- Any grade 4 arrythmias possibly associated with AMG 176
- Symptoms of clinically significant cardiac dysfunction, ECG changes, or diagnostic evidence of decreased cardiac function or cardiac injury irrespective of any cardiac troponin level (centrally or locally obtained). Study subjects that meet permanent discontinuation criteria require continuous cardiac monitoring (telemetry) for at least 24 hours, and a cardiologist evaluation that includes transthoracic echocardiography to assess the study subject and provide

recommendations for further cardiac care. Monitoring should continue according to local SOC.

- Hepatotoxicity (as defined in Section 11.7)
- The dosing is delayed > 4 weeks due to AMG 176-related adverse events

6.2.2.2 AMG 176 Management of Toxicities

6.2.2.2.1 Management of Anemia

Anemia is one of the MM- and AML-related organ/tissue dysfunction and is generally related to bone marrow infiltration or renal dysfunction. In AML, patients often present with a normocytic, normochromic anemia which worsens with chemotherapy. Subjects should be monitored for changes in hemoglobin as described in the schedule of assessments (see Section 1.3). Increased monitoring should be implemented in subjects whose hemoglobin < 8 g/dL. Subjects should have anemia corrected in accordance with the local practice and institutional guidelines. Hemoglobin parameters of grade 3 but not considered as clinically relevant (ie, without symptoms of anemia and not leading to a clinical intervention including withdrawal of investigational product treatment, transfusion, or significant additional concomitant therapy) will not require discontinuation of AMG 176. A sudden decrease in hemoglobin levels requires the investigation of hemolysis. Treatment should be discontinued for persistent (ie, ongoing > 3 weeks after the end of a treatment cycle) grade 3 or 4 anemia in the absence of detectable MM or AML which may reflect a prolonged marrow toxic effect of AMG 176.

6.2.2.2.2 Management of Infections

Subjects with evidence of existing infection should be closely monitored while being treated with AMG 176. Subjects with active systemic infections requiring IV antibiotics, antivirals, or antifungals should not be dosed with AMG 176 until infection has resolved and if being treated with an anti-infectious therapy, the course of such therapy should have been completed. Management should be tailored to the appropriate prophylaxis and/or treatment for the underlying infection according to the local SOC and institutional guidelines with the exception of excluded medications detailed in Section 6.1.7.

Infection Prophylaxis

Subjects who may experience neutropenia are at a high risk for infectious complications. As appropriate, these subjects should be administered prophylactic antibacterial and antifungal per institutional guidelines.

These subjects should be monitored for early signs of breakthrough infections after the initiation of antibacterial therapy to prompt additional evaluation and possible therapy

modification. Subjects experiencing diarrhea should be closely monitored for their electrolyte levels.

6.2.2.2.3 Management of Cardiac Arrhythmia

Subjects with risk factors for, or evidence of, existing heart disease should be closely monitored throughout their treatment with AMG 176. Subjects should be clinically monitored on ongoing basis for cardiac function (blood pressure, heart rate, ECHO, and ECG) according to the schedule of assessments (see Section 1.3). The administration of AMG 176 should be withheld if grade 3 or 4 arrhythmias (including tachycardia) develop or appear to be exacerbated by AMG 176 treatment. For any grade 3 arrhythmia related to AMG 176 administration, the AMG 176 dose should be reduced. Treatment may be resumed once the signs and symptoms resolve to baseline value or grade 1. Management should be tailored to the appropriate treatment for the underlying cardiac disorder according to the local SOC and institutional guidelines. For any grade 4 arrythmia related to AMG 176 administration, AMG 176 should be permanently discontinued.

6.2.2.2.4 Management of Renal Toxicities

Renal dysfunction is one of the MM-related organ/tissue dysfunction. Renal function must be monitored closely during treatment with AMG 176. Serum chemistry values, including blood urea nitrogen (BUN), serum creatinine, and urine for urinalysis and microscopic exam (microscopic exam only needed for positive dipstick), must be obtained and reviewed prior to each dose of AMG 176 per the schedule of assessments (see Section 1.3). AMG 176 must be held for subjects with CrCl or estimated glomerular filtration rate < 30 mL/min/1.73 m^2 or any other grade 3 or 4 renal toxicity any time during study treatment participation. Management should be tailored to the appropriate treatment for the underlying renal disorder according to the local SOC and institutional guidelines. AMG 176 can be restarted when the toxicity has improved to at least a grade 2.

6.2.2.2.5 Management of Gastrointestinal Toxicities

Gastrointestinal toxicity (vomiting and diarrhea) have been observed with the use of AMG 176. AMG 176 must be withheld from subjects with grade 3 or 4 gastrointestinal toxicity at any time during study treatment participation. Management should be tailored to the appropriate treatment according to the local SOC and institutional guidelines. AMG 176 can be restarted when the toxicity has improved to at least a grade 2.

6.2.2.2.6 Prophylaxis and Management of Tumor Lysis Syndrome

Refer to Section 11.8 for guidance.

6.2.2.2.7 Management of Troponin and Other Cardiac Enzymes Elevation

Subjects with risk factors for, or evidence of, existing heart disease should be closely monitored throughout their treatment with AMG 176. Subjects should be clinically monitored with local and central cardiac monitoring tests for elevated troponin and cardiac enzymes diagnostic of cardiac injury. Local troponin testing will be performed to guide immediate clinical care. Central testing of troponin-I with ADVIA Centaur XP troponin-I assay will be performed for all screening, grading, and withholding decisions.

6.2.2.2.8 SARS-CoV-2 and COVID-19 Guidance

Grade	Interruption/Delay	Specific Management	Restart Guidance	Permanent Discontinuation
SARS-CoV-2 infection and COVID-19 disease				
Asymptomatic	Interruption required until at least 10 days since positive SARS-CoV-2 test. UNLESS subject previously fully vaccinated against SARS-CoV-2. If subject previously vaccinated and tests positive, then discuss with medical monitor.	Follow local guidelines and SOC for COVID-19 treatment and isolation Contact Amgen medical monitor within 1 business day to ensure appropriate documentation and management of study activities	• Restart possible upon agreement between investigator and Amgen medical monitor provided: – There are no new findings on physical exam related to SARS-CoV-2, AND – Subject tests negative for SARS-CoV-2 by RT-PCR, OR – If subject continues to test positive for SARS-CoV-2 more than 10 days after initial positive test, or if subject initially tests positive in the setting of prior COVID vaccination, resume investigational product only after discussion with subject and reassessment of individual risk/benefit • Consider chest imaging, ECG, ECHO, and cardiology assessment prior to restart • Consider hospitalization for restart of IP based on length of treatment interruption, risk of CRS at restart, and amount of time since subject was last treated • Dose modification: resume at the same dose or reduce to next lower dose, if clinically indicated • Premedication and assessments: follow guidance in SOA tables	Immediately stop the infusion (if applicable) and permanently discontinue IP therapy, if: Subject required treatment interruption greater than 28 days and upon discussion with Amgen medical monitor the decision is made to permanently discontinue treatment OR Initial benefit/risk assessment for individual subject is not maintained any longer

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Abbreviations defined on last page of table.

Grade	Interruption/Delay	Specific Management	Restart Guidance	Permanent Discontinuation
SARS-CoV-2 infection and COVID-19 disease				
Symptomatic	Interruption required until at least 10 days since complete resolution of acute symptoms	Follow local guidelines and SOC for COVID-19 treatment and isolation Contact Amgen medical monitor within 1 business day to ensure appropriate documentation and management of study activities	• Restart possible upon agreement between investigator and Amgen medical monitor provided: – There are no new findings on physical exam and chest imaging, related to SARS-CoV-2 – Subject tests negative for SARS-CoV-2 by RT-PCR, • OR – If subject continues to test positive for SARS-CoV-2 more than 10 days after initial positive test, resume IP only after discussion with subject and reassessment of individual risk/benefit • Consider chest imaging, ECG, ECHO, and cardiology assessment prior to restart • Consider hospitalization for restart of IP based on length of treatment interruption, risk of CRS at restart, and amount of time since patient was last treated • Dose modification: resume at the same dose or reduce to next lower dose if clinically indicated • Premedication and assessments: follow guidance in SOA tables	Immediately stop the infusion (if applicable) and permanently discontinue IP therapy if: Subject required treatment interruption greater than 28 days due to severe or life-threatening COVID-19 OR Initial benefit/risk assessment for individual subject is not maintained any longer

COVID-19 = coronavirus disease 2019; CRS = cytokine release syndrome; ECG = electrocardiogram; ECHO = echocardiogram; RT-PCR = real-time polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SOA = Schedule of Activities; SOC = standard of care

6.2.2.3 Non-Investigational Products: Azacitidine and Itraconazole

The reason for dose change of non-investigational products is to be recorded on each subject's CRF(s). For contraindications, warnings, precautions, and potential drug interactions please refer to the current prescribing information for azacitidine.

6.2.2.3.1 Azacitidine

Azacitidine dose adjustments based on hematology laboratory values:

- Hematological toxicity is defined as the lowest count reached in a given cycle (nadir) if platelets $\leq 50.0 \times 10^9$/L and/or ANC $\leq 1 \times 10^9$/L.

  Recovery is defined as an increase of cell line(s) where hematological toxicity was observed of at least half of the difference of nadir and the baseline count plus the nadir count (ie, blood count at recovery $\geq$ to nadir count + (0.5 × [baseline count - nadir count]).
- Subjects without reduced baseline blood counts (ie, WBC $\geq 3.0 \times 10^9$/L and ANC $\geq 1.5 \times 109$/L, and platelets $\geq 75.0 \times 10^9$/L) prior to the first treatment.

For subjects with baseline (start of treatment) WBC $\geq 3.0 \times 10^9$/L, ANC $\geq 1.5 \times 10^9$/L, and platelets $\geq 75.0 \times 10^9$/L, adjust the dose as follows, based on nadir counts for any given cycle:

Table 6-2. Azacitidine Hematology Dose-Reduction Guidance

Nadir counts		% Dose in the Next Cycle
ANC (x 10^9/L)	Platelets (x 10^9/L)	
$<$ 0.5	$<$ 25.0	50%
0.5 to 1.5	25.0 to 50.0	67%
$>$ 1.5	$>$ 50.0	100%

ANC = absolute neutrophil count

For patients whose baseline counts are WBC $< 3.0 \times 10^9$/L, ANC $< 1.5 \times 10^9$/L, or platelets $< 75.0 \times 10^9$/L, dose adjustments should be based on nadir counts and bone marrow biopsy cellularity at the time of the nadir as noted below, unless there is clear improvement in differentiation (percentage of mature granulocytes is higher and ANC is higher than at onset of that course) at the time of the next cycle, in which case the dose of the current treatment should be continued.

Table 6-3. Azacitidine Dose Reduction Based on Bone Marrow Cellularity

WBC or Platelet Nadir % decrease in counts from baseline	Bone Marrow Biopsy Cellularity at Time of Nadir (%)		
	30 to 60	15 to 30	< 15
	% Dose in the Next Cycle		
50 to 75	100	50	33
> 75	75	50	33

WBC = white blood cell

If a nadir as defined in the table above has occurred, the next course of treatment should be given 28 days after the start of the preceding course, provided that both the WBC and the platelet counts are > 25% above the nadir and rising. If a > 25% increase above the nadir is not seen by day 28, counts should be reassessed every 7 days. If a 25% increase is not seen by day 42, then the subject should be treated with 50% of the scheduled dose.

Following dose modifications, a new cycle will be started and duration should return to 28 days.

Dose adjustment based on renal function and serum electrolytes:

- Unexplained reduction of sodium bicarbonate to < 20 mEq/L – reduce dose by 50% on the next cycle.
- Unexplained elevation of BUN or serum creatinine ≥ 2-fold above baseline – delay next cycle until values return to normal or baseline and dose reduce by 50% in the next treatment cycle.

6.2.2.3.2 Itraconazole

Discontinue administration of itraconazole if there are signs or symptoms of congestive heart failure or acute cardiac injury. Refer to the itraconazole capsule USPI for additional information regarding itraconazole-specific adverse reactions and instructions for dose modifications or withdrawal.

6.2.3 Hepatotoxicity Stopping and Rechallenge Rules

Refer to Section 11.7 for details regarding drug-induced liver injury guidelines, as specified in the *Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009*.

6.3 Preparation/Handling/Storage/Accountability

Guidance and information on preparation, handling, storage, accountability, destruction, or return of the investigational product and/or other protocol-required therapies during the study are provided in the IPIM.

6.4 Measures to Minimize Bias: Randomization and Blinding

6.4.1 Method of Treatment Assignment

The treatment assignment date is to be documented in the subject's medical record and on the enrollment CRF.

An Amgen representative will notify the site in writing when a cohort is open to screen and enroll subjects. The notification will include the cohort number and dose level in which subjects will be enrolled.

Enrollment of subjects in Part 1a and Part 1b will be based on availability in the cohort and agreement between the investigator and Amgen medical monitor.

6.4.2 Blinding

This is an open-label study; blinding procedures are not applicable.

6.5 Treatment Compliance

When subjects are dosed at the site, they will receive AMG 176 and azacitidine (Parts 4 and 5 only) directly from the investigator or designee, under supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the CRF.

For subjects enrolled in Part 3d, itraconazole dosing will be documented in the source documents and CRF. For days when subjects will self-administer itraconazole, they will be given a dosing diary to record the self-administered itraconazole doses. The diary should be reviewed at the next clinic visit and documented in the source documents and CRF.

6.6 Treatment of Overdose

Higher doses of AMG 176 may be associated with cardiac troponin elevation.
For management of troponin and other cardiac enzyme elevation, please refer to Section 6.2.2.1 and Section 6.2.2.2.7.

Refer to the approved product label for azacitidine for information related to azacitidine overdose.

6.7 Prior and Concomitant Treatment

6.7.1 Prior Treatment

The investigator or designee will collect relevant prior therapy which includes previous chemotherapy or radiotherapy, anticancer therapies (eg, stem cell transplant).

For prior therapies, collect therapy name, regimen, start and stop dates, reason for stopping therapy, best response, and date of progression.

6.7.2 Concomitant Treatment

Throughout the study, investigators may prescribe any concomitant medications or treatments, including RBC and platelet transfusions as deemed necessary to provide adequate supportive care except for those listed in Section 11.8.1 and Section 6.1.7.

Concomitant therapies (including vaccines) are to be collected from screening start through 30 days (+3 days) after the last dose of protocol-required therapies. Collect therapy name, indication, dose, unit, frequency, route, start date and stop date.

The investigator must be informed as soon as possible about any medication taken from the time of screening until the end of the clinical phase of the study (final study visit). Any concomitant medication(s), including herbal preparations, taken during the study will be recorded in the eCRF. The minimum requirement is that drug name, dose, and the dates of administration are to be recorded. Additionally, a complete list of all prior cancer therapies will be recorded in the eCRF.

Subjects should receive full supportive care during the study, including transfusions of blood and blood products, and treatment with antibiotics, anti-emetics, anti-diarrheals, and analgesics, G-CSF and other care as deemed appropriate, and in accordance with their institutional guidelines. Hydroxyurea may be administered according to standard practice prior to the first cycle of AMG 176 treatment for subjects with high WBC (> 15 000 cells/ul) and during the first cycle but not on days of AMG 176 administration. Hydroxyurea is unapproved for AML in Japan.

6.7.2.1 Bone Disease Therapy (Multiple Myeloma Subjects Only)

Bisphosphonate or denosumab therapy is strongly recommended for all MM subjects with evidence of lytic destruction of bone or with osteopenia (Gralow et al, 2013; Terpos et al, 2013). Commercially available IV bisphosphonates (pamidronate and zoledronic acid) or denosumab are preferred when available, and should be used according to the manufacturer's recommendations, as described in the prescribing information, for subjects with osteolytic or osteopenic myelomatous bone disease. Oral bisphosphonates may be used as alternatives if IV bisphosphonates or denosumab are not available at the study site. It is preferred that investigators use the same route of bisphosphonate therapy for all subjects at their sites.

Investigators should not start bisphosphonate therapy during the study, unless it has been agreed with the sponsor that there is no sign of disease progression. Subjects with evidence of lytic destruction of bone or with osteopenia who are not using a bisphosphonate at the time of enrollment should start a bisphosphonate within the first 2 cycles of study drug.

6.7.2.2 Antifungal Prophylaxis

Use of micafungin (or other echinocandins), posaconazole (or other azole antifungals), and amphotericin B for antifungal prophylaxis is allowed for neutropenic subjects with AML.

6.7.2.3 Concomitant Cautions to Consider

Caution is recommended during concomitant use of known CYP1A2, CYP2D6, CYP2C9, or CYP2C8 sensitive substrates with a narrow therapeutic window (such as thioridazine) due to the potential of AMG 176 to inhibit these enzymes based on in vitro data.

6.7.2.4 Vaccines

Every effort should be made to fully vaccinate subjects at least 14 days prior to first dose of AMG 176. The use of vaccines except live vaccines will be allowed during therapy per regional and institutional SOC. SARS-CoV-2 vaccinations should be avoided during screening (within 14 days from the first dose of AMG 176) and should be also avoided in the first treatment cycle for better assessment of safety parameters. Throughout study participation, SARS-CoV-2 vaccination should be avoided within 3 days after the administration of AMG 176 due to the potential of overlapping adverse events.

7. Discontinuation Criteria

Subjects have the right to withdraw from investigational product and/or other protocol-required therapies, protocol procedures, or the study as a whole at any time and for any reason without prejudice to their future medical care by the physician or at the institution.

The investigator and/or sponsor can decide to withdraw a subject(s) from investigational product, device, and/or other protocol-required therapies, protocol procedures, or the study as a whole at any time prior to study completion for the reasons listed in Section 7.1 and Section 7.2.1.

7.1 Discontinuation of Study Treatment

Subjects (or a legally acceptable representative) can decline to continue receiving investigational product and/or other protocol-required therapies or procedures at any time during the study but continue participation in the study. If this occurs, the investigator is to discuss with the subject the appropriate processes for discontinuation from investigational product or other protocol-required therapies and must discuss with the subject the possibilities for continuation of the Schedule of Activities (see Section 1.3) including different options of follow-up (eg, in person, by phone/mail, through family/friends, in correspondence/communication with other treating physicians, from the review of medical records) and collection of data, including endpoints, adverse events, and must document this decision in the subject's medical records. Subjects who have discontinued investigational product and/or other protocol-required therapies or procedures should not be automatically removed from the study. Whenever safe and feasible, it is imperative that subjects remain on-study to ensure safety surveillance and/or collection of outcome data.

Subjects may be eligible for continued treatment with Amgen investigational product(s) and/or other protocol-required therapies by a separate protocol or as provided for by the local country's regulatory mechanism, based on parameters consistent with Section 11.3.

Reasons for early removal from protocol-required investigational product(s) or procedural assessments may include any of the following:

- decision by sponsor (other than subject request, safety concern, or lost to follow-up)
- lost to follow-up
- death
- subject request
- safety concern (eg, due to an adverse event)
- ineligibility determined
- protocol deviation
- non-compliance (eg, procedural or dosing as defined in Section 6.5)
- confirmed disease progression per International Myeloma Working Group Uniform Response Criteria (IMWG-URC) in MM subjects (Section 11.9)
- confirmed disease progression per 2017 ELN criteria (Section 11.15) in AML subjects
- AML: Hematological or extramedullary relapse subsequent to complete response (CR)/CRh*/CRi/morphologic leukemia-free state on protocol treatment.

Exception: a blast equivalent count > 5% at the pre-dose assessment (after the infusion-free interval) would not lead to permanent treatment discontinuation even if the count had been < 5% directly after the previous treatment cycle.

- requirement for alternative therapy
- pregnancy

7.2 Discontinuation From the Study

Withdrawal of consent for a study means that the subject does not wish to receive further protocol-required therapies or procedures, and the subject does not wish to or is unable to continue further study participation. Subject data up to withdrawal of consent will be included in the analysis of the study, and where permitted, publicly available data can be included after withdrawal of consent. The investigator is to discuss with the subject appropriate procedures for withdrawal from the study, and must document the subject's decision to withdraw in the subject's medical records.

If a subject withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must notify Amgen accordingly (see Section 11.6 for further details). Refer to the Schedule of Activities (Section 1.3) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

7.2.1 Reasons for Removal From Study

Reasons for removal of a subject from the study are:

- decision by sponsor
- withdrawal of consent from study
- death
- lost to follow-up

7.3 Lost to Follow-up

A subject will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a subject fails to return to the clinic for a required study visit:

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or is able to continue in the study.
- In cases in which the subject is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the subject (where

possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts are to be documented in the subject's medical record.

- If the subject continues to be unreachable, he/she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.
- For subjects who are lost to follow-up, the investigator can search publicly available records (where permitted) to ascertain survival status. This ensures that the data set(s) produced as an outcome of the study is/are as comprehensive as possible.

8. Study Assessments and Procedures

Study procedures and their time points are summarized in the Schedule of Activities (see Section 1.3).

As protocol waivers or exemptions are not allowed if an enrolled subject is subsequently determined to be ineligible for the study, this must be discussed with the sponsor immediately upon occurrence or awareness to determine if the subject is to continue or discontinue study treatment.

Adherence to the study design requirements, including those specified in the Schedule of Activities, is essential and required for study conduct.

8.1 General Study Periods

A signed and dated IRB-approved informed consent must be obtained before any study specific procedures are performed. Procedures that are part of routine care are not considered study-specific procedures and may be used at screening to determine eligibility. All subjects will be screened for eligibility before enrollment. Only eligible subjects will be enrolled into the study.

Demographic data including sex, age, race, and ethnicity will be collected in order to study their possible association with subject safety and treatment effectiveness. Additionally, demographic data will be used to study the impact [redacted] and PK.

Cycle 1 and 2 visits should be done on days specified as possible. All subsequent visits beginning on cycle 3 will have a ± 1-day window unless otherwise specified.

8.1.1 Screening, Enrollment and/or Randomization

After obtaining informed consent, all screening procedures and tests establishing eligibility will be performed within a period of 14 days prior to enrollment unless otherwise noted in the schedule of assessments. Core bone marrow biopsy or bone marrow aspirate performed as SOC can be used to meet screening requirements if

performed within 4 weeks from enrollment and no curative anti-cancer therapy was administered during the time from biopsy to enrollment. The procedures to be completed during the screening period are described in the Schedule of Assessments (see Section 1.3).

All blood and urine samples collected for screening assessments will be submitted and analyzed by the local/central laboratory as applicable (see Section 8.2.5). Screening laboratory assessments used to determine subject eligibility may be repeated once (up to a total of 2 times during the 14-day screening period), if necessary. The investigator must provide appropriate rationale prior to repeating any other screening procedures or tests during the screening period. Testing for HIV is not required unless mandated by local regulatory authorities.

After the subject has signed the informed consent, the current medication list should be sent to Amgen's medical monitor for review and approval. Written documentation of this review and Amgen acknowledgment is required for subject participation. In addition, any new medication other than what is indicated for TLS prophylaxis, should be reviewed and approved by the principal investigator and the Amgen medical monitor prior to start of the treatment.

Rescreening

Subjects may be re-screened up to 2 additional times at the discretion of the Investigator. The subject must sign a new informed consent form if the re-screening attempt occurs outside of the 14-day screening period. For subjects undergoing re-screening, a bone marrow biopsy and imaging procedures are not needed if performed within the last 4 weeks from enrollment.

8.1.2 Treatment Period

Visits will occur per the Schedule of Assessments (see Section 1.3). The date of the first dose of AMG 176 is defined as day 1. AMG 176 is to be administered after all protocol-specific pre-dose assessments have been performed during each visit that it is required. Subjects will receive treatment until disease progression (see Section 8.2.2.1 and Section 8.2.2.2), unacceptable toxicity, withdrawal of consent, or death (whichever occurs first); this is also applicable to subjects enrolled in Part 3d after they crossover to Part 3b or Part 4.

8.1.3 End of Treatment

The EOT visit will occur upon the decision to end treatment with protocol-required therapies. For subjects who choose to discontinue investigational product treatment, the EOT visit should occur as soon as possible after the last dose of protocol-required therapies is administered. Serious adverse events considered related to the investigational product, by the investigator, or Amgen will be followed until resolved or considered stable (see Section 11.4).

8.1.4 Safety Follow-up

A safety follow-up visit must be performed 30 days (+3 days) after the last dose of protocol-required therapies. All efforts should be made to conduct this visit. If it is not possible to conduct the safety follow-up visit, documentation of efforts to complete the visit should be provided in the source documents and noted as not done in the eCRFs.

8.1.5 Long-term Follow-up

Long-term follow-up assessments will occur every 3 months (± 14 days) after EOT for 1 year and will include survival, subsequent anti-cancer therapy, and any cardiac associated serious adverse events or clinical diagnostic studies performed. Additionally, the first long-term follow-up visit will require an echocardiogram (see Section 8.2.3.4.2).

8.1.6 End of Study

The end of study visit for an individual subject will be the final long-term follow-up visit.

8.2 Description of General Study Assessments and Procedures

The sections below provide a description of the individual study procedures for required time points.

8.2.1 General Assessments

8.2.1.1 Informed Consent

All subjects must sign and personally date the IRB/IEC approved informed consent before any study-specific procedures are performed.

8.2.1.2 Demographics

Demographic data collection including sex, age, race, and ethnicity will be collected in order to study their possible association with subject safety and treatment effectiveness. Additionally, demographic data will be used to study the impact on [redacted] and pharmacokinetics of the protocol-required therapies.

8.2.1.3 Medical History

The investigator or designee will collect a complete medical and surgical history that started at least 2 years prior to enrollment through the first dose of AMG 176. Medical history will include information on the subject's concurrent medical health conditions, relevant past medical conditions, and surgical history. Record all findings on the medical history eCRF.

Relevant medical history, including antecedent hematologic or oncologic disease, other diseases/symptoms such as fatigue, bleeding and infection (resolved and ongoing) will be collected. The current toxicity grade will be collected for each condition that has not resolved.

8.2.1.4 Physical Examination

A complete physical examination will be performed by the investigator or designee according to local practices at screening and time points specified in the Schedule of Assessments (Section 1.3). Physical examination findings should be recorded on the appropriate case report form (CRF) (eg, medical history, event).

8.2.1.5 Physical Measurements

Height (cm) will be measured without shoes at screening. Weight (kg) without shoes will be obtained at screening and time points specified in the Schedule of Assessments (see Section 1.3).

8.2.1.6 Eastern Cooperative Oncology Group Performance Status

Eastern Cooperative Oncology Group Performance Status (Section 11.10) assessments will occur at time points specified in the Schedule of Assessments (see Section 1.3).

8.2.2 Efficacy Assessments

8.2.2.1 Multiple Myeloma Tumor Assessment and Disease Assessment

Disease assessment will be performed at screening and every 28 days (± 7 days) until confirmed PD (Section 8.2.2.1.7) irrespective of cycle duration including dose delays and treatment discontinuation as per the schedule of assessments (Section 1.3). For subjects who do not progress during treatment, disease assessments will continue to be measured every 28 days (± 7 days) until PD.

Disease response and progression assessments include: serum protein electrophoresis (SPEP), urine protein electrophoresis (UPEP), SFLC, serum and urine immunofixation (SIFE, UIFE, respectively) (Section 8.2.2.1.1) bone marrow aspirate sample evaluation

(Section 8.2.2.1.2), serum calcium, skeletal survey evaluation (Section 8.2.2.1.6), and plasmacytoma evaluation (Section 8.2.2.1.5).

8.2.2.1.1 Serum Protein Electrophoresis, Urine Protein Electrophoresis, Serum Free Light Chain, Serum Immunofixation, and Urine Immunofixation

Serum protein electrophoresis and 24-hour UPEP is required for all subjects at screening. Thereafter, SPEP is to be done at each time point for all subjects as indicated in the schedule of assessments. Serum free light chain assay and ratio will be performed at each time point as specified in the schedule of assessments.

Urine protein electrophoresis with 24-hour urine collection is required at each time point only if screening UPEP shows measurable paraprotein in the urine and for confirmation of very good partial response (VGPR) or complete remission as per IMWG-URC. If screening UPEP is negative, spot urine is required at each time point. If positive for paraprotein, a 24-hour urine collection with UPEP must be done at the next assessment and at each subsequent assessment unless the UPEP shows an absence of paraprotein. Immunofixation is required at next assessment only if SPEP or UPEP results are zero/undetectable.

8.2.2.1.2 Bone Marrow Sample Evaluation

Bone marrow aspirate samples will be collected from all subjects during screening to quantify percent myeloma involvement and for [redacted], both to be performed at the study center. Core bone marrow biopsies will also be collected for disease assessment unless these samples cannot be collected; for these institutions, the bone marrow aspirate is sufficient. In case of dry tap or if there is concern of hemodilution, a bone marrow biopsy will be collected instead of aspirate sample.

An additional bone marrow aspirate sample will only be required to confirm a complete response.

An aliquot of the bone marrow aspirate collected at screening will be sent to the central laboratory for minimal residual disease (MRD) clone type status determination by next-generation sequencing (NGS). Additional bone marrow aspirates will be collected for MRD disease assessments for subjects who achieve complete response and 12 months following a complete response if this response persists.

8.2.2.1.3 Quantitative Immunoglobulin

Quantitative Ig will be performed at screening and quantitative IgA and IgD at every disease assessment in subjects with IgA or IgD myeloma, respectively. For subjects with other myeloma subtypes, quantitative Ig will be repeated only if clinically indicated. For example, if frequent infection despite MM disease control or deemed clinically indicated by the investigator.

8.2.2.1.4 Beta-2 Microglobulin

Beta-2 microglobulin will be performed at screening. In addition, it will be performed at each time point for all subjects as indicated in the schedule of assessments as part of risk stratification.

8.2.2.1.5 Plasmacytoma in Multiple Myeloma Subjects

Plasmacytoma survey will be performed at the time points as specified in the schedule of assessments (see Section 1.3). For subjects without a history of extramedullary disease, assessment by physical examination at screening is acceptable. Plasmacytoma evaluation is to be repeated during treatment only to confirm a response of partial response or better, to confirm PD, or if clinically indicated. If clinically indicated due to history of extramedullary disease, the same technique (may include ultrasound, X-ray, computed tomography [CT] scan, magnetic resonance imaging [MRI], positron emission tomography [PET], or other SOC method) must be employed for each measurement.

8.2.2.1.6 Skeletal Survey in Multiple Myeloma Subjects

Bone lesion assessment is required at screening on all MM subjects. A bone lesion survey by standard radiography (X-ray) will include lateral radiograph of the skull, anteroposterior and lateral views of the spine, and anteroposterior views of the pelvis, ribs, femora, and humeri. Low-dose whole body CT, fluorodeoxyglucose-PET (FDG PET)/CT, or MRI may be used in place of standard radiography. Bone lesion assessment at screening (all subjects) may be done within 30 days prior to enrollment, if performed as a part of SOC. It should be repeated if worsening clinical symptoms suggest PD or as clinically indicated. These imaging studies will be read locally.

8.2.2.1.7 Disease Response Assessment in Multiple Myeloma

Subjects will be evaluated for disease response and progression according to the IMWG response criteria in Section 11.9. Disease status categories include stringent complete response, complete response, VGPR, partial response, minimal response, stable disease, and PD.

The following confirmation assessments are required for all response categories (ie, stringent complete response, complete response, VGPR, partial response, minimal response). Refer to definitions in Section 11.9:

- All response categories require 2 consecutive laboratory assessments made at any time before initiation of any new therapy.
- All categories also require no known evidence of progression including new bone lesions if radiographic studies were performed.
- Confirmation of complete response and stringent complete response requires bone marrow assessment (aspirate or biopsy).
- Extramedullary plasmacytoma evaluation (if present at screening).

Confirmation of PD is required by 2 consecutive assessments of laboratory-based parameters using a local laboratory. Consecutive assessments of imaging parameters are NOT required for confirmation of PD as per IMWG-URC criteria. The assessments outlined in Section 11.9 are required for PD. Subjects will be considered to have PD if they meet the criteria for progression by a variable regardless of whether it was considered measurable at baseline; however, for subjects who had a measurable serum or urine M spike at baseline, progression cannot be defined by increases in SFLC alone (Kumar et al, 2016).

8.2.2.2 Acute Myeloid Leukemia Tumor Assessment and Disease Assessment

8.2.2.2.1 Bone Marrow Aspirate

The following samples will be obtained for cytomorphological assessment, cytogenetics, mutation status, and MRD assessment (Parts 4 and 5 only):

- Hematocytology and cytochemistry to establish WHO subtype of AML – local site laboratory according to local procedures using slides of bone marrow and peripheral blood.
- Immunological phenotyping to verify the myeloid malignancy. Additional immunological phenotyping will be performed/done at the investigator's discretion, for relapsed and/or for response confirmation.
- Cytomorphology: bone marrow smears (slides) at screening, pre-dose on (or within 3 days prior to) day 1 of cycle 2 and cycle 3 and thereafter prior to every other cycle or when clinically indicated until disease progression.
- Cytogenetics and molecular genetic testing at screening, bone marrow aspirate will be used to determined cytogenetic aberrations by conventional cytogenetics and [redacted]

[redacted]

Previous bone marrow aspirate or biopsy performed within 4 weeks of enrollment and without administration of curative anti-cancer therapy during the time from biopsy to enrollment may be used to meet screening requirements and determine eligibility for subjects.

- Additional cytogenetics will be performed/done at the investigator's discretion, for relapsed and/or for response confirmation.
- MRD (Parts 4 and 5 only): aliquots will be collected and analyzed at a central laboratory at screening for immunophenotyping towards future MRD status determination for all subjects. Additional subsequent MRD collections may be taken at the same time as the bone marrow aspirates collections for disease response assessment, which is based on the following guidelines: For subjects that achieve peripheral blood blast cell frequencies below 1% during peripheral blood disease assessment after completion of the first and/or second induction cycle or when the investigator suspects a CR, bone marrow aspirates will be collected for MRD status determination alongside disease assessment prior to initiation of the subsequent cycle. For subjects who achieve CRi, additional bone marrow samples will be taken upon count recovery for minimal residual disease negativity (MRD[-]) CR status determination. For subjects with confirmed CR, additional bone marrow aspirates for MRD status determination will be collected every 8 weeks thereafter or when clinically indicated, until blast counts in whole blood rise above 1% and/or subject shows signs of clinical progression.

Core bone marrow biopsies will also be collected for disease assessment unless these samples cannot be collected; for these institutions, the bone marrow aspirate is sufficient. In case of dry tap or if there is concern of hemodilution, a bone marrow biopsy will be collected instead of aspirate sample.

The degree of bone marrow infiltration defined by the percentage of leukemic blasts in bone marrow will be evaluated by the local laboratory as per cytological assessment.

Additional bone marrow sampling may occur at other time points at the investigator's discretion as clinically indicated. Unscheduled bone marrow aspirate and biopsy results will be captured in the respective eCRFs.

8.2.2.2.2 Peripheral Blood

Blood samples will be collected for peripheral blood counts by local laboratory. Peripheral blood counts will include ANC, platelets, blasts and hemoglobin as described in the Section 1.3 and Table 11-1.

8.2.2.2.3 Disease Response Assessment in Acute Myeloid Leukemia

Disease response assessments will be based upon review of bone marrow aspirates and/or core biopsies as well as peripheral blood counts. Refer to the 2017 ELN criteria

in Section 11.15 for additional detail. Complete remission/CRi must be established from bone-marrow samples supplemented with neutrophil, platelet, and peripheral blast counts.

In case of transplantation, a CR or CRi must be confirmed within 4 weeks prior to transplantation.

8.2.3 Safety Assessments

Planned time points for all safety assessments are listed in the Schedule of Activities see (Section 1.3).

8.2.3.1 Vital Signs

The following measurements must be performed: systolic blood pressure (SBP), diastolic blood pressure (DBP), respiratory rate, heart rate and temperature. Subject must be in rested and calm state for at least 5 minutes before BP assessments are conducted. The position selected for a subject should be the same that is used throughout the study and documented on the vital sign eCRF. Record all measurements on the vital signs eCRF.

The temperature location selected for a subject should be the same that is used throughout the study and documented on the vital signs/temperature eCRF. Vital signs will be recorded at screening and time points specified in the Schedule of Assessments (see Section 1.3).

Abnormal measurements may be repeated at the discretion of the investigator and must be reported on the corresponding eCRF page. When vital signs and blood sample collection occur at the same time, vital signs should be performed before blood samples are drawn, where permitted.

8.2.3.2 Electrocardiograms (ECGs)

The subject should rest for at least 5 minutes before ECG assessment is conducted. Electrocardiograms should be performed in a standardized method, in triplicate (at designated time points), and run consecutively (approximately 1 minute apart), prior to blood draws or other invasive procedures. Each ECG must include the following measurements: QRS, QT, QTc, RR, and PR intervals.

Electrocardiograms will be performed as follows (at time points indicated in Section 1.3):

- Screening: Single ECG
- Baseline (pre-dose cycle 1 day 1): Three baseline ECGs will be collected approximately 15 minutes apart (± 5 minutes), with each baseline ECG in

triplicate run consecutively (ie, all 3 ECGs should be completed within a total of 5 minutes from the start of the first to the completion of the third) for a total of 9 ECGs

- Cycles 1 through 4: Triplicate ECGs run consecutively (ie, all 3 ECGs should be completed within a total of 5 minutes from the start of the first to the completion of the third)
- Cycle 5 and all subsequent cycles: single ECG

The principal investigator or designated site physician will review all ECGs.

Once signed, the original ECG tracing will be retained with the subject's source documents and transferred electronically to a central ECG vendor for reconciliation and storage per Amgen instructions. At the request of Amgen, a copy of the original ECG will be made available to Amgen.

Note: ECGs will be transferred electronically to an ECG central vendor for reconciliation and storage per Amgen instructions.

Standard ECG machines should be used for all study-related ECG requirements. These will be provided to the site as ECG data will need to be transmitted to the selected vendor.

8.2.3.3 Vital Status

Vital status must be obtained for all subjects within the limits of local law. This includes subjects who may have discontinued study visits with or without withdrawing consent and should include interrogation of public databases, if necessary. If deceased, the date and reported cause of death should be obtained.

8.2.3.4 Other Safety

8.2.3.4.1 Peripheral Neuropathy Assessment in Multiple Myeloma Subjects

The peripheral neuropathy assessment should be done at screening and safety follow-up (Section 1.3). These assessments must be reported on the corresponding eCRF page (see Section 11.13 for peripheral neuropathy assessment tool).

8.2.3.4.2 Echocardiogram (ECHO)/Multigated Acquisition (MUGA) Scan/Cardiac MRI

Transthoracic echocardiography or MUGA that at least includes measures of both right and left atrial and ventricular structure and function will be performed at screening, with any clinically significant cardiac event, symptoms of cardiac dysfunction or clinically significant elevation of either cardiac troponin, CK-MB, or NT-pro-BNP during treatment, EOT, and the first long-term follow-up visit. If available, cardiac MRI at baseline, EOT, and the first long-term follow-up visit is recommended. If cardiac imaging was performed

within 4 weeks of C1D1, one does not need to be performed again at screening as long as the same modality is used throughout the study.

8.2.4 Adverse Events and Serious Adverse Events

8.2.4.1 Time Period and Frequency for Collecting and Reporting Safety Event Information

8.2.4.1.1 Disease-related Events

The investigator is responsible for ensuring that all disease-related events observed by the investigator or reported by the subject that occur after the first dose of investigational medicinal product(s)/study treatment/protocol-required therapies through the safety follow-up visit are reported using the Event CRF. Additionally, the investigator is required to report a fatal disease-related event on the Event CRF.

Events assessed by the investigator to be related to the investigational medicinal product(s)/study treatment/protocol-required therapies, and determined to be serious, require reporting of the event on the Event CRF.

8.2.4.1.2 Adverse Events

The adverse event grading scale to be used for this study will be the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 and is described in Section 11.4.

The investigator is responsible for ensuring that all adverse events observed by the investigator or reported by the subject that occur after first dose of investigational product through the safety follow-up visit are reported using the Event CRF.

8.2.4.1.3 Serious Adverse Events

The investigator is responsible for ensuring that all serious adverse events observed by the investigator or reported by the subject that occur after signing of the informed consent through safety follow-up visit are reported using the Events CRF. Exception: cardiac-associated serious adverse events will be collected from signing of the informed consent through the end of long-term follow-up.

All serious adverse events will be collected, recorded and reported to the sponsor or designee immediately and no later than 24 hours of the investigator's awareness of the event, as indicated in Section 11.4. The investigator will submit any updated serious adverse event data to the sponsor immediately and no later than 24 hours of it being available.

The criteria for grade 4 in the CTCAE grading scale differs from the regulatory criteria for serious adverse events. It is left to the investigator's judgment to report these grade 4 abnormalities as serious adverse events.

8.2.4.1.4 Serious Adverse Events After the Protocol-required Reporting Period

If the investigator becomes aware of serious adverse events suspected to be related to investigational product after the protocol-required reporting period (as defined in Section 8.2.4.1.3) is complete, then these serious adverse events will be reported to Amgen immediately and no later than 24 hours following the investigator's awareness of the event on the Events CRF. In addition, the investigator will also need to collect/report fatal serious adverse events (regardless of causality) to Amgen immediately and no later than 24 hours following investigator's awareness of the event.

After end of study, there is no requirement to actively monitor study subjects after the study has ended with regards to study subjects treated by the investigator. However, if the investigator becomes aware of serious adverse events suspected to be related to investigational product, then these serious adverse events will be reported to Amgen immediately and no later than 24 hours following the investigator's awareness of the event.

Serious adverse events reported outside of the protocol-required reporting period will be captured within the safety database as clinical trial cases and handled accordingly based on relationship to investigational product.

If further safety related data is needed to fulfill any regulatory reporting requirements for a reportable event, then additional information may need to be collected from the subject's records after the subject ends the study.

The method of recording, evaluating, and assessing causality of adverse events, and serious adverse events and the procedures for completing and transmitting serious adverse event reports are provided in Section 11.4.

8.2.4.2 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:

Term	Definition	Comments
Reasonable Possibility	After consideration of factors including timing of the event, biologic plausibility, clinical judgement, and potential alternative causes, there is insufficient evidence (information) to suggest an alternative cause.	Events assessed as having a Reasonable Possibility of being related to the study drug will be considered "related".
No Reasonable Possibility	After consideration of factors including timing of the event, biologic plausibility, clinical judgement, and potential alternative causes, there is sufficient evidence (information) to suggest a reasonable cause. NOTE: 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.	Events assessed as having No Reasonable Possibility of being related to study drug will be considered "not related".
Not Applicable	Not applicable causality should be used when the investigative drug product has not been administered to the subject.	

8.2.4.3 Method of Detecting Adverse Events and Serious Adverse Events

Care will be taken not to introduce bias when detecting adverse events and/or serious adverse events. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about adverse event occurrence.

8.2.4.4 Follow-up of Adverse Events and Serious Adverse Events

After the initial adverse event/serious adverse event report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All adverse events and serious adverse events will be followed until resolution, stabilization, until the event is otherwise explained, or the subject is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is given in Section 11.4.

All new information for previously reported serious adverse events must be sent to Amgen immediately and no later than 24 hours following awareness of the new information. If specifically requested, the investigator may need to provide additional follow-up information, such as discharge summaries, medical records, or extracts from the medical records. Information provided about the serious adverse event must be consistent with that recorded on the Events CRF.

8.2.4.5 Regulatory Reporting Requirements for Serious Adverse Events

If subject is permanently withdrawn from protocol-required therapies because of a serious adverse event, this information must be submitted to Amgen.

Prompt notification by the investigator to the sponsor of serious adverse events is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a study treatment under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/IECs, and investigators.

Individual safety reports must be prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives an individual safety report describing a serious adverse event or other specific safety information (eg, summary or listing of serious adverse events) from the sponsor will file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

8.2.4.6 Safety Monitoring Plan

Subject safety will be routinely monitored as defined in Amgen's safety surveillance and signal management processes.

8.2.4.7 Pregnancy and Lactation

Details of all pregnancies and/or lactation in female subjects and female partners of male subjects will be collected after the start of study treatment and until 3 months after the last dose of investigational product.

If a pregnancy is reported, the investigator is to inform Amgen immediately and no later than 24 hours of learning of the pregnancy and/or lactation and is to follow the procedures outlined in Section 11.5. Amgen Global Patient Safety will follow-up with the investigator regarding additional information that may be requested.

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered serious adverse events.

Further details regarding pregnancy and lactation are provided in Section 11.5.

8.2.5 Clinical Laboratory Assessments

Refer to Section 11.2 for the list of clinical laboratory tests to be performed and to the Schedule of Activities (Section 1.3) for the timing and frequency.

The investigator is responsible for reviewing laboratory test results and recording any clinically relevant changes occurring during the study in the Event CRF. The investigator must determine whether an abnormal value in an individual study subject represents a clinically significant change from the subject's baseline values. In general, abnormal laboratory findings without clinical significance (based on the investigator's judgment) are not to be recorded as adverse events. However, laboratory value changes that require treatment or adjustment in current therapy are considered adverse events. Where applicable, clinical sequelae (not the laboratory abnormality) are to be recorded as the adverse event.

All protocol-required laboratory assessments, as defined in Section 11.2, must be conducted in accordance with the laboratory manual and the Schedule of Activities (Section 1.3).

8.2.5.1 Hepatitis Serology

All subjects will be tested at screening for hepatitis B and hepatitis C infection as follows:

- HBsAg, total HBsAb, and total HBcAb
  - If results are HBsAb and/or HBcAb positive and HBsAg positive, no additional testing is necessary
  - If results are HBsAb and/or HBcAb positive and HBsAg negative, additional testing for hepatitis B virus DNA by PCR is necessary
- HCVAb
  - If results are HCVAb positive, additional testing for hepatitis C virus RNA by PCR is necessary.

8.2.5.2 Tumor Lysis Syndrome Laboratory Monitoring

Tumor lysis syndrome prophylaxis must be initiated prior to all **ramp-up** dosing of AMG 176 and prior to all subsequent dose escalations (ie, first dose on the targeted cohort dose level). Subjects must be hospitalized and monitored the night before AMG 176 administration and will continue until at least 24 hours post-dose (QW schedule) or until 48 hours post the first dose in the BIW dosing schedule. Chemistry labs must include serum potassium, phosphorous, calcium, uric acid, and creatinine, and be performed pre-dose (within 4 hours before AMG 176 administration), 2, 4, 8, 12 and 24 hours after the start of AMG 176 infusion.

8.2.5.3 Cardiac Monitoring Tests

Local and central cardiac monitoring test are required. Local assessment should include troponin (I or T), CK-MB, and NT-pro-BNP. Serum samples are collected for centralized assessment.

8.2.5.4 Pregnancy Testing

Females of childbearing potential will have a local laboratory pregnancy test (urine or serum) performed at screening, prior to each treatment cycle (pre-dose), end of treatment, and at the safety follow-up visit.

Note: Females who have undergone a bilateral tubal ligation/occlusion should have pregnancy testing per protocol requirements. (If a female subject, or the partner of a male subject, becomes pregnant it must be reported on the Pregnancy Notification Form, see Figure 11-2). Refer to Section 11.5 for contraceptive requirements.

Additional on-treatment pregnancy testing may be performed at the investigator's discretion or as required per local laws and regulations.

8.2.6 Pharmacokinetic Assessments

For pharmacokinetic assessment blood samples for quantitative determination of AMG 176 and azacitidine, will be collected at time points specified in the Schedule of Assessments (see Section 1.3). Sample collection, processing, storage, and shipping instructions are provided in a separate laboratory manual. Please NOTE: Pharmacokinetic and [redacted] samples are required to be shipped the day of the draw. Backup samples are to be shipped separately and can be batched weekly for shipment.

Note: Pharmacokinetic samples must not be drawn from the IV site where investigational product has been administered. Pharmacokinetic samples must be drawn from a site which is distal (eg, opposite arm) from the site where the investigational product has been administered to avoid contamination of the PK samples and to better estimate PK parameters. Additionally, all sites should document the site of drug infusion and the site of PK sample collection relative to the site of drug infusion.

8.2.7 Pharmacogenetic Assessments

If the subject consents to the optional pharmacogenetic portion of this study (saliva sample), DNA analyses may be extracted and performed. These optional pharmacogenetic analyses focus on inherited genetic variations to evaluate their possible correlation to the disease and/or responsiveness to the therapies used in this study. The goals of the optional studies include the use of genetic markers to help in the

investigation of cancer and/or to identify subjects who may have positive or negative response to AMG 176. An additional saliva sample will be collected for all subjects on study in Parts 1a, 1b, 3a, 3b, and 4. A saliva sample will not be collected for Part 3c and subjects in Japan in Part 4.

The final disposition of samples will be described in Section 11.6.

[redacted]

[redacted]

[redacted]

8.2.9 Optional Substudies

[redacted]

9. Statistical Considerations

9.1 Statistical Hypotheses

At least one dose level of AMG 176 administered as monotherapy will achieve acceptable safety and tolerability in subjects with relapsed or refractory MM with evidence of biologic impact as shown by either evidence of reduction in MCL1 activity in circulating monocytes/circulating blasts and/or evidence of anti-tumor activity.

At least 1 dose level of AMG 176 administered as a monotherapy or in combination with azacitidine will achieve acceptable safety and tolerability in subjects with relapsed or refractory AML with evidence of biologic impact, as shown by either evidence of reduction in MCL1 activity in circulating monocytes/circulating blasts and/or evidence of anti-tumor activity.

9.2 Sample Size Determination

It is anticipated that **approximately** 21**9** subjects will be enrolled in the different parts of this study. Multiple myeloma Part 1a enrolled 36 subjects for dose escalation. Multiple myeloma Part 1b enrolled 12 subjects for dose escalation. Acute myeloid leukemia Part 3a enrolled 17 subjects for dose escalation. Part 3b enrolled 11 subjects. Acute

myeloid leukemia Part 3c enrolled 4 subjects in Japan. Part 3d will enroll **about** 11 subjects in the US. Part 4 will enroll approximately 60 subjects. Part 5 will enroll approximately 6**8** subjects.

For each part, the sample size is based on practical considerations and it is consistent with conventional oncology studies with the objective to identify the MTD or MTCD and to evaluate DDI. With 3 subjects in a cohort, there is a 27% to 70% probability of observing at least one DLT if the true DLT rate is 10% to 33% and with 6 or 9 subjects in a cohort there is a 47% to 91% probability and 61% to 97% probability, respectively.

9.3 Analysis Sets, Subgroups, and Covariates

9.3.1 Analysis Sets

The analysis of all endpoints (see Section 3), unless noted otherwise, will be conducted on the Full Analysis Set (FAS), and by cohort. The FAS is defined as all subjects that are enrolled and receive at least 1 dose of AMG 176. The analysis of DLT will be restricted to DLT evaluable subjects (see Section 6.2.1.2.1). The PK Analysis Set will contain all subjects who have received at least 1 dose of the investigational product and have at least 1 PK sample collected. These subjects will be evaluated for PK analysis unless the number of data points required for analysis is not enough, or significant protocol deviations have affected the data, or if key dosing or sampling information is missing.

9.3.2 Covariates

The relationship of covariates to efficacy endpoints will be explored if appropriate. [redacted] may be incorporated in additional [redacted] The analyses of [redacted] performed after collection of all samples during the conduct of the study and therefore may be reported after the primary analysis of efficacy endpoints.

9.4 Statistical Analyses

The statistical analysis plan will be developed and finalized before database lock. Below is a summary of the timing and methods for the planned statistical analyses. To preserve study integrity, the final analysis will be conducted and reported following the end of study, as defined in Section 4.5.1.

9.4.1 Planned Analyses

9.4.1.1 Interim Analyses

No formal interim efficacy analysis is planned. Interim safety analyses will be performed to support the evaluation of safety as summarized in Table 9-1.

Table 9-1. Summary of Interim Analyses

Part	Interim Analysis	Method
Multiple myeloma Part 1a AMG 176 BIW Monotherapy	Safety/Dosing Decisions - DLRT	Standard 3+3 Design (see Section 4.1.1)
Multiple myeloma Part 1b AMG 176 QW Monotherapy	Safety/Dosing Decisions - DLRT	Standard 3+3 Design (see Section 4.1.1)
Acute myeloid leukemia Part 3a AMG 176 BIW Monotherapy	Safety/Dosing Decisions - DLRT	Standard 3+3 Design (see Section 4.1.1)
Acute myeloid leukemia Part 3b AMG 176 QW Monotherapy	Safety/Dosing Decisions - DLRT	mTPI Design (see Section 4.1.1)
Acute myeloid leukemia Part 3c AMG 176 QW Monotherapy (Japan Cohort)	Safety/Dosing Decisions - DLRT	Standard 3+3 Design (see Section 4.1.2)
Acute myeloid leukemia Part 4 AMG 176 QW and BIW in combination with azacitidine	Safety/Dosing Decisions - DLRT	mTPI Design (see Section 4.1.1)
Acute myeloid leukemia Part 5A AMG 176 (QW or BIW) in combination with azacitidine	**Safety/Dosing Decisions**	**Simon's Two-stage Minimax Design (see Section 4.1.1)**

BIW = twice weekly; DLRT = dose-level review team; mTPI = modified Toxicity Probability Interval; QW = once weekly

Safety data will be reviewed on an ongoing basis. The DLRT (see Section 11.3) will review all available cumulative data by cohort prior to making dose escalation recommendations. Adverse events and DLTs observed in all subjects will be evaluated continually and considered in all enrollment and dosing decisions.

In Part 5A, Simon's two-stage minimax design (Simon, 1989) will be used to provide interim futility criteria to minimize the number of subjects exposed to a potentially ineffective treatment. The null hypothesis is that the true response rate of CR or CRi is 0.1 and the alternative hypothesis is that the true response rate of CR or CRi is 0.32. In each cohort, the trial is carried out in two stages. In stage I, a total number of 18 subjects is accrued. If there are 3 (16.7%) or fewer responses (CR or CRi) among these 18 subjects, the study may be early stopped based on the totality of the data. Otherwise, additional 6 subjects will be accrued in stage II, resulting in a total number sample size of 24. If there are 6 (25%) or

more responses (CR or CRi) among these 24 subjects, we will reject the null hypothesis and claim that the treatment is promising. The design controls the two-sided type I error rate at 0.05 and yields the power of 0.8.

[redacted] and preliminary efficacy data will be reviewed on an ongoing basis as part of an evaluation of evidence of biologic impact. In particular, the number of overall responses (per IMWG for MM subjects or 2017 ELN criteria for AML subjects) and the level of AMG 176 inactivation of MCL1 by the activation of BAX and caspase 3 in circulating monocytes and /or the decrease of circulating monocytes will be regularly reviewed.

Additional interim analyses will be performed when the target number of subjects enrolled in each part has had the opportunity to complete 6 months of treatment.

9.4.1.2 Primary Analysis

A primary analysis will occur when the last subject has had opportunity to complete 6 cycles of the treatment of AMG 176.

9.4.1.3 Final Analysis

A final analysis is planned after all subjects have had the opportunity to complete the last study visit.

9.4.2 Methods of Analyses

9.4.2.1 General Considerations

Descriptive statistics will be provided for selected demographics, safety, PK, PD and [redacted] by dose, dose schedule, and time as appropriate. Descriptive statistics on continuous data will include means, medians, standard deviations and ranges, while categorical data will be summarized using frequency counts and percentages. Graphical summaries of the data may also be presented. Unless otherwise specified, statistical analyses will be done using the FAS, which includes subjects that are enrolled and received at least 1 dose of AMG 176. Data will be analyzed by dose level for each part.

9.4.2.2 Efficacy Analyses

9.4.2.2.1 Multiple Myeloma (Part 1a, and Part 1b)

Endpoint	Statistical Analysis Methods
Primary	There are no primary efficacy endpoints in MM
Secondary	Summaries of BAX and caspase 3 levels in the circulating monocytes will be provided. Summaries will be described over time using the absolute level and also using changes from baseline levels. Plots of the relationship between AMG 176 concentrations and BAX/caspase 3 levels and/or monocyte counts will be provided. The proportion of subjects with overall response to treatment per the IMWG for MM subjects with corresponding 2-sided exact 9**5**% CI will be calculated using the Clopper-Pearson method (Clopper and Pearson, 1934) and tabulated for subjects treated at the MTD Kaplan-Meier curve will be presented for PFS, time to response (partial response or better) and DOR with estimates for rates and 2-sided 95% CI at selected weeks.
Exploratory	Will be described in the statistical analysis plan finalized before database lock

9.4.2.2.2 Acute Myeloid Leukemia (Part 3a, Part 3b, Part 3c, Part 3d, Part 4, and Part 5)

Endpoint	Statistical Analysis Methods
Primary	There are no primary efficacy endpoints in AML
Secondary	The proportion of subjects with overall response using 2017 ELN criteria for AML subjects with corresponding 2-sided exact 95% CI will be calculated using the Clopper-Pearson method (Clopper and Pearson, 1934) and tabulated for subjects treated at the MTCD. Kaplan-Meier curve will be presented for EFS, time to response, and DOR with estimates for rates and 2-sided 95% CI at selected weeks.
Exploratory	Will be described in the statistical analysis plan finalized before database lock

9.4.2.3 Safety Analyses

9.4.2.3.1 Analyses of Primary Safety Endpoint(s)

Endpoint	Statistical Analysis Methods
Primary	The analysis of the probability of DLT will include data from DLT evaluable- subjects (see Section 6.2.1.2.1 for definition of DLT-evaluable). The primary analysis for each part will only include DLTs that occur within the protocol defined DLT evaluation interval.

9.4.2.3.2 Adverse Events

The Medical Dictionary for Regulatory Activities (MedDRA) version 19.1 or later will be used to code all events categorized as adverse events or disease-related events.

Subject incidence of all treatment-emergent adverse events will be tabulated by system organ class and preferred term. Tables of fatal adverse events, serious adverse events, adverse events leading to withdrawal from investigational product or other protocol required therapies, and treatment emergent adverse events will also be provided. Subject incidence of disease-related events, fatal disease-related events, and device-related events, if applicable, will be tabulated by system organ class and preferred term. Similar summaries will also be provided to events of interest. Subject-level data may be provided instead of tables if the subject incidence is low.

9.4.2.3.3 Laboratory Test Results

The analyses of safety laboratory endpoints will include summary statistics over time. Shifts in grades of safety laboratory values between baseline and the worst on-study value will be tabulated by cohorts.

9.4.2.3.4 Vital Signs

The analyses of vital signs will include summary statistics over time. Shifts in vital sign values between baseline and the worst on-study value will be tabulated by cohorts.

9.4.2.3.5 Electrocardiogram

Summaries over time and/or changes from baseline over time will be provided for all ECG parameters. Subjects' maximum change from baseline in QT interval corrected by Fridericia's formula will be categorized and the number and percentage of subjects in each group will be summarized. Subjects' maximum post baseline values will also be categorized and the number and percentage of subjects in each group will be summarized. All on-study ECG data will be reviewed and select parameters of interest may be plotted.

9.4.2.3.6 Exposure to Investigational Product

Descriptive statistics will be produced to describe the exposure to AMG 176. The number of cycles initiated, completed, discontinued will be summarized. In addition, the duration, total dose, and dose intensity of AMG 176 will be summarized.

9.4.2.3.7 Exposure to Non-investigational Product

Descriptive statistics will be produced to describe the exposure to azacitidine. The number of cycles initiated, completed, discontinued, the duration of therapy and total dose will be summarized. Subject-level data may be provided instead of the summary if the subject incidence is low or single dose is given.

9.4.2.3.8 Exposure to Concomitant Medication

The number and proportion of subjects receiving concomitant medications of interest from study day 1 through safety follow-up will be summarized by preferred term as coded by the World Health Organization Drug (WHODRUG) dictionary. In addition, the number and proportion of subjects receiving anti-cancer therapies during long-term follow-up will be summarized.

9.4.2.4 Other Analyses

9.4.2.4.1 Pharmacokinetic Analyses

The analysis of pharmacokinetic endpoints will include data from all subjects who have received at least 1 dose of the investigational product and have at least 1 pharmacokinetic sample collected.

The PK parameters for AMG 176 including, but not limited to C_{max}, minimum observed concentration (C_{min}), AUC, CL, and, if feasible, $t_{½}$ will be estimated using standard non-compartmental PK methods and summarized by dose groups using means, standard deviations, medians, minimums**,** and maximums for intensive and peak/trough determinations. AMG 176 concentrations at each time point along with PK parameter values may be reviewed for each subject. Individual AMG 176 concentration/time profiles will be plotted by dose groups. Summary statistics will be computed for each sampling time and parameter as appropriate. For subjects in Part 3d (DDI assessment with itraconazole), AMG 176 PK parameters (C_{max}, AUC) will be compared from day 1 (with itraconazole) to day 15 (without itraconazole) to evaluate the effect of itraconazole on the PK of AMG 176. Geometric mean ratios for C_{max} and AUC values and associated 90% CI (Test/Reference) will be estimated. The “Test” treatment will be AMG 176 co-administered with itraconazole on day 1, while the “Reference” treatment will be AMG 176 administered without itraconazole on day 15. Analysis of the relationship between AMG 176 dose and exposure parameters (AUC and C_{max}) will be conducted and plots of the relationship between AMG 176 dose and exposure parameters along with dose proportionality assessment will be provided. Additional analyses to explore relationship between exposure and safety and exposure and efficacy may also be performed. Pharmacokinetic parameters such as C_{max}, AUC, and $t_{½}$, if feasible, will be estimated and summarized for azacitidine.

9.4.2.4.2 Prior Anti-cancer Therapy Summary

Prior anti-cancer therapies for current malignancy will be summarized.

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11. Appendices

11.1 Appendix 1. List of Abbreviations and Definitions of Terms

Abbreviation or Term	Definition/Explanation
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AML	acute myeloid leukemia
ANC	absolute neutrophil count
APL	acute promyelocytic leukemia
AST	aspartate aminotransferase (SGOT)
ASXL1	additional sex combs like-1
AUC	area under the concentration-time curve
$AUC_{0\text{-}168\ hr}$	area under the concentration-time curve from 0 to 168 hours
BAK	B-cell receptor associated kinases
BAX	B-cell lymphoma/leukemia 2 associated X protein
BCL2	B-cell lymphoma/leukemia 2
BCL2-L1	BCL2 like 1
BCR-ABL1	breakpoint cluster region protein-Abelson murine leukemia viral oncogene homolog 1
BCL-XL	B-cell lymphoma extra large
BCRP	breast cancer resistance protein
BIL	Bilirubin
BIM	Bcl-2-interacting mediator of cell death
BIW	twice weekly
BLI	bioluminescence imaging
BP	blood pressure
BSA	body surface area
BUN	blood urea nitrogen
CBC	complete blood count
CBFB-MYH11	core-binding factor subunit beta-myosin, heavy chain 11
CEBPA	CCAAT enhancer binding protein alpha
CK-MB	creatine kinase-muscle/brain
CL	Clearance
C_{max}	maximum observed concentration
C_{min}	minimum observed concentration
COVID-19	coronavirus disease 2019
CR	complete response
CrCl	creatinine clearance

Abbreviation or Term	Definition/Explanation
CRi	incomplete hematologic recovery; complete response/remission with incomplete recovery of peripheral blood counts
CRF	case report form
CRO	contract research organization
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP3A4	Cytochrome P450 3A4
D	Day
DDI	drug-drug interaction
DILI	drug-induced liver injury
DLRM	dose-level review meeting
DLRT	dose-level review team
DLT	dose-limiting toxicity
DMSO	dimethylsulfoxide
DOCR	duration of complete remission
DOR	duration of response
DBP	diastolic blood pressure
DR	durable response
ECG	electrocardiogram
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
ED_{50}	pharmacologically active dose causing 50% tumor size reduction
EDC	electronic data capture
EFS	event free survival
ELN	European LeukemiaNet
End of Study/EOS	defined as the date when the last subject across all sites is assessed or receives an intervention for evaluation in the study (ie, last subject last visit), following any additional parts in the study (eg, long-term follow-up), as applicable.
End of Study for Individual Subject	defined as the last day that protocol-specified procedures are conducted for an individual subject.
End of Study (primary completion)	defined as the date when the last subject is assessed or receives an intervention for the final collection of data for the primary endpoint(s), for the purposes of conducting the last primary analysis, whether the study concluded as planned in the protocol or was terminated early.
End of Treatment/EOT	defined as the last assessment for the protocol specified treatment phase of the study for an individual subject

Abbreviation or Term	Definition/Explanation
EOI	end of infusion
eSAE	electronic serious adverse event
FAS	Full Analysis Set
FDA	Food and Drug Administration
FDG	Fluorodeoxyglucose
FIH	first in human
[redacted]	[redacted]
FLC	serum light chain
FLT3	fms-like tyrosine kinase 3
FLT3 ITD	fms-like tyrosine kinase 3 internal tandem duplication
FSH	follicle stimulation hormone
FU	follow-up
GCP	Good Clinical Practice
G-CSF	granulocyte-colony stimulating factor;
GGT	gamma-glutamyl transferase
G-CSF	granulocyte colony stimulating factor
GLP	Good Laboratory Practices
GM-CSF	granulocyte macrophage colony stimulating factor
h, hr	Hour
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HCVAb	hepatitis C virus antibody
heart rate/HR	number of cardiac cycles per unit of time
HiDAC	high dose cytarabine
HIV	human immunodeficiency virus
HNSTD	highest-non-severely-toxic dose
HRT	hormone replacement therapy
HSCT	hematopoietic stem cell transplant
IC_{50}	half maximal inhibitory concentration
ICF	informed consent form
ICH	International Council for Harmonisation
ICMJE	International Committee of Medical Journal Editors
IEC	Independent Ethics Committee
Ig	Immunoglobulin

Abbreviation or Term	Definition/Explanation
IMWG	International Myeloma Working Group
IMWG-URC	International Myeloma Working Group - Uniform Response Criteria
INR	international normalized ratio
IPIM	Investigational Product Instruction Manual
IQ-CPLG	Innovation and Quality of Pharmaceutical Development's Clinical Pharmacology Leadership Group
IQR	**interquartile range**
IRB	Institutional Review Board
IRC	Independent Review Committee
ISS	International Staging System
ITD	internal tandem duplication
IV	intravenous or roman numeral 4
Ki	inhibitory constant
LAIP	leukemia-associated immunophenotype
LDH	lactate dehydrogenase
LKM1	Liver Kidney Microsomal antibody 1
LVEF	left ventricular ejection fraction
MAD	maximum administrated dose
MCL1	myeloid cell leukemia sequence 1
MDS	myelodysplastic syndrome**s**
MDSC	myeloid derived suppressor cells
MedDRA	Medical Dictionary for Regulatory Activities
MFI	medium fluorescent intensity
MLFS	morphologic leukemia free state
MM	multiple myeloma
MOMP	mitochondrial outer membrane permeabilization
MRD	minimal residual disease
MRD[-]	minimal residual disease negativity
MRI	magnetic resonance imaging
MTCD	maximum tolerated combination dose
MTD	maximum tolerated dose
mTPI	modified Toxicity Probability Interval
MUGA	multigated acquisition scan
N, n	Number
NCCN	National Clinical Cancer Network
NGS	next-generation sequencing

Abbreviation or Term	Definition/Explanation
NK	natural killer
NPM1	nucleophism 1
NT-pro-BNP	N-terminal prohormone of brain natriuretic peptide
OATP	organic anion polypeptide transporters
OBD	optimal biological dose
OR	overall response
OS	overall survival
PBMC	peripheral blood mononuclear cell
PBPK	physiologically based pharmacokinetic
PCR	polymerase chain reaction
PD	pharmacodynamics
PET	positron emission tomography
PFS	progression free survival
P-gp	P-glycoprotein
PK	Pharmacokinetics
PML-RARA	promyelocytic leukemia-reintoic acid receptor alpha
PR	partial response
PR interval	PR interval is measured from the beginning of the P wave to the beginning of the QRS complex in the heart's electrical cycle as measured by ECG or partial response
PT	prothrombin time
PUMA	p53 up-regulated modulator of apoptosis
Q8W	every 8 weeks
QRS	QRS interval is the interval between the Q wave and the S wave in the heart's electrical cycle as measured by ECG; represents the time it takes for the depolarization of the ventricles
QT	QT interval is a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle as measured by ECG
QTc	QT interval corrected for heart rate using accepted methodology
QTcF	QT interval corrected for heart rate using Fridericia’s formula
QW	once weekly
R/R	relapsed or refractory
RP2D	recommended phase 2 dose
RBC	red blood cell
RCV	reference change value
RT-PCR	real-time polymerase chain reaction
RUNX1	runt-related transcription factor 1

Abbreviation or Term	Definition/Explanation
RUNX1-RUNX1T1	runt-related transcription factor 1-RUNX1 translocation partner 1
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SBE-β-CD	sulfobutylether-β-cyclodextrin
SBP	systolic blood pressure
SC	subcutaneous(ly)
sCR	stringent complete response
Screen	Screening
SD	standard deviation
SFLC	serum free light chain
SFU	safety follow-up
SIFE	serum immunofixation
SOC	standard of care
SPEP	serum protein electrophoresis
STD10	severely toxic dose in 10% of the animals
$t_{½}$	half-life
TBA	total bile acid
TBL	total bilirubin
TDI	time-dependent inhibition
t_{max}	time of maximum observed serum concentration
TLS	tumor lysis syndrome
TP53	tumor protein p53
UIFE	urine immunofixation
ULN	upper limit of normal
UPEP	urine protein electrophoresis
UPM	unit probability mass
US	United States
USPI	US Prescribing Information
VGPR	very good partial response
WBC	white blood cell
WHO	World Health Organization
WHODRUG	World Health Organization Drug

11.2 Appendix 2. Clinical Laboratory Tests

The tests detailed in Table 11-1 will be performed by the central laboratory and/or by the local laboratory. All locally obtained test results are to be recorded in the eCRF. Pharmacokinetic, [redacted] samples will be sent to the central laboratory for processing. Additional analyte test results may be reported by the local or central laboratory, in accordance with standard laboratory procedures (eg, components of a hematology panel).

Protocol-specific requirements for inclusion or exclusion of subjects are detailed in Section 5.1 to Section 5.2 of the protocol.

Blood samples will be obtained by venipuncture before study drug administration. All laboratory tests must be reviewed by the investigator or qualified designee. Additional safety laboratory assessments may be performed if clinically indicated at the discretion of the investigator. The following tests listed in Table 11-1 will be conducted on samples collected by standard laboratory procedures.

Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 11-1. Analyte Listing

Local Laboratory[b]				Central Laboratory
Chemistry	**Hematology**	**Urinalysis**	**For MM Subjects Only**	**Other Labs**
Albumin ALP ALT AST Bicarbonate (optional) NT-Pro BNP (or BNP if NT-Pro BNP not available) BUN or Urea Calcium Chloride CK-MB Creatinine Direct bilirubin GGT Glucose LDH Magnesium Phosphorus Potassium Sodium Total bilirubin Total protein Total bile acid Troponin (I or T) Uric acid Haptoglobin	ANC[a] Hematocrit Hemoglobin[b] MCH MCHC MCV Platelets RBCs WBCs Differential: ▪ Neutrophils ▪ Lymphocytes ▪ Monocytes ▪ Eosinophils ▪ Basophils Blasts[a]	Specific gravity pH Blood Protein Ketones Bilirubin Glucose Leucocytes esterase (WBC) Microscopic exam (only needed for positive dipstick and should include the following): ▪ Epithelial ▪ Bacteria ▪ Casts ▪ Crystal ▪ RBCs ▪ WBCs	SPEP UPEP SFLC Quantitative Immunoglobulin Beta-2 microglobulin	PK [redacted] (see Section 8.2.8) Bone marrow aspirate (as applicable) Bone marrow biopsy (as applicable) Cardiac enzymes including troponin-I, CK-MB, and NT-pro-BNP
	Coagulation	**Other Labs**		
	PT or INR aPTT	Pregnancy HBsAg HBsAb HBcAb Hepatitis C antibody HCV PCR (if applicable) HBV PCR (if applicable) SARS-CoV-2		

Table 11-1. Analyte Listing (continued)

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AML = acute myeloid leukemia; ANC = absolute neutrophil count; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; BNP = B-type natriuretic protein; BUN = blood urea nitrogen; CK-MB = creatinine kinase-muscle/brain; eCRF= electronic case report form [redacted]; GGT = gamma-glutamyl transferase; HBcAb = hepatitis B core antibody; HBsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; INR = international normalized ratio; LDH = lactate dehydrogenase; MCH = mean cell hemoglobin; MCHC = mean cell hemoglobin concentration; MCV = mean cell volume; NT-pro-BNP = N-terminal prohormone of brain natriuretic peptide PCR = polymerase chain reaction; PK = pharmacokinetics; PT = prothrombin time; PTT = partial thromboplastin time; RBC = red blood cell; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SFLC = serum-free light chain; SPEP = serum protein electrophoresis; UPEP = urine protein electrophoresis; WBC = white blood cell

[a] Peripheral blood counts for AML disease assessments will include ANC, platelets, hemoglobin, and blasts.

[b] For local laboratory tests, all available analytes listed in the table should be recorded in the eCRF.

11.3 Appendix 3. Study Governance Considerations

Dose-Level Review Team

Dose-Level Review Meetings (DLRM)

The DLRT will hold meetings to review data, monitor safety, and make decisions on dose-escalation or dose de-escalation or changes. The DLRT will be composed of the investigators or designees (for Part 3c, the Japan site investigators only), and the following Amgen representatives: early development lead, medical monitor, global safety officer or designee, clinical study manager, biostatistician; additional members may be added as needed (eg, clinical pharmacologist). The following members are responsible for DLRT recommendations: investigators, Amgen medical monitor, and global safety officer or designee. All available study data, including data collected after the initial DLT evaluation period, and including demographics, investigational product administration, medical history, concomitant medications, adverse events, ECGs, vital signs, laboratory data, and PK/PD information will be reviewed. In addition to DLTs, all ≥ grade 3 toxicities not meeting DLT criteria will be reviewed and may be considered in DLRT decisions. Data to be reviewed will be queried. The DLRT may review the available PK, PD and PK/PD information from all previous cohorts with known non-clinical data and safety information. The planned dose will be adapted accordingly, if needed. Modeling of available potential safety risk data (eg, for anemia) to predict safety risk for dose escalation recommendations may also be considered.

A quorum, defined as > 50% of the participating **i**nvestigators or their qualified designee (ie, sub-investigator, research nurse or study coordinator possessing a hard copy document [eg, email] of the **i**nvestigator's vote regarding the dose-level review; this email is required to be submitted to Amgen), must be in attendance for the dose-level review meeting (DLRM). The decision to proceed to the next dose level or an interim dose level will be made by the sponsor in conjunction with the investigators after careful consideration of all available safety, laboratory, and PK information. Safety data from all enrolled subjects in preceding cohorts and dose levels will also be considered. Additionally, further enrollment into a cohort can be stopped at any time to evaluate safety.

Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines
- Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines
- Applicable ICH laws and regulations

The protocol, protocol amendments, informed consent form, Investigator's Brochure, and other relevant documents (eg, subject recruitment advertisements) must be submitted to an Institutional Review Board (IRB)/Independent Ethics Committee (IEC) by the investigator and reviewed and approved by the IRB/IEC. A copy of the written approval of the protocol and informed consent form must be received by Amgen before recruitment of subjects into the study and shipment of Amgen investigational product.

Amgen may amend the protocol at any time. The investigator must submit and, where necessary, obtain approval from the IRB/IEC for all protocol amendments and changes to the informed consent document that Amgen distributes to the site. The investigator must send a copy of the approval letter from the IRB/IEC and amended protocol Investigator's Signature page to Amgen prior to implementation of the protocol amendment at their site.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Obtaining annual IRB/IEC approval/renewal throughout the duration of the study. Copies of the investigator's reports and the IRB/IEC continuance of approval must be sent to Amgen
- Notifying the IRB/IEC of serious adverse events occurring at the site, deviations from the protocol or other adverse event reports received from Amgen, in accordance with local procedures
- Overall conduct of the study at the site and adherence to requirements of Title 21 of the US Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, and all other applicable local regulations

Informed Consent Process

An initial sample informed consent form is provided for the investigator to prepare the informed consent document to be used at his/her site. Updates to the sample informed

consent form are to be communicated formally in writing from the Amgen Trial Manager to the investigator. The written informed consent form is to be prepared in the language(s) of the potential patient population.

The investigator or his/her delegated representative will explain to the subject, or his/her legally authorized representative, the aims, methods, anticipated benefits, and potential hazards of the study before any protocol-specific screening procedures or any investigational product(s) is/are administered, and answer all questions regarding the study.

Subjects must be informed that their participation is voluntary. Subjects will then be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act requirements, where applicable, and the IRB/IEC or study site.

The medical record must include a statement that written informed consent was obtained before the subject was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the informed consent form.

The investigator is also responsible for asking the subject if the subject has a primary care physician and if the subject agrees to have his/her primary care physician informed of the subject's participation in the clinical study unless it is a local requirement. The investigator shall then inform the primary care physician. If the subject agrees to such notification, the investigator is to inform the subject's primary care physician of the subject's participation in the clinical study. If the subject does not have a primary care physician and the investigator will be acting in that capacity, the investigator is to document such in the subject's medical record.

The acquisition of informed consent and the subject's agreement or refusal of his/her notification of the primary care physician is to be documented in the subject's medical records, and the informed consent form is to be signed and personally dated by the subject and by the person who conducted the informed consent discussion. Subject withdrawal of consent or discontinuation from study treatment and/or procedures must also be documented in the subject's medical records; refer to Section 7.

Subjects must be re-consented to the most current version of the informed consent form(s) during their participation in the study.

The original signed informed consent form is to be retained in accordance with institutional policy, and a copy of the informed consent form(s) must be provided to the subject or the subject's legally authorized representative.

If a potential subject is illiterate or visually impaired and does not have a legally acceptable representative, the investigator must provide an impartial witness to read the informed consent form to the subject and must allow for questions. Thereafter, both the subject and the witness must sign the informed consent form to attest that informed consent was freely given and understood. (Refer to ICH GCP guideline, Section 4.8.9.)

A subject who is rescreened is not required to sign another informed consent form if the re-screening occurs within 14 days from the previous informed consent form signature date.

The informed consent form (ICF) will contain a separate section that addresses the use of remaining mandatory samples for optional future research. The investigator or authorized designee will explain to each subject the objectives of the future research. Subjects will be told that they are free to refuse to participate and may withdraw their specimens at any time and for any reason during the storage period. A separate signature will be required to document a subject's agreement to allow any remaining specimens to be used for future research. Subjects who decline to participate will not provide this separate signature.

Data Protection/Subject Confidentiality

The investigator must ensure that the subject's confidentiality is maintained for documents submitted to Amgen.

Subject will be assigned a unique identifier by the sponsor. Any subject records or datasets that are transferred to the sponsor will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred.

On the case report form (CRF) demographics page, in addition to the unique subject identification number, include the age at time of enrollment.

For serious adverse events reported to Amgen, subjects are to be identified by their unique subject identification number, initials (for faxed reports, in accordance with local laws and regulations), and age (in accordance with local laws and regulations).

Documents that are not submitted to Amgen (eg, signed informed consent forms) are to be kept in confidence by the investigator, except as described below.

In compliance with governmental regulations/ICH GCP Guidelines, it is required that the investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the IRB/IEC direct access to review the subject's original medical records for verification of study-related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study.

The investigator is obligated to inform and obtain the consent of the subject to permit such individuals to have access to his/her study-related records, including personal information.

Publication Policy

To coordinate dissemination of data from this study, Amgen may facilitate the formation of a publication committee consisting of several investigators and appropriate Amgen staff, the governance and responsibilities of which are set forth in a Publication Charter. The committee is expected to solicit input and assistance from other investigators and to collaborate with authors and Amgen staff, as appropriate, as defined in the Publication Charter. Membership on the committee (both for investigators and Amgen staff) does not guarantee authorship. The criteria described below are to be met for every publication.

Authorship of any publications resulting from this study will be determined on the basis of the International Committee of Medical Journal Editors (ICMJE) Recommendations for the Conduct of Reporting, Editing, and Publications of Scholarly Work in Medical Journals, which states: Authorship credit is to be based on: (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; (3) final approval of the version to be published; and (4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Authors need to meet conditions 1, 2, 3, and 4.

When a large, multicenter group has conducted the work, the group is to identify the individuals who accept direct responsibility for the manuscript. These individuals must fully meet the criteria for authorship defined above. Acquisition of funding, collection of data, or general supervision of the research group, alone, does not justify authorship. All persons designated as authors must qualify for authorship, and all those who qualify are

to be listed. Each author must have participated sufficiently in the work to take public responsibility for appropriate portions of the content. All publications (eg, manuscripts, abstracts, oral/slide presentations, book chapters) based on this study must be submitted to Amgen for review. The Clinical Trial Agreement among the institution, investigator, and Amgen will detail the procedures for, and timing of, Amgen's review of publications.

Investigator Signatory Obligations

Each clinical study report is to be signed by the investigator or, in the case of multicenter studies, the coordinating investigator.

The coordinating investigator, identified by Amgen, will be any or all of the following:

- A recognized expert in the therapeutic area
- An **i**nvestigator who provided significant contributions to either the design or interpretation of the study
- An **i**nvestigator contributing a high number of eligible subjects

Data Quality Assurance

All subject data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data, centrally or adjudicated data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

The sponsor or designee is responsible for the data management of this study including quality checking of the data.

Clinical monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of subjects are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements per the sponsor's monitoring plan.

The investigator agrees to cooperate with the clinical monitor to ensure that any problems detected in the course of these monitoring visits, including delays in completing CRFs, are resolved.

The Amgen representative(s) and regulatory authority inspectors are responsible for contacting and visiting the investigator for the purpose of inspecting the facilities and, upon request, inspecting the various records of the clinical study (eg, CRFs and other pertinent data) provided that subject confidentiality is respected.

In accordance with ICH GCP and the sponsor's audit plans, this study may be selected for audit by representatives from Amgen's Global Research and Development Compliance and Audit function (or designees). Inspection of site facilities (eg, pharmacy, protocol-required therapy storage areas, laboratories) and review of study-related records will occur to evaluate the study conduct and compliance with the protocol, ICH GCP, and applicable regulatory requirements.

Retention of study documents will be governed by the Clinical Trial Agreement.

All written information and other material to be used by subjects and investigative staff must use vocabulary and language that are clearly understood.

Source Documents

The investigator is to maintain a list of appropriately qualified persons to whom he/she has delegated study duties. All persons authorized to make entries and/or corrections on CRFs will be included on the Amgen Delegation of Authority Form.

Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Source documents are original documents, data, and records from which the subject's CRF data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence. Source documents may also include data captured in the IRT system (if used, such as subject ID and randomization number) and CRF entries if the CRF is the site of the original recording (ie, there is no other written or electronic record of data, such as paper questionnaires for a clinical outcome assessment).

Data reported on the CRF or entered in the electronic CRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or

transfer records, depending on the study. Also, current medical records must be available.

The investigator and study staff are responsible for maintaining a comprehensive and centralized filing system of all study-related (essential) documentation, suitable for inspection at any time by representatives from Amgen and/or applicable regulatory authorities.

Elements to include:

- Subject files containing completed CRFs, informed consent forms, and subject identification list
- Study files containing the protocol with all amendments, Investigator's Brochure, copies of prestudy documentation, and all correspondence to and from the IRB/IEC and Amgen
- Investigational product-related correspondence including Proof of Receipts, Investigational Product Accountability Record(s), Return of Investigational Product for Destruction Form(s), Final Investigational Product Reconciliation Statement, as applicable

Retention of study documents will be governed by the Clinical Trial Agreement.

Study and Site Closure

Amgen or its designee may stop the study or study site participation in the study for medical, safety, regulatory, administrative, or other reasons consistent with applicable laws, regulations, and GCP.

Both Amgen and the investigator reserve the right to terminate the **i**nvestigator's participation in the study according to the Clinical Trial Agreement. The investigator is to notify the IRB/IEC in writing of the study's completion or early termination and send a copy of the notification to Amgen.

Subjects may be eligible for continued treatment with Amgen investigational product(s) by an extension protocol or as provided for by the local country's regulatory mechanism. However, Amgen reserves the unilateral right, at its sole discretion, to determine whether to supply Amgen investigational product(s) and by what mechanism, after termination of the study and before the product(s) is/are available commercially.

Compensation

Any arrangements for compensation to subjects for injury or illness that arises in the study are described in the Compensation for Injury section of the Informed Consent that is available as a separate document.

11.4 Appendix 4. Safety Events: Definitions and Procedures for Recording, Evaluating, Follow-up and Reporting

Definition of Disease-related Event

Disease-related Event Definition
• Disease-related events are events (serious or non-serious) anticipated to occur in the study population due to the underlying disease. • Expected disease-related events pre-defined for this study in subjects with MM and AML are listed in Table 11-2 and Table 11-3. • Note: Disease related events assessed by the investigator to be more severe than expected and/or related to the investigational product(s)/study treatment/protocol-required therapies, and determined to be serious, must be reported on the Event CRF as serious adverse events.

Disease-related Events that do not qualify as Adverse Events or Serious Adverse Events
• An event which is part of the normal course of disease under study (eg, disease progression in oncology or hospitalization due to disease progression) is to be reported as a Disease-related Event.

Disease-related Events that would qualify as an Adverse Event or Serious Adverse Event
• An event based on the underlying disease that is worse than expected as assessed by the investigator for the subject's condition, or for which the investigator believes there is a causal relationship between the investigational product(s)/study treatment/protocol-required therapies and disease worsening must be reported as an adverse event or serious adverse event.

Definition of Adverse Event

Adverse Event Definition
• An adverse event is any untoward medical occurrence in a clinical study subject irrespective of a causal relationship with the study treatment. • Note: An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a treatment, combination product, medical device or procedure. • Note: Treatment-emergent adverse events will be defined in the SAP.

Events Meeting the Adverse Event Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, electrocardiogram, radiological scans, vital signs measurements), including those that worsen from baseline, that are considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction (DDI). • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an adverse event/serious adverse event unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses are to be reported regardless of sequelae. • For situations when an adverse event or serious adverse event is due to MM or AML report all known signs and symptoms. Death due to disease progression in the absence of signs and symptoms should be reported as the primary tumor type (eg, metastatic pancreatic cancer). Note: The term "disease progression" should not be used to describe the disease-related event or adverse event. • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an adverse event or serious adverse event. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as adverse event or serious adverse event if they fulfill the definition of an adverse event or serious adverse event.

Events NOT Meeting the Adverse Event Definition
• Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the adverse event. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Definition of Serious Adverse Event

A Serious Adverse Event is defined as any untoward medical occurrence that, meets at least 1 of the following serious criteria (unless it meets the definition of a disease-related event):
Results in death (fatal)
Immediately life-threatening The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
Requires in-patient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are an adverse event. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the adverse event is to be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an adverse event.
Results in persistent or significant disability/incapacity The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
Is a congenital anomaly/birth defect
Other medically important serious event Medical or scientific judgment is to be exercised in deciding whether serious adverse event reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent 1 of

the other outcomes listed in the above definition. These events are typically to be considered serious.

Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Recording Adverse Events and Serious Adverse Events

Adverse Event and Serious Adverse Event Recording

- When an adverse event or serious adverse event occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The investigator will then record all relevant adverse event/serious adverse event information in the Event case report form (CRF).
- The investigator must assign the following adverse event attributes:
  - Adverse event diagnosis or syndrome(s), if known (if not known, signs or symptoms);
  - Dates of onset and resolution (if resolved);
  - Did the event start prior to first dose of investigational product;
  - Assessment of seriousness;
  - Severity (or toxicity defined below);
  - Assessment of relatedness to investigational product or other protocol-required therapies; and
  - Action taken; and
  - Outcome of event.
- If the severity of an adverse event worsens from the date of onset to the date of resolution, record a single event for each increased level of severity on the Event eCRF
- It is not acceptable for the investigator to send photocopies of the subject's medical records to Amgen in lieu of completion of the Event CRF page.
- If specifically requested, the investigator may need to provide additional follow-up information, such as discharge summaries, medical records, or extracts from the medical records. In this case, all subject identifiers, with the exception of the subject number, will be blinded on the copies of the medical records before submission to Amgen.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the adverse event/serious adverse event.

Evaluating Adverse Events and Serious Adverse Events

Assessment of Severity
The investigator will make an assessment of severity for each adverse event and serious adverse event reported during the study. The assessment of severity will be based on: The Common Terminology Criteria for Adverse Events (CTCAE), version 4.0 which is available at the following location: http://evs.nci.nih.gov/ftp1/CTCAE/About.html.

Assessment of Causality
• The investigator is obligated to assess the relationship between investigational product, protocol-required therapies, and/or study-mandated procedures and each occurrence of each adverse event/serious adverse event. • Relatedness means that there are facts or reasons to support a relationship between investigational product and the event. • The investigator will use clinical judgment to determine the relationship. • Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated. • The investigator will also consult the Investigator's Brochure and/or Product Information, for marketed products, in his/her assessment. • For each adverse event/serious adverse event, the investigator must document in the medical notes that he/she has reviewed the adverse event/serious adverse event and has provided an assessment of causality. • There may be situations in which a serious adverse event has occurred and the investigator has minimal information to include in the initial report. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the serious adverse event data. • The investigator may change his/her opinion of causality in light of follow-up information and send a serious adverse event follow-up report with the updated causality assessment. • The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.

Follow-up of Adverse Event and Serious Adverse Event
• The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Amgen to elucidate the nature and/or causality of the adverse event or serious adverse event as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

- If a subject is permanently withdrawn from protocol-required therapies because of a serious adverse event, this information must be submitted to Amgen.
- New or updated information will be recorded in the originally completed Event CRF.
- The investigator will submit any updated serious adverse event data to Amgen immediately and no later than 24 hours of receipt of the information.

Reporting of Serious Adverse Event

Serious Adverse Event Reporting via Electronic Data Collection Tool
• The primary mechanism for reporting serious adverse event will be the electronic data capture (EDC) system. • If the EDC system is unavailable for more than 24 hours, then the site will report the information to Amgen using an electronic Serious Adverse Contingency Report Form (see Figure 11-1) immediately and no later than 24 hours of the investigator's awareness of the event. • The site will enter the serious adverse event data into the electronic system as soon as it becomes available. • After the study is completed at a given site, the EDC system will be taken off-line to prevent the entry of new data or changes to existing data. • If a site receives a report of a new serious adverse event from a study subject or receives updated data on a previously reported serious adverse event after the EDC has been taken off-line, then the site can report this information on a paper Serious Adverse Event Report Form (see Figure 11-1). • Once the study has ended, serious adverse event(s) suspected to be related to investigational product will be reported to Amgen if the investigator becomes aware of a serious adverse event. The investigator should use the paper-based Serious Adverse Event Contingency Report Form to report the event.

Figure 11-1. Sample Electronic Serious Adverse Event Contingency Form

A **Study # 20150161** **AMG 176**	**Electronic Serious Adverse Event Contingency Report Form** **For Restricted Use**

Reason for reporting this event via fax

The Clinical Trial Database (eg. Rave):

☐ Is not available due to internet outage at my site
☐ Is not yet available for this study
☐ Has been closed for this study

<<For completion by COM prior to providing to sites: SELECT OR TYPE IN A FAX#>>

1. SITE INFORMATION

Site Number	Investigator	Country

Reporter	Phone Number	Fax Number
	( )	( )

2. SUBJECT INFORMATION

Subject ID Number	Age at event onset	Sex	Race	If applicable, provide End of Study date
		☐F ☐M		

If this is a follow-up to an event reported in the **EDC system (eg, Rave)**, provide the adverse event term: _____
and start date: Day ____ Month ____ Year _____

3. SERIOUS ADVERSE EVENT

Provide the date the Investigator became aware of this information: Day____ Month____ Year_____

Serious Adverse Event diagnosis or syndrome If diagnosis is unknown, enter signs / symptoms and provide diagnosis, when known, in a follow-up report *List one event per line. If event is fatal, enter the cause of death. Entry of "death" is not acceptable, as this is an outcome.*	Date Started Day Month Year	Date Ended Day Month Year	Check only if event occurred before first dose of IP	Is event serious?	If serious, enter Serious Criteria code (see codes below)	Relationship Is there a reasonable possibility that the Event may have been caused by IP or an Amgen device used to administer the IP?								Outcome of Event -Resolved -Not resolved -Fatal -Unknown	Check only if event is related to study procedure eg, biopsy
						AMG 176		azacitidine		<Device>		<Device>			
						No✓	Yes✓	No✓	Yes✓	No✓	Yes✓	No✓	Yes✓		
				☐Yes ☐No											
				☐Yes ☐No											
				☐Yes ☐No											

Serious Criteria: 01 Fatal; 02 Immediately life-threatening; 03 Required/prolonged hospitalization; 04 Persistent or significant disability /incapacity; 05 Congenital anomaly / birth defect; 06 Other medically important serious event

4. Was subject hospitalized or was a hospitalization prolonged due this event? ☐No ☐Yes If yes, please complete all of Section 4

Date Admitted Day Month Year	Date Discharged Day Month Year

5. Was IP/drug under study administered/taken prior to this event? ☐No ☐Yes If yes, please complete all of Section 5

IP/Amgen Device:		Date of Initial Dose Day Month Year	Prior to, or at time of Event Date of Dose Day Month Year	Dose	Route	Frequency	Action Taken with Product 01 Still being Administered 02 Permanently discontinued 03 Withheld	Lot # and Serial #
AMG 176	☐ blinded ☒ open label							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown
azacitidine	☐ blinded ☒ open label							Lot # _____ ☐ Unknown

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A Study # 20150161 AMG 176	Electronic Serious Adverse Event Contingency Report Form For Restricted Use

								Serial # ☐ Unavailable / Unknown

Site Number	Subject ID Number

6. CONCOMITANT MEDICATIONS (eg, chemotherapy) Any Medications? ☐ No ☐ Yes If yes, please complete:

Medication Name(s)	Start Date (Day Month Year)	Stop Date (Day Month Year)	Co-suspect No✓	Co-suspect Yes✓	Continuing No✓	Continuing Yes✓	Dose	Route	Freq.	Treatment Med No✓	Treatment Med Yes✓

7. RELEVANT MEDICAL HISTORY *(include dates, allergies and any relevant prior therapy)*

8. RELEVANT LABORATORY VALUES *(include baseline values)* Any Relevant Laboratory values? ☐ No ☐ Yes If yes, please complete:

Date (Day Month Year)	Test											
	Unit											

9. OTHER RELEVANT TESTS *(diagnostics and procedures)* Any Other Relevant tests? ☐ No ☐ Yes If yes, please complete:

Date (Day Month Year)	Additional Tests	Results	Units

A **Study # 20150161** **AMG 176**	**Electronic Serious Adverse Event Contingency Report Form** **For Restricted Use**

Site Number	Subject ID Number

10. CASE DESCRIPTION ***(Provide narrative details of events listed in section 3)*** Provide additional pages if necessary. For each event in section 3, where relationship=Yes, please provide rationale.

Signature of Investigator or Designee - *I confirm by signing this report that the information on this form, including seriousness and causality assessments, is being provided to Amgen by the investigator for this study, or by a Qualified Medical Person authorized by the investigator for this study.*	Title	Date

Table 11-2. Expected Disease-related Events by System Organ Class (SOC) for Multiple Myeloma

System Organ Class	Disease-Related Adverse Events
Blood and lymphatic system disorders	Anemia, neutropenia, leukopenia, thrombocytopenia.
Cardiovascular disorders	Shortness of breath (from renal failure), Oedema peripheral (renal failure)
Eye disorders	Blurred vision (hyperviscosity)
Gastrointestinal disorders	Nausea, constipation (hypercalcemia), abdominal pain (hypercalcemia)
General disorders and administration site reaction	Fatigue, malaise, pain, chest pain, mass, excessive thirst,
Immune system disorders	Infection in an immunocompromised host
Investigations	Hemoglobin decreased, platelet count decreased, white blood cell count decreased, total protein increase, creatinine increase, abnormal serum electrophoresis, immunoglobulin level increased or decreased, weight decreased.
Metabolism and nutrition disorders	Anorexia, hypoalbuminemia, hypercalcemia, dehydration
Musculoskeletal and connective tissue disorders	Skeletal pain, pathological fractures, osteoporosis, osteopenia, bone pain, pain in extremity, back pain, muscle weakness
Neoplasms benign, malignant and unspecified	Plasmacytoma
Nervous system disorders	Lethargy, confusion (from hypercalcemia), peripheral neuropathy, dizziness (hyperviscosity), headache (hyperviscosity)
Renal and urinary disorders	Renal failure, nephrotic syndrome, oliguria
Vascular disorders	venous thromboembolism
Other	Arthroplasty, osteotomy, bone fixation

Table 11-3. Expected Disease-related Events by System Organ Class (SOC) for Acute Myeloid Leukemia

System Organ Class	Disease-Related Adverse Events
Blood and lymphatic system disorders	Febrile neutropenia, anemia, neutropenia, thrombocytopenia, leukopenia, leukocytosis, disseminated intravascular coagulation
Cardiovascular disorders	Palpitations, tachycardia
Ear and labyrinth disorders	Ear pain, tinnitus
Eye disorders	Blurred vision
Gastrointestinal disorders	Abdominal distension, abdominal pain, constipation, diarrhea, gingival pain, nausea
General disorders and administration site reaction	Fatigue, pyrexia, malaise, pain, chest pain
Infections and infestations	Infection[a], sepsis
Investigations	Alanine aminotransferase increased, aspartate aminotransferase increased, alkaline phosphatase increased, white blood cell decreased, hemoglobin decreased, platelet count decreased
Metabolism and nutrition disorders	Decreased appetite, hypokalemia, hyponatremia, hypocalcemia, hyperuricemia
Musculoskeletal and connective tissue disorders	Skeletal pain, muscular pain, arthralgia, generalized muscle weakness, neck pain
Nervous system disorders	Cranial nerve disorder, dizziness, headache, lethargy, meningismus, syncope
Respiratory, thoracic, and mediastinal disorders	Cough, dyspnea, epistaxis, pleuritic pain
Other	Hemorrhage[b]

[a] Represents preferred terms under Infections and infestations SOC
[b] Represents haemorrhage HLGT preferred terms contained within multiple SOCs. Coded: MedDRA 17.0

11.5 Appendix 5. Contraceptive Guidance and Collection of Pregnancy and Lactation Information

Study-specific contraception requirements for male and female subjects of childbearing potential are outlined in Section 5.2.

Male and female subjects of childbearing potential must receive pregnancy prevention counseling and be advised of the risk to the fetus if they become pregnant during treatment and for 3 months after the last dose of protocol-required therapies or father a child during treatment and for 4 months after the last dose of protocol-required therapies.

Additional medications given during the study may alter the contraceptive requirements. These additional medications may require female subjects to use highly effective methods of contraception and/or for an increased length of time. In addition, male subjects may also be required to use contraception for an increased length of time. The investigator must discuss these contraceptive changes with the subject.

Definition of Females of Childbearing Potential

A female is considered fertile following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

Females in the following categories are not considered female of childbearing potential:

- Premenopausal female with 1 of the following:
  - Documented hysterectomy;
  - Documented bilateral salpingectomy; or
  - Documented bilateral oophorectomy.

  Note: Site personnel documentation from the following sources is acceptable: 1) review of subject's medical records; 2) subject's medical examination; or 3) subject's medical history interview.
- Premenarchal female
- Postmenopausal female
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
  - Females on HRT and whose menopausal status is in doubt will be required to use 1 of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment

Contraception Methods for Female Subjects

Highly Effective Methods of Contraception

- Non-hormonal (ie, copper) intrauterine device (IUD)
- Bilateral tubal ligation/occlusion
- Vasectomized partner (provided that partner is the sole sexual partner of the female subject of childbearing potential and that the vasectomized partner has received medical assessment of the surgical success)
- Sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments; the reliability of sexual abstinence must be evaluated in relation to the duration of the trial and the preferred and usual lifestyle of the subject)

Potential DDI between the study drug(s) and hormone-based contraceptives are not established. The hormonal contraceptive methods listed below therefore may have decreased effectiveness, and consequently may not prove as reliable with regard to prevention of pregnancy on study.

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, or transdermal) Progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, or implantable)
- Hormone-releasing intrauterine device
- Intrauterine hormonal-releasing system

Study subjects should utilize any or all appropriate measures to prevent pregnancy while on study.

Contraception Methods for Male Subjects

- Sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of risk associated with protocol-required therapies; the reliability of sexual abstinence must be evaluated in relation to the duration of the trial and the preferred and usual lifestyle of the subject)
- Use a condom with spermicide during treatment and for an additional 4 months after the last dose of protocol-required therapies

The female partner should consider using an acceptable method of effective contraception such as: hormonal, IUD, intrauterine hormonal-releasing system (IUS), female barrier method (diaphragm, cap, sponge [a female condom is not an option because there is a risk of tearing when both partners use a condom]).

Note: If the male's sole female partner is of non-childbearing potential or has had a bilateral tubal ligation/occlusion, he is not required to use additional forms of contraception during the study.

Unacceptable Methods of Birth Control for Male and Female Subjects

Birth control methods that are considered unacceptable in clinical trials include:

- Periodic abstinence (calendar, symptothermal, post-ovulation methods)
- Withdrawal (coitus interruptus)
- Spermicides only
- Lactational amenorrhea method

Collection of Pregnancy Information

Female Subjects Who Become Pregnant

- Investigator will collect pregnancy information on any female subject who becomes pregnant while taking protocol-required therapies through 3 months after the last dose of investigational product.
- Information will be recorded on the Pregnancy Notification Form (see Figure 11-2). The form must be submitted to Amgen Global Patient Safety immediately and no later than 24 hours of learning of a subject's pregnancy. (Note: Sites are not required to provide any information on the Pregnancy Notification Form that violates the country or regions local privacy laws).
- After obtaining the female subject's signed consent for release of pregnancy and infant health information, the investigator will collect pregnancy and infant health information and complete the pregnancy questionnaire for any female subject who becomes pregnant while taking protocol-required therapies through 3 months after the last dose of investigational product of the study drug. This information will be forwarded to Amgen Global Patient Safety. Generally, infant follow-up will be conducted up to 12 months after the birth of the child (if applicable).
- Any termination of pregnancy will be reported to Amgen Global Patient Safety, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an adverse event or serious adverse event, any pregnancy complication or report of a congenital anomaly or developmental delay, fetal death, or suspected adverse reactions in the neonate will be reported as an adverse event or serious adverse event. Note that an elective termination with no information on a fetal congenital malformation or maternal complication is generally not considered an adverse event, but still must be reported to Amgen as a pregnancy exposure case.
- If the outcome of the pregnancy meets a criterion for immediate classification as a serious adverse event (eg, female subject experiences a spontaneous abortion, stillbirth, or neonatal death or there is a fetal or neonatal congenital anomaly) the investigator will report the event as a serious adverse event.
- Any serious adverse event occurring as a result of a post-study pregnancy which is considered reasonably related to the study treatment by the investigator, will be reported to Amgen Global Patient Safety as described in Section 11.4. While the investigator is not obligated to actively seek this information in former study

subjects, he or she may learn of a serious adverse event through spontaneous reporting.

- Any female subject who becomes pregnant while participating will discontinue study treatment (see Section 7.1 for details).

Male Subjects With Partners Who Become Pregnant

- In the event a male subject fathers a child during treatment, and for an additional 4 months after the last dose of investigational product after discontinuing protocol-required therapies, the information will be recorded on the Pregnancy Notification Form. The form (see Figure 11-2) must be submitted to Amgen Global Patient Safety immediately and no later than 24 hours of the site's awareness of the pregnancy. (Note: Sites are not required to provide any information on the Pregnancy Notification Form that violates the country or regions local privacy laws).
- The investigator will attempt to obtain a signed consent for release of pregnancy and infant health information directly from the pregnant female partner to obtain additional pregnancy information.
- After obtaining the female partner's signed consent for release of pregnancy and infant health information, the investigator will collect pregnancy outcome and infant health information on the pregnant partner and her baby and complete the pregnancy questionnaires. This information will be forwarded to Amgen Global Patient Safety.
- Generally, infant follow-up will be conducted up to 12 months after the birth of the child (if applicable).
- Any termination of the pregnancy will be reported to Amgen Global Patient Safety regardless of fetal status (presence or absence of anomalies) or indication for procedure.

Collection of Lactation Information

- Investigator will collect lactation information on any female subject who breastfeeds while taking protocol-required therapies through 3 months after the last dose of investigational product.
- Information will be recorded on the Lactation Notification Form (see below) and submitted to Amgen Global Patient Safety immediately and no later than 24 hours of the investigator's awareness of event.
- Study treatment will be discontinued if female subject breastfeeds during the study as described in exclusion criterion 233.
- With the female subjects signed consent for release of mother and infant health information, the investigator will collect mother and infant health information and complete the lactation questionnaire on any female subject who breastfeeds while taking protocol-required therapies through 3 months after the last dose of investigational product after discontinuing protocol-required therapies.

Figure 11-2. Pregnancy and Lactation Notification Forms

AMGEN® Pregnancy Notification Form

Report to Amgen at: USTO fax: +1-888-814-8653, Non-US fax: +44 (0)207-136-1046 or email (worldwide): svc-ags-in-us@amgen.com

1. Case Administrative Information

Protocol/Study Number: 20150161

Study Design: ☐ Interventional ☐ Observational (If Observational: ☐ Prospective ☐ Retrospective)

2. Contact Information

Investigator Name _____ **Site #** _____

Phone (_____)_____ **Fax** (_____)_____ **Email** _____

Institution _____

Address _____

3. Subject Information

Subject ID # _____ **Subject Gender:** ☐ Female ☐ Male **Subject age (at onset):** ____(in years)

4. Amgen Product Exposure

Amgen Product	Dose at time of conception	Frequency	Route	Start Date
				mm_____/dd_____/yyyy_____

Was the Amgen product (or study drug) discontinued? ☐ Yes ☐ No

If yes, provide product (or study drug) stop date: mm _____/dd_____/yyyy_____

Did the subject withdraw from the study? ☐ Yes ☐ No

5. Pregnancy Information

Pregnant female's last menstrual period (LMP) mm_____/ dd_____/ yyyy_____ ☐Unknown ☐ N/A

Estimated date of delivery mm_____/ dd_____/ yyyy_____

If N/A, date of termination (actual or planned) mm_____/ dd__/ yyyy_____

Has the pregnant female already delivered? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If yes, provide date of delivery: mm _____/ dd_____/ yyyy_____

Was the infant healthy? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If any Adverse Event was experienced by the infant, provide brief details:_____

_____

_____

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

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AMGEN® Lactation Notification Form

Report to Amgen at: USTO fax: +1-888-814-8653, Non-US fax: +44 (0)207-136-1046 or email (worldwide): svc-ags-in-us@amgen.com

1. Case Administrative Information

Protocol/Study Number: 20150161

Study Design: ☐ Interventional ☐ Observational (If Observational: ☐ Prospective ☐ Retrospective)

2. Contact Information

Investigator Name _____ **Site #** _____

Phone (____)_____ **Fax** (____)_____ **Email** _____

Institution _____

Address _____

3. Subject Information

Subject ID # _____ **Subject age (at onset):**____(in years)

4. Amgen Product Exposure

Amgen Product	Dose at time of breast feeding	Frequency	Route	Start Date
				mm____/dd____/yyyy____

Was the Amgen product (or study drug) discontinued? ☐ Yes ☐ No

If yes, provide product (or study drug) stop date: mm ____/dd____/yyyy____

Did the subject withdraw from the study? ☐ Yes ☐ No

5. Breast Feeding Information

Did the mother breastfeed or provide the infant with pumped breast milk while actively taking an Amgen product? ☐ Yes ☐ No

If No, provide stop date: mm_____/dd_____/yyyy_____

Infant date of birth: mm_____/dd_____/yyyy_____

Infant gender: ☐ Female ☐ Male

Is the infant healthy? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If any Adverse Event was experienced by the mother or the infant, provide brief details:_____

_____

_____

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

FORM-115201 Version 1.0 Effective Date: 24-Sept-2018

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11.6 Appendix 6. Sample Storage and Destruction

Any blood and tumor samples collected according to the Schedule of Activities (Section 1.3) can be analyzed for any of the tests outlined in the protocol and for any tests necessary to minimize risks to study subjects. This includes testing to ensure analytical methods produce reliable and valid data throughout the course of the study. This can also include, but is not limited to, investigation of unexpected results, incurred sample reanalysis, and analyses for method transfer and comparability.

All samples and associated results will be coded prior to being shipped from the site for analysis or storage. Samples will be tracked using a unique identifier that is assigned to the samples for the study. Results are stored in a secure database to ensure confidentiality.

If informed consent is provided by the subject, Amgen can do additional testing on remaining samples (ie, residual and back-up) to investigate and better understand MM and AML, the dose response and/or prediction of response to AMG 176, and characterize aspects of the molecule (eg, mechanism of action/target, [redacted]s). Results from this analysis are to be documented and maintained but are not necessarily reported as part of this study. Samples can be retained for up to 20 years.

Since the evaluations are not expected to benefit the subject directly or to alter the treatment course, the results of [redacted] are not placed in the subject's medical record and are not to be made available to the subject, members of the family, the personal physician, or other third parties, except as specified in the informed consent.

The subject retains the right to request that the sample material be destroyed by contacting the investigator. Following the request from the subject, the investigator is to provide the sponsor with the required study and subject number so that any remaining blood or tumor samples and any other components from the cells can be located and destroyed. Samples will be destroyed once all protocol-defined procedures are completed. However, information collected from samples prior to the request for destruction, will be retained by Amgen.

The sponsor is the exclusive owner of any data, discoveries, or derivative materials from the sample materials and is responsible for the destruction of the sample(s) at the request of the subject through the investigator, at the end of the storage period, or as appropriate (eg, the scientific rationale for experimentation with a certain sample type no

longer justifies keeping the sample). If a commercial product is developed from this research project, the sponsor owns the commercial product. The subject has no commercial rights to such product and has no commercial rights to the data, information, discoveries, or derivative materials gained or produced from the sample. See Section 11.3 for subject confidentiality.

11.7 Appendix 7. Hepatotoxicity Stopping Rules: Suggested Actions and Follow-up Assessments and Study Treatment Rechallenge Guidelines

Subjects with abnormal hepatic laboratory values (ie, alkaline phosphatase [ALP], aspartate aminotransferase [AST], alanine aminotransferase [ALT], total bilirubin [TBL]) and/or international normalized ratio (INR) and/or signs/symptoms of hepatitis (as described below) may meet the criteria for withholding or permanent discontinuation of Amgen investigational product or other protocol-required therapies, as specified in the *Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009*.

Criteria for Withholding and/or Permanent Discontinuation of Amgen Investigational Product and Other Protocol-required Therapies Due to Potential Hepatotoxicity

The following stopping and/or withholding rules apply to subjects for whom another cause of their changes in liver [redacted] (TBL, INR and transaminases) has not been identified.

Important alternative causes for elevated AST/ALT and/or TBL values include, but are not limited to:

- hepatobiliary tract disease
- viral hepatitis (eg, hepatitis A/B/C/D/E, Epstein-Barr Virus, cytomegalovirus, herpes simplex virus, varicella, toxoplasmosis, and parvovirus)
- right-sided heart failure, hypotension or any cause of hypoxia to the liver causing ischemia
- exposure to hepatotoxic agents/drugs or hepatotoxins, including herbal and dietary supplements, plants and mushrooms
- heritable disorders causing impaired glucuronidation (eg, Gilbert's syndrome, Crigler-Najjar syndrome) and drugs that inhibit bilirubin glucuronidation (eg, indinavir, atazanavir)
- alpha-one antitrypsin deficiency
- alcoholic hepatitis
- autoimmune hepatitis
- Wilson's disease and hemochromatosis
- nonalcoholic fatty liver disease including steatohepatitis
- non-hepatic causes (eg, rhabdomyolysis, hemolysis)

If investigational product(s) is/are withheld, the subject is to be followed for possible drug induced liver injury (DILI) according to recommendations in the last section of this appendix.

Rechallenge may be considered if an alternative cause for impaired liver tests (ALT, AST, ALP) and/or elevated TBL, is discovered and the laboratory abnormalities resolve to normal or baseline (see next section in this appendix).

Table 11-4. Conditions for Withholding and/or Permanent Discontinuation of Amgen Investigational Product and Other Protocol-required Therapies Due to Potential Hepatotoxicity

Analyte	Temporary Withholding	Permanent Discontinuation
TBL	> 3 × ULN at any time	> 2 × ULN
		OR
INR	--	> 1.5 × (for subjects not on anticoagulation therapy)
	OR	AND
AST/ALT	> 8 × ULN at any time > 5 × ULN but < 8 × ULN for ≥ 2 weeks > 5 × ULN but < 8 × ULN and unable to adhere to enhanced monitoring schedule > 3 × ULN with clinical signs or symptoms that are consistent with hepatitis (such as right upper quadrant pain/tenderness, fever, nausea, vomiting, and jaundice)	In the presence of no important alternative causes for elevated AST/ALT and/or TBL values > 3 × ULN (when baseline was < ULN)
	OR	
ALP	> 8 × ULN at any time	--

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; INR = international normalized ratio; TBL = total bilirubin; ULN = upper limit of normal

Criteria for Rechallenge of Amgen Investigational Product and Other Protocol-required Therapies After Potential Hepatotoxicity

The decision to rechallenge the subject is to be discussed and agreed upon unanimously by the subject, investigator, and Amgen medical monitor.

If signs or symptoms recur with rechallenge, then AMG 176 is to be permanently discontinued. Subjects who clearly meet the criteria for permanent discontinuation (as described in Table 11-4) are never to be rechallenged.

Drug-induced Liver Injury Reporting and Additional Assessments

Reporting

To facilitate appropriate monitoring for signals of DILI, cases of concurrent AST or ALT and TBL and/or INR elevation, according to the criteria specified in the above, require the following:

- The event is to be reported to Amgen as a serious adverse event within 24 hours of discovery or notification of the event (ie, before additional etiologic investigations have been concluded).
- The appropriate **c**ase **r**eport **f**orm (CRF) (eg, Event CRF) that captures information necessary to facilitate the evaluation of treatment-emergent liver abnormalities is to be completed and sent to Amgen.

Other events of hepatotoxicity and potential DILI are to be reported as serious adverse events if they meet the criteria for a serious adverse event defined in Section 11.4.

Additional Clinical Assessments and Observation

All subjects in whom investigational product(s) or protocol-required therapies is/are withheld (either permanently or conditionally) due to potential DILI as specified in Table 11-4 or who experience AST or ALT elevations > 3 × upper limit of normal (ULN) or 2-fold increases above baseline values for subjects with elevated values before drug are to undergo a period of “close observation” until abnormalities return to normal or to the subject’s baseline levels.

Assessments that are to be performed during this period include:

- Repeat AST, ALT, ALP, bilirubin (BIL) (total and direct), and INR within 24 hours
- In cases of TBL > 2 × ULN or INR > 1.5, retesting of liver tests, BIL (total and direct), and INR is to be performed every 24 hours until laboratory abnormalities improve

Testing frequency of the above laboratory tests may decrease if the abnormalities stabilize or the investigational product(s) or protocol-required therapies has/have been discontinued AND the subject is asymptomatic.

Initiate investigation of alternative causes for elevated AST or ALT and/or elevated TBL. The following are to be considered depending on the clinical situation:

- complete blood count with differential to assess for eosinophilia
- serum total immunoglobulin (Ig)G, anti-nuclear antibody anti-smooth muscle antibody, and liver kidney microsomal antibody-1 to assess for autoimmune hepatitis
- serum acetaminophen (paracetamol) levels

- a more detailed history of:
  - prior and/or concurrent diseases or illness
  - exposure to environmental and/or industrial chemical agents
  - symptoms (if applicable) including right upper quadrant pain, hypersensitivity-type reactions, fatigue, nausea, vomiting and fever
  - prior and/or concurrent use of alcohol, recreational drugs and special diets
  - concomitant use of medications (including non-prescription medicines and herbal and dietary supplements), plants, and mushrooms
- viral serologies
- creatine phosphokinase, haptoglobin, lactate dehydrogenase and peripheral blood smear
- appropriate liver imaging if clinically indicated
- appropriate blood sampling for pharmacokinetic analysis if this has not already been collected
- hepatology consult (liver biopsy may be considered in consultation with a hepatologist)

Follow the subject and the laboratory tests (ALT, AST, TBL, INR) until all laboratory abnormalities return to baseline or normal or considered stable by the investigator. The “close observation period” is to continue for a minimum of 4 weeks after discontinuation of all investigational product(s) and protocol-required therapies.

The potential DILI event and additional information such as medical history, concomitant medications and laboratory results must be captured in the corresponding CRFs.

11.8 Appendix 8. Additional Guidance for Tumor Lysis Syndrome

11.8.1 Recommendations for Initial Management of Electrolyte Abnormalities and Prevention of Tumor Lysis Syndrome (TLS)

All subjects will receive TLS prophylaxis as described in Section 6.1.4.1. Allopurinol or equivalent should be used to reduce uric acid level. This should be initiated at least 72 hours prior to dosing. Treatment may need to be continued for up to 5 weeks. Other agents to reduce uric acid level, such as rasburicase, may be used per investigator discretion and institutional guidelines.

Allopurinol is unapproved for TLS prophylaxis in Japan.

Within the first 24 hours after either the first dose or dose escalation, if any laboratory criteria below are met, no additional AMG 176 doses should be administered until resolution. A rapidly rising serum potassium is a medical emergency.

Nephrology (or other acute dialysis service) should be contacted/consulted (per institutional guidelines to ensure emergency dialysis is available) on admission for any subject hospitalized prophylactically or in response to laboratory changes.

Intravenous (IV) fluids (eg, D5 1/2 normal saline) should be 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 (eg, fever, chills, tachycardia, nausea, vomiting, diarrhea, diaphoresis, hypotension, muscle aches, weakness, paresthesias, mental status changes, confusion and seizures). If any clinical features are observed, recheck potassium, phosphorus, uric acid, calcium, and creatinine within 1 hour and perform electrocardiogram (ECG).

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 (Roberts et al, 2016). 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)	• Recheck potassium, phosphorus, uric acid, calcium and creatinine in 1-hour STAT. 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 within normal limits, hospitalization is at discretion of the investigator. Potassium phosphorus, uric acid, calcium and creatinine must be rechecked within 24 hours.
• Potassium > upper limit of normal	• Perform STAT ECG and commence telemetry. • Nephrology 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 STAT. – If potassium < ULN 1 hour later, repeat potassium phosphorus, uric acid, calcium and creatinine 1, 2, and 4 hours, if no other evidence of tumor lysis.
• Potassium ≥ 6.0 mmol/L (6.0 mEq/L) and/or symptomatic (eg, muscle cramps, weakness, paresthesias, nausea, vomiting, diarrhea)	• Perform STAT ECG and commence telemetry. • Nephrology (or other acute dialysis service) 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 arrhytmias. Do not administer in same IV line as sodium bicarbonate. • Recheck potassium, phosphorus, uric acid, calcium and creatinine every hour STAT.

Hyperuricemia	
• Uric acid ≥ 8.0 mg/dL (476 μmol/L)	• Consider rasburicase (0.2 mg/kg as an intravenous infusion over 30 minutes). – 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-hour STAT.
• 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 (0.2 mg/kg as an intravenous infusion over 30 minutes). – When rasburicase is used, sodium bicarbonate should not be used as this may exacerbate calcium phosphate precipitation. • Consult nephrology (or other acute dialysis service). • Recheck potassium, phosphorus, uric acid, calcium and creatinine in 1-hour STAT. • If uric acid < 8.0 mg/dL 1 hour later, repeat potassium, phosphorus, uric acid, calcium and creatinine 2 and 4 hours later, if no other evidence of tumor lysis
Hypocalcemia	
• Calcium ≤ 7.0 mg/dL (1.75 mmol/L) • AND • Patient symptomatic (eg, 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-hour STAT. • If calcium normalized 1 hour later, repeat potassium, phosphorus, uric acid, calcium and creatinine 2 and 4 hours 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 (eg, aluminum hydroxide, calcium carbonate, sevelamer hydroxide, or lanthanum carbonate). • Nephrology (or other acute dialysis service) notification (dialysis required for phosphorus uric ≥ 10 mg/dL). • Recheck potassium, phosphorus, uric acid, calcium and creatinine in 1 hour STAT. • If phosphorus < 5.0 mg/dL 1 hour later, repeat potassium, phosphorus, uric acid, calcium and creatinine 2 and 4 hours 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 STAT.

Reference: Protocol for: Roberts AW, Davids MS, Pagel JM, et al. Targeting BCL2 with venetoclax in relapsed chronic lymphocytic leukemia. *N Engl J Med*. 2016;374:311-322.

11.8.2 Cairo-Bishop Definition of Laboratory Tumor Lysis Syndrome

Two or more of the following criteria occurring within 3 days before or 7 days after therapy:

Element	Value		Change from Baseline
Uric Acid	≥ 476 µmol/L (8 mg/dL)	OR	25% increase from baseline
Potassium	≥ 6.0 mmol/L (6 mg/dL)	OR	25% increase from baseline
Inorganic phosphorus	≥ 1.45 mmol/L (4.5 mg/dL)	OR	25% increase from baseline
Calcium	≤ 1.75 mmol/L (7.0 mg/dL)	OR	25% decrease from baseline

11.8.3 Cairo-Bishop Clinical Tumor Lysis Syndrome Definition and Grading

One or more of the following, in a subject meeting criteria for laboratory TLS:

	Grade					
Complication	**0**	**1**	**2**	**3**	**4**	**5**
Creatinine[a, b]	Normal	≤ 1.5 × ULN	> 1.5 – 3.0 × ULN	> 3.0 – 6.0 × ULN	> 6.0 × ULN	Death
Cardiac Arrhythmia[a]	None	Intervention not indicated	Nonurgent medical intervention indicated	Symptomatic and incompletely controlled medically or controlled with device (eg, defibrillator)	Life-threatening (eg, arrhythmia associated with CHF, hypotension, syncope, shock)	Death
Seizure[a]	None	N/A	One brief, generalized seizure(s) well controlled by anticonvulsants or infrequent focal motor seizures not interfering ADL	Seizure in which consciousness is altered; poorly controlled seizure disorder; with breakthrough generalized seizures despite medical intervention	Seizure of any kind which are prolonged repetitive or difficult to control (eg, status epilepticus, intractable epilepsy)	Death

ADL = activities of daily living; CHF = congestive heart failure; N/A = not applicable; ULN = upper limit of normal

[a] Not directly or probably attributable to therapeutic agent.

[b] If no institutional ULN is specified, age/sex ULN creatine may be defined as follows: Cairo-Bishop Clinical Tumor Lysis Syndrome Definition and Grading.

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

References:

1. Coiffier B, Altman A, Pui CH, et al. Guidelines for the management of pediatric and adult tumor lysis syndrome: an evidence-based review. *J Clin Oncol*. 2008;26(16):2767-2778.
2. Cairo MS, Bishop M. Tumour lysis syndrome: new therapeutic strategies and classification. *Br J Haematol*. 2004;127(1):3-11.

11.9 Appendix 9. International Myeloma Working Group Uniform Response Criteria for Multiple Myeloma (IMWG-URC)

Response Subcategory[a]	Multiple Myeloma Response Criteria
sCR[b]	• CR as defined below and • Normal SFLC ratio and • Absence of clonal cells in bone marrow[c] by immunohistochemistry or immunofluorescence[c]
CR[b]	• Negative immunofixation on the serum and urine and • Disappearance of any soft tissue plasmacytomas and • < 5% plasma cells in bone marrow[c]
VGPR[b]	• Serum and urine M-protein detectable by immunofixation but not on electrophoresis or • ≥ 90% reduction in serum M-protein with urine M-protein level< 100 mg/24 hours • If the serum and urine M-protein are not measurable, a decrease of ≥ 90% in the difference between the involved and uninvolved FLC levels required in place of the M-protein criteria. However, documentation of VGPR requires collection and analysis of 24-hour urine sample for UPEP and immunofixation and confirmed to be negative. • If present at Baseline, a ≥ 50% reduction in the size of soft tissue plasmacytomas is also required.
PR[b]	• ≥ 50% reduction of serum M-protein and reduction in 24 hour urinary M-protein by ≥ 90% or to < 200 mg/24 h • If the serum and urine M-protein are unmeasurable, a ≥ 50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria. • If serum and urine M-protein are not measurable, and serum free light assay is also not measurable, ≥ 50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow cell percentage was ≥ 30% • If present at Baseline, a ≥ 50% reduction in the size of soft tissue plasmacytomas is also required
MR	• 25%-49% reduction in the level of serum M-protein and a 50%–89% reduction in 24-hour urinary M-protein, which still exceeds 200 mg per 24 hours • If the serum and urine M-protein are not measurable, a decrease of 25%-49% in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria. • If present at Baseline, a 25%–49% reduction in the size of soft tissue plasmacytomas is also required
Stable disease	• Not meeting criteria for CR, VGPR, PR, or PD

Footnotes defined on next page

Response Subcategory[a]	Multiple Myeloma Response Criteria
PD[b]	Any one or more of the following: • Increase of ≥ 25% from lowest response value in: ➢ Serum M-component and/or (the absolute increase must be ≥ 0.5 g/dL) ○ Urine M-component and/or (the absolute increase must be ≥ 200 mg/24 h) ○ Only in patients without measurable serum and urine M-protein levels; the difference between involved and uninvolved FLC levels. The absolute increase must be > 10 mg/dL ➢ Bone marrow plasma cell percentages (absolute percentage must be ≥ 10%) • Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas[e, f, g] • Development of hypercalcemia (corrected serum calcium > 11.5 mg/dL or 2.65 mmol/L) that can be attributed solely to the plasma cell proliferative disorder

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Source: Durie et al, 2006; Rajkumar et al, 2011 (*modified for protocol purposes*).

CR = complete response; sCR = stringent complete response; FLC = serum light chain; MR = minor response; PD = progressive disease; PR = partial response; SFLC = serum-free light chain; SPEP = serum protein electrophoresis; UPEP = urine protein electrophoresis; VGPR = very good partial response

Note: Patients with measurable disease in both serum (SPEP) and urine (UPEP) at study entry are required to meet response criteria in both UPEP and SPEP in order to qualify for a MR or better. Conversely, it should be noted criteria for PD only needs to be met, and confirmed, in 1 parameter. For patients without measurable protein on UPEP at Baseline, UPEP will need to be repeated to confirm a response.

[a] Patients with measurable disease in both serum (SPEP) and urine (UPEP) at study entry are required to meet response criteria in both UPEP and SPEP in order to qualify for a MR or better. Conversely, it should be noted that criteria for PD only needs to be met, and confirmed, in one parameter.

[b] All response categories (CR, sCR, VGPR, PR) require 2 consecutive assessments made at any time before the institution of any new therapy, as well as no known evidence of progressive or new bone lesions if radiographic studies were performed. Radiographic studies are not required to satisfy these response requirements. Bone marrow, plasmacytoma, and skeletal survey assessments are not required to be confirmed by repeat testing. SD requires a duration of ≥ 6 weeks.

[C] Presence/absence of clonal cells is based upon the κ/λ ratio. An abnormal κ/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 κ/λ of > 4:1 or < 1:2.

[d] Determination of PD while on study requires 2 consecutive assessments made at any time before classification of PD and/or the institution of new therapy. Serum M-component increases of ≥ 1 g/dL from nadir are sufficient to define progression if nadir M-component is ≥ 5 g/dL.

[e] Plasmacytomas: A definite increase in the size is defined as a ≥ 50% increase as measured serially by the sum of the products of the cross-diameters of the measurable lesion. A plasmacytoma is considered measurable if the longest diameter is at least 1 cm and the product of the cross diameters is at least 1 cm^2. Plasmacytomas of lesser size will be considered non-measurable.

[f] The requirement for bi-directional measurements applies only to plasmacytomas.

[g] The plasmacytoma specifications for PD are based on interpretation of the IMWG-URC and practical considerations for study execution.

11.10 Appendix 10. ECOG Performance Status and NYHA Classification

Eastern Cooperative Oncology Group (ECOG) Performance Status

0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (eg, light housework, office work).
2	Ambulatory and capable of all selfcare, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry out any selfcare. Totally confined to bed or chair.
5	Dead.

New York Heart Association Functional Classification

Class I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation or dyspnea.
Class II	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation or dyspnea.
Class III	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation or dyspnea.
Class IV	Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency may be present even at rest. If any physical activity is undertaken, discomfort is increased.

11.11 Appendix 11. Medications That may Cause QTc Prolongation

List of medications known to cause QTc interval prolongation is available at the following link: **https://crediblemeds.org/**.

If **subject** in this study does not have access to the internet, they can contact the institution investigational pharmacy or contact their study physician to obtain a list.

The following table presents a list of drugs that may prolong the QTc. This is not an inclusive list of drugs and is provided for guidance only. The **subject** is encouraged to follow the list in this link above for the most up-to-date information. These drugs are prohibited during the study with the exception of ciprofloxacin for use in neutropenic subjects with acute myeloid leukemia (AML). Washout period is based on roughly 5 half-lives and rounded to a convenient interval. This list includes (but is not limited to) the following:

Compounds	Compound Half-life	Possible Washout Period – Hours	Possible Washout Period – Days
Alfuzosin	~ 10 hours		7
Amantadine	17 ± 4 hours (10-25)		4
Amiodarone (cordarone)	58 days (15-142) 36 days (active metabolite)		180
Amitriptyline*	> 24 hours, wide interpatient variability		
Arsenic trioxide	Not characterized		
Azithromycin	40 hours		
Bepridil	42 hours (26-64)		10
Chloral hydrate	Readily converted to Trichloroethanol (active metabolite $t_{½}$ = 7 - 10 hours)	48	
Chloroquine	Prolonged (days to weeks)		
Chlorpromazine	30 ± 7 hours		
Clarithromycin	Non-linear PK3-4 hour (250 mg Q12) 5-7 hour (500 mg Q12)	36	
Chloroquine	6-60 days; mean 20 days		
Desipramine*	> 24 hours, wide interpatient variability		
Disopyramide	6.7 hour (4-10)	36	
Dofetilide	10 hours	48	
Dolasetron	8.1 hours		
Domperidone	7-8 hours	48	
Doxepin*	> 24 hours, wide interpatient variability		
Droperidol	2.2 hours	10	

Footnotes defined on last page of the table.

Compounds	Compound Half-life	Possible Washout Period – Hours	Possible Washout Period - Days
Erythromycin	*Each salt form has different Half-Life*		
Felbamate	20-23 hours		5
Flecainide	20 hours (12-27)		5
Foscarnet	87.5 ± 41.8 hours *distribution and release from bone*		20
Fosphenytoin	12-29 hours		6
Gatifloxacin	7-14 hours	48	
Gemifloxacin	7 hours	48	
Grepafloxacin	16 hours		3
Halofantrine	6-10 days (variable among individual)		45
Haloperidol	18 ± 5 hours		5
Ibutilide	6 hours (2-12) *variable among subject*	36	
Imipramine*	> 24 hours, wide interpatient variability		
Indapamide	14 hours (biphasic elimination)		3
Isradipine	8 hours (multiple metabolites)	48	
Levofloxacin	6-8 hours	48	
Levomethadyl	Multiple compartment PK with active metabolite 2.6 days for LAAM, 2 days for nor-LAAM, 4 days for dinor-LAAM		20
Lithium	24 hours (10-50)		7
Mesoridazine	24-48 hours (animal study)		10
Methadone	15-30 hours		7
Moexipril/HCTZ	2-9 hour (include active metabolite) for moexipril; 5.6-14.8 hours for HCTZ	48	
Moxifloxacin	12 ± 1.3 hours	72	
Naratriptan	6 hours	36	
Nicardipine	~ 2 hours post IV infusion	12	
Nortriptyline*	> 24 hours, wide interpatient variability		
Octreotide	1.7 hours	12	
Ofloxacin	5 to 7.5 hours		2
Ondansetron	4 hours (IV/IM); 3 hours (**QD**)		1 to 3
Pentamidine	6.4 ± 1.3 hours	36	
Pimozide	55 hours		10
Procainamide	3-4 hours for PA and NAPA (active metabolite)	24	
Protriptyline*	> 24 hours, wide interpatient variability		

Footnotes defined on last page of the table.

Compounds	Compound Half-life	Possible Washout Period – Hours	Possible Washout Period - Days
Quetiapine	6 hours	36	
Quinidine	6-8 hours in adult; 3-4 hours in children	36	
Quinine	4-5 hours		
Risperidone	3-20 hours (extensive to poor metabolizer) 9-hydroxyrisperidone (active metabolite) $t_{½}$ = 21-30 hours (extensive to poor metabolizer)		4
Salmeterol	5.5 hours (only one datum)	36	
Sotalol	12 hours	72	
Sparfloxacin	20 hours (16-30)		4
Sumatriptan	2.5 hours	12	
Tacrolimus	~ 34 hours in healthy; ~ 19 hours in Kidney transplant		7
Tamoxifen	5-7 days (biphasic)		30
Telithromycin	2-3 hours	24	
Thioridazine	20-40 hours (Phenothiazines)		7
Tizanidine	2.5 hours	12	
Vardenafil	4 to 5 hours		
Venlafaxine	5 ± 2 hours for parent comp. 11 ± 2 hours for OVD (active metabolite)	60	
Voriconazole	6 hours; dose dependent		
Ziprasidone	7 hours	36	
Zolmitriptan	2.8-3.7 hours (higher in female)	18	

HCTZ = hydrochlorothiazide; IV = intravenous; IM = intramuscular; LAAM = levo-alpha-acetylmethadol; NAPA = N-acetylprocainamide; PK = pharmacokinetics; **QD**= once daily.

* Weakly associated with Torsades de pointes and/or QT prolongation but that are unlikely to be a risk for Torsades de pointes when used in usual recommended dosages and in patients without other risk factors (eg, concomitant QT prolonged drugs, bradycardia, electrolyte disturbances, congenital long QT syndrome, concomitant drugs that inhibit metabolism).

References:

Physician's Desk Reference 2002.
Facts and Comparison (update to June 2005).
The Pharmacological Basis of Therapeutics 9th Edition, 1999.

11.12 Appendix 12. Definition of Relapsed or Refractory Progressive Disease and Line of Therapies

Relapsed disease is defined as progression occurs in the absence of therapy.

Refractory disease is defined as disease that is nonresponsive while on primary or salvage therapy, or progresses within 60 days of last therapy.

Progressive Disease (PD) for Subjects with MM requires any one or more of the following:

- Increase of ≥ 25% from lowest response value in any of the following
  - Serum M-component and/or (the absolute increase must be ≥ 0.5 g/dl)
  - Urine M-component and/or (the absolute increase must be ≥ 200 mg/24 h)
  - Only in subjects without measurable serum and urine M-protein levels: the difference between involved and uninvolved serum light chain (FLC) levels (the absolute increase must be > 10 mg/dl)
  - Bone marrow plasma cell percentage: the absolute % must be ≥ 10%
- Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas
- Development of hypercalcemia (corrected serum calcium > 11.5 mg/dL or 2.65 mmol/L) that can be attributed solely to the plasma cell proliferative disorder

A line of therapy is defined as one or more cycles of a planned treatment program. This may consist of one or more planned cycles of single-agent therapy or combination therapy, as well as a sequence of treatments administered in a planned manner. For example, a planned treatment approach of induction therapy followed by autologous stem cell transplantation, followed by maintenance is considered one line of therapy. A new line of therapy starts when a planned course of therapy is modified to include other treatment agents (alone or in combination) as a result of disease progression, relapse, or toxicity. A new line of therapy also starts when a planned period of observation off therapy is interrupted by a need for additional treatment for the disease (Rajkumar 2011).

Progressive Disease in Subjects with AML is defined as:

Evidence for an increase in bone marrow blast percentage and/or increase of absolute blast counts in the blood:

- > 50% increase in bone marrow blasts over baseline (a minimum 15% point increase is required in cases with < 30% blasts at baseline; or persistent marrow blast percentage of > 70% over at least 3 months; without at least a 100% improvement in absolute neutrophil count (ANC) to an absolute level (> 0.5 x 10^9/L [500/μL], and/or platelet count to > 50 x 10^9/L [50,000/μL] nontransfused); or

- $>$ 50% increase in peripheral blasts (WBC x % blasts) to $>$ 25 x 10^9/L ($>$ 25,000/μL) (in the absence of differentiation syndrome)†; or
- New extramedullary disease

Relapse After Complete Remission for Subjects with AML is defined as:

- Bone marrow blasts $\geq$ 5%; or
- reappearance of blasts in the blood; or
- development of extramedullary disease

These response criteria were published in 2010, "Diagnosis and management of AML in adults: Recommendations from an international expert panel, on behalf of the European LeukemiaNet" (Döhner et al, 2010).

The criteria for PD were suggested in the 2017 ELN recommendations (Döhner et al, 2017).

11.13 Appendix 13. Peripheral Neuropathy Assessment

TNSr Items	0	1	2	3	4
Symptom extension (tingling, numbness, neuropathic pain)[a]	None	Symptoms limited to fingers or toes	Symptoms extend to ankle or wrist	Symptoms extend to knee or elbow	Symptoms above knees or elbows or functionally Disability
Pin sensibility	Normal	Reduced in fingers/toes	Reduced up to wrist/ankle	Reduced up to elbow/knee	Reduced up to above elbow/knee
Vibration sensibility	Normal	Reduced in fingers/toes	Reduced up to wrist/ankle	Reduced up to elbow/knee	Reduced up to above elbow/knee
Strength[b]	Normal	Mild weakness	Moderate weakness	Severe Weakness	Paralysis
Tendon reflexes	Normal	Ankle reflex reduced	Ankle reflex absent	Ankle reflex absent/others reduced	All reflexes absent

[a] The worse score of the 3 subcomponents (tingling/paresthesia, numbness, and neuropathic pain proximal extension) was used as the subjective symptom extension score.
[b] The muscle with the worse score is used as the strength score (toe, ankle, wrist and finger extensors and flexors, quadriceps, hamstrings, biceps, and triceps). TNSr and pain items were adapted with permission [Smith, 2010].

11.14 Appendix 14. World Health Organization Classification for Acute Myeloid Leukemia

Definition AML: ≥ 20% myeloblasts in blood or in bone marrow.

Abnormal promyelocytes in acute promyelocytic leukemia, promonocytes in AML with monocytic differentiation and megakaryoblasts in acute megakaryocytic leukemia are considered blast equivalents. Subjects with APL are not eligible for this study. First, AML should be classified as AML with recurrent cytogenetic abnormalities. If this is not applicable the leukemia is classified as AML with multilineage dysplasia or therapy related and if this subtype is also not applicable as AML not otherwise categorized. Acute Myeloid Leukemia and Related Precursor Neoplasms, and Acute Leukemias of Ambiguous Lineage (**Arber et al**, 2016):

AML and related neoplasms	
AML with recurrent genetic abnormalities	AML with t(8;21)(q22;q22.1); *RUNX1-RUNX1T1*
	AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11*
	Acute promyelocytic leukemia with *PML-RARA**
	AML with t(9;11)(p21.3;q23.3); *MLLT3-KMT2A*†
	AML with t(6;9)(p23;q34.1); *DEK-NUP214*
	AML with inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2,MECOM(EVI1)*
	AML (megakaryoblastic) with t(1;22)(p13.3;q13.3*); RBM15-MKL1*‡
	Provisional entity: AML with *BCR-ABL1*
	AML with mutated *NPM1*§
	AML with biallelic mutations of *CEBPA*§
	Provisional entity: AML with mutated *RUNX1*
AML with myelodysplasia-related changes‖	
Therapy-related myeloid neoplasms{	
AML, NOS	AML with minimal differentiation
	AML without maturation
	AML with maturation
	Acute myelomonocytic leukemia
	Acute monoblastic/monocytic leukemia #
	Acute megakaryoblastic leukemia
	Acute basophilic leukemia
	Acute panmyelosis with myelofibrosis

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Footnotes defined on last page of table

Myeloid sarcoma	
Myeloid proliferations related to Down syndrome	Transient abnormal myelopoiesis Myeloid leukemia associated with Down syndrome
Blastic plasmacytoid dendritic cell neoplasm	
Acute leukemias of ambiguous lineage	Acute undifferentiated leukemia MPAL with t(9;22)(q34.1;q11.2); *BCR-ABL1*** MPAL with t(v;11q23.3); *KMT2A* rearranged MPAL, B/myeloid, NOS MPAL, T/myeloid, NOS

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For a diagnosis of AML, a marrow blast count of ≥ 20% is required, except for AML with the recurrent genetic abnormalities t(15;17), t(8;21), inv(16), or t(16;16). Adapted from Arber et al, 2016.

MDS = myelodysplastic syndromes; MPAL = mixed phenotype acute leukemia; NK = natural killer

* Other recurring translocations involving *RARA* should be reported accordingly: for example, AML with t(11;17)(q23;q12); *ZBTB16-RARA*; AML with t(11;17)(q13;q12);*NUMA1-RARA*; AML with t(5;17)(q35;q12*); NPM1-RARA*; or AML with *STAT5B-RARA* (the latter having a normal chromosome 17 on conventional cytogenetic analysis).

† Other translocations involving *KMT2A* (MLL) should be reported accordingly: for example, AML with t(6;11)(q27;q23.3); *MLLT4-KMT2A*; AML with t(11;19)(q23.3;p13.3); *KMT2A-MLLT*1; AML with t(11;19)(q23.3;p13.1); *KMT2A-ELL*; AML with t(10;11)(p12;q23.3); *MLLT10-KMT2A*.

‡ Rare leukemia most commonly occurring in infants.

§ Diagnosis is made irrespective of the presence or absence of multilineage dysplasia.

|| At least 20% (≥ 20%) blood or marrow blasts AND any of the following: previous history of MDS or MDS/MPN; myelodysplasia-related cytogenetic abnormality (see list below); multilineage dysplasia; AND absence of both prior cytotoxic therapy for unrelated disease and aforementioned recurring genetic abnormalities. Cytogenetic abnormalities sufficient to diagnose AML with myelodysplasia-related changes are: Complex karyotype (defined as 3 or more chromosomal abnormalities in the absence of 1 of the WHO-designated recurring translocations or inversions, that is, t(8;21), inv(16) or t(16;16), t(9;11), t(v;11)(v;q23.3), t(6;9), inv(3) or t(3;3); AML with BCRABL1); Unbalanced abnormalities: 27 or del(7q); 25 or del(5q); i(17q) or t(17p); 213 or del(13q); del(11q); del(12p) or t(12p); idic(X)(q13); Balanced abnormalities: t(11;16)(q23.3;p13.3); t(3;21)(q26.2;q22.1); t(1;3)(p36.3;q21.2); t(2;11)(p21;q23.3); t(5;12)(q32;p13.2); t(5;7)(q32;q11.2); t(5;17)(q32;p13.2); t(5;10)(q32;q21.2); t(3;5)(q25.3;q35.1).

{ Cases should be classified with the related genetic abnormality given in the diagnosis.

The former subgroup of acute erythroid leukemia, erythroid/myeloid type (≥ 50% bone marrow erythroid precursors and ≥ 20% myeloblasts among nonerythroid cells) was removed; myeloblasts are now always counted as percentage of total marrow cells. The remaining subcategory AML, NOS, pure erythroid leukemia requires the presence of > 80% immature erythroid precursors with ≥ 30% proerythroblasts.

** *BCR-ABL1* leukemia may present as MPAL; treatment should include a tyrosine kinase inhibitor.

11.15 Appendix 15. European LeukemiaNet (ELN) Response Criteria in Acute Myeloid Leukemia (2017)

Category	Definition	Comment
Response		
• CR without minimal residual disease (CR_{MRD-})	If studied pretreatment, CR with negativity for a genetic marker by RT-qPCR, or CR with negativity by MFC	Sensitivities vary by marker tested, and by method used; therefore, test used and sensitivity of the assay should be reported; analyses should be done in experienced laboratories (centralized diagnostics)
• Complete remission (CR)	Bone marrow blasts < 5%; absence of circulating blasts and blasts with Auer rods; absence of extramedullary disease; ANC ≥1.0 x 10^9/L (1000/μL); platelet count ≥100 x 10^9/L (100 000/μL)	MRD^+ or unknown
• CR with incomplete hematologic recovery (CRi)	All CR criteria except for residual neutropenia (<1.0 x 10^9/L [1 000/μL]) or thrombocytopenia (<100 x 10^9/L [100 000/μL])	
• Morphologic leukemia-free state (MLFS)	Bone marrow blasts <5%; absence of blasts with Auer rods; absence of extramedullary disease; no hematologic recovery required	Marrow should not merely be "aplastic"; at least 200 cells should be enumerated or cellularity should be at least 10%
• Partial remission (PR)	All hematologic criteria of CR; decrease of bone marrow blast percentage to 5% to 25%; and decrease of pretreatment bone marrow blast percentage by at least 50%	Especially important in the context of phase 1-2 clinical trials
Treatment failure		
• Primary refractory disease	No CR or CRi after 2 courses of intensive induction treatment; excluding subjects with death in aplasia or death due to indeterminate cause	Regimens containing higher doses of cytarabine are generally considered as the best option for subjects not responding to a first cycle of 7+3; the likelihood of responding to such regimens is lower after failure of a first
• Death in aplasia	Deaths occurring ≥ 7 d following completion of initial treatment while cytopenic; with an aplastic or hypoplastic bone marrow obtained within 7 d of death, without evidence of persistent leukemia	
• Death from indeterminate cause	Deaths occurring before completion of therapy, or < 7 d following its completion; or deaths occurring ≥ 7 d following completion of initial therapy with no blasts in the blood, but no bone marrow examination available	

Footnotes defined on next page

Category	Definition	Comment
Response criteria for clinical trials only		
• Stable disease	Absence of CR_{MRD-}, CR, CRi, PR, MLFS; and criteria for PD not met	Period of stable disease should last at least 3 mo
• Progressive disease (PD)[a,b]	Evidence for an increase in bone marrow blast percentage and/or increase of absolute blast counts in the blood: • > 50% increase in marrow blasts over baseline (a minimum 15% point increase is required in cases with < 30% blasts at baseline; or persistent marrow blast percentage of > 70% over at least 3 mo; without at least a 100% improvement in ANC to an absolute level (> 0.5 x 10^9/L [500/μL], and/or platelet count to > 50 x 10^9/L [50000/μL] nontransfused); or • > 50% increase in peripheral blasts (WBC x % blasts) to > 25 x 10^9/L (> 25000/μL) (in the absence of differentiation syndrome)[b]; or • New extramedullary disease	Category mainly applies for older subject given low intensity or single-agent "targeted therapies" in clinical trials. In general, at least 2 cycles of a novel agent should be administered. Some protocols may require blast increase in 2 consecutive marrow assessments at least 4 wk apart; the date of progression should then be defined as of the first observation date. Some protocols may allow transient addition of hydroxyurea to lower blast counts. Hydroxyurea is unapproved for AML in Japan. "Progressive disease" is usually accompanied by a decline in ANC and platelets and increased transfusion requirement and decline in performance status or increase in symptoms.
Relapse		
• Hematologic relapse (after CR_{MRD-}, CR, CRi)	Bone marrow blasts ≥ 5%; or reappearance of blasts in the blood; or development of extramedullary disease	
• Molecular relapse (after CR_{MRD-})	If studied pretreatment, reoccurrence of MRD as assessed by RT-qPCR or by MFC	Test applied, sensitivity of the assay, and cutoff values used must be reported; analyses should be done in experienced laboratories (centralized diagnostics)

ANC = absolute neutrophil count; d = day(s); IDH = isocitrate dehydrogenase; MLFS = morphologic leukemia-free state; mo = month(s); WBC = white blood cell; wk = week(s)

[a] The authors acknowledge that this new provisional category is arbitrarily defined; the category aims at harmonizing the various definitions used in different clinical trials.

[b] Certain targeted therapies, for example, those inhibiting mutant IDH proteins, may cause a differentiation syndrome, that is, a transient increase in the percentage of bone marrow blasts and an absolute increase in blood blasts; in the setting of therapy with such compounds, an increase in blasts may not necessarily indicate PD.

11.16 Appendix 16. Modified Toxicity Probability Interval Design

A modified Toxicity Probability Interval (mTPI) design will be used to guide dose exploration. The MTD is defined as the highest dose with a probability of DLT lower than or close to a targeted toxicity probability of 0.2. The doses are considered close to the MTD if the toxicity probabilities belong to the proper dosing interval [0.15, 0.25] which corresponds to staying at the current dose (S). The underdosing interval is defined as (0, 0.15) in which the doses are deemed lower than the MTD and corresponds to a dose escalation (E). The overdosing interval is (0.25, 1) in which the doses are deemed higher than the MTD and corresponds to a dose de-escalation (D).

The dose-finding decisions are guided based on Bayesian decision rule by minimizing the posterior expected loss through calculating the unit probability mass (UPM). At each dose level, the UPM is computed for the dosing intervals using the observed data enrolled at current dose. The dose-finding decision is determined as the interval with maximum UPM. A set of independent and non-informative prior Beta (0.5, 0.5) is used for each dose level, which provides equal prior expected loss for the decisions (Ji et al, 2010). Dose escalation will not occur unless at least 6 subjects are treated at the current dose level. In addition, any dose whose posterior probability of toxicity is greater than the target toxicity exceeds 80% will be considered as unacceptable toxicity. This dose and higher doses will not be used again in the trial. Dose exploration will continue until either the maximum number of subjects for Part 3b (n = 11 subjects) and Part 4 (n = approximately 60 subjects) are treated or all doses are determined to be intolerable.

Operating Characteristics

The operating characteristics of the mTPI were evaluated via simulations. The cohort size was fixed to 6 subjects. A total of 3 dose levels were considered for AML Part 3b and 4 dose levels were considered for AML Part 4.

For Part 3b, the design was evaluated for 3 possible dose-response scenarios: Low, Middle, and High MTD. For Part 4, the design was evaluated for 4 possible dose-response scenarios: Low, Middle, and High MTD. Table 11-5 and Table 11-7 show the dose level and true probability of DLT for each scenario used in the simulated studies estimating the MTD. Table 11-6 and Table 11-8 report the operating characteristics from 1 000 simulated studies.

Table 11-5. True Probability of DLT by Scenario for Simulated Studies Estimating MTD for Part 3b

MTD scenario	Dose Level 1	Dose Level 2	Dose Level 3
Low	0.20	0.30	0.40
Middle	0.15	0.22	0.28
High	0.10	0.17	0.23

MTD = maximum tolerated dose

Table 11-6. Operating Characteristics by Scenario for Simulated Studies Estimating the MTD Using the mTPI Design for Part 3b

MTD scenario	Low	Middle	High
Number of subjects			
Median (IQR)	20 (6, 20)	20 (20, 20)	20 (20,20)
Number of DLTs			
Median (IQR)	4 (3, 5)	3 (2, 4)	3 (2, 4)
Proportion of DLT (%)			
Median (IQR)	30.0 (20.0, 33.3)	20.0 (15.0, 30.0)	15.0 (10.0, 20.0)
Percentage of studies selecting MTD			
Dose Level 1	38.1%	31.0%	23.8%
Dose Level 2	19.8%	28.8%	31.6%
Dose Level 3	4.0%	16.5%	27.4%

DLT = dose-limiting toxicity; IQR = Interquartile range; MTD = maximum tolerated dose

Table 11-7. True Probability of DLT by Scenario for Simulated Studies Estimating MTD for Part 4

MTD scenario	Dose Level 1	Dose Level 2	Dose Level 3	Dose Level 4
Low	0.20	0.30	0.40	0.45
Middle	0.10	0.15	0.20	0.25
High	0.05	0.10	0.15	0.2

MTD = maximum tolerated dose

Table 11-8. Operating Characteristics by Scenario for Simulated Studies Estimating the MTD Using the mTPI Design for Part 4

MTD scenario	Low	Middle	High
Number of subjects			
Median (IQR)	36 (6, 50)	50 (48, 50)	50 (50, 50)
Number of DLTs			
Median (IQR)	8 (2, 11)	7 (5, 9)	6 (4, 8)
Proportion of DLT (%)			
Median (IQR)	29.2 (22.2, 33.3)	16.7 (14.0, 21.4)	12.0 (1.0, 16.0)
Percentage of studies selecting MTD			
Dose Level 1	42.7%	21.4%	11.2%
Dose Level 2	9.29%	28.2%	21.6%
Dose Level 3	0.47%	25.8%	31.2%
Dose Level 4	0.03%	10.0%	24.1%

DLT = dose-limiting toxicity; IQR = Interquartile range; MTD = maximum tolerated dose

Approval Signatures

Document Name: Protocol Amendment AMG 176 20150161 16

Document Description: Protocol amendment 16: AMG 176 20150161

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Amendment 11

Protocol Title: A Phase 1 First in Human Study Evaluating the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of AMG 176 in Subjects With Relapsed or Refractory Multiple Myeloma and Subjects With Relapsed or Refractory Acute Myeloid Leukemia

Amgen Protocol Number AMG 176 2015061

Amendment Date:	05 February 2021
Superseding Amendment Date:	18 February 2021

Rationale:

This protocol is being amended to include the following updates:

- A drug-drug interaction (DDI) assessment in a separate cohort for acute myeloid leukemia (AML) subjects in the United States (US.) was added.
  - Up to 8 subjects will receive AMG 176 once weekly (QW) intravenously (IV) in combination with oral itraconazole (200 mg) starting on day -3 through day 4 (total of 7 days) in cycle 1 only.
  - A fixed sequence design where AMG 176 will be co-administered with itraconazole during week 1, followed by dosing of AMG 176 alone in subsequent weeks, will be used to evaluate the effect of itraconazole (strong cytochrome P450 (CYP)3A4 inhibitor and P-glycoprotein (P-gp) inhibitor) on the pharmacokinetics (PK) of AMG 176

  Patients with AML are susceptible to invasive fungal infections and often require prophylaxis and treatment with antifungal agents such as voriconazole and posaconazole, which are known to inhibit CYP3A4 and P-gp. AMG 176 is metabolized, in part, by CYP3A4, and is a P-gp substrate; hence, co-administration with inhibitors of CYP3A4/P-gp may lead to increases in AMG 176 exposure. As a result, clinical trials with AMG 176 prohibit the use of medications that are strong CYP3A4/P-gp inhibitors, including voriconazole and posaconazole.
- Removed exclusion criterion #227 (related to the use of CYP1A2, CYP2C9, and CYP2D6 sensitive substrates with a narrow therapeutic window), based on the following:

  An updated DDI assessment predicting a less than 2-fold increase in exposure of these substrates during co-administration with AMG 176. AMG 176 inhibited CYP1A2, CYP2C9 and CYP2D6, in human liver microsomes, with Ki (inhibition concentrations that are half of maximal) estimates of 4.4, 2.6, and 6.2 μM, respectively. The Simcyp Simulator (version 17), a commercially available physiologically based pharmacokinetic (PBPK) software platform was used to predict the magnitude of a DDI with sensitive CYP substrates during co-administration with

AMG 176 at doses of 60, 120, and 180 mg/m^2 given on a QW schedule. These simulations incorporated the unbound fraction of AMG 176 in both human plasma and human liver microsomes. A compound file for AMG 176 was developed and verified based on in vitro and available clinical data. Simcyp library model files were used for sensitive substrates of CYP1A2 (caffeine), CYP2C9 (S-warfarin), and CYP2D6 (dextromethorphan). The PBPK model was used to simulate the effect of AMG 176 given as an intravenous infusion over 2 hours QW (60, 120, and 180 mg/m^2) on sensitive substrates given concurrently with the 3rd weekly dose of AMG 176. The predicted area under the concentration-time curve (AUC) ratio ranged from 1.4 to 1.9 for caffeine, 1.2 to 1.4 for S-warfarin, and 1.3 to 1.7 for dextromethorphan for the AMG 176 doses evaluated. Based on these simulations, a weak DDI (1.25 to $<$ 2-fold increase in substrate exposure) is predicted when AMG 176 is co-administered with sensitive substrates of CYP1A2, CYP2C9, and CYP2D6. Medications that are sensitive substrates of these enzymes can be allowed with caution during co-administration with AMG 176.

- Editorial changes (including typographical, grammatical, and formatting) have been made throughout the document.

On 18 February 2021, the protocol amendment 11 was superseded to include the following:

- To update the language for non-investigational product to clarify that Azacitidine will not be supplied by Amgen for this study unless required by local regulation or in response to a regional supply shortage.

Amendment 12

Protocol Title: A Phase 1 First in Human Study Evaluating the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of AMG 176 in Subjects With Relapsed or Refractory Multiple Myeloma and Subjects With Relapsed or Refractory Acute Myeloid Leukemia

Amgen Protocol Number AMG 176 20150161

Amendment Date: 16 September 2021

Rationale:

The rationale for this protocol amendment is to include the following updates:

- In Parts 3b and 4 of the study, an additional AMG 176 dose level (240 mg/m^2) at the once per week dosing schedule (QW) has been added as part of dose exploration (monotherapy and in combination with azacitidine). It has been added to complete the evaluation of all the dose levels previously identified in the study as safe and without evidence of troponin elevations. Additionally, an additional cohort has been added to Part 4 to explore 2-consecutive days per week dosing schedule (QD2) at 240 mg/m^2.
- Part 5 (AMG 176 + azacitidine combination therapy) has been added to the study as a dose expansion once the maximum tolerated combination dose (MTCD) is determined in Part 4.
- Updated to include guidance relating to coronavirus disease 2019 (COVID-19):
  - Eligibility criteria was updated to exclude subjects that have severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection
  - Guidance for COVID-19 vaccinations was added (Sections 6.7.2 and 6.7.2.4)
  - Section 6.2.2.2.8 was added to include management for subjects with asymptomatic and symptomatic SARS-CoV-2 infection and COVID-19 disease
- A new subsection has been added (Section 8.2.4.2 – Relationship to Study Drug) to provide guidance for investigators assessing the relationship of an adverse event to the use of study drug.
- Minor corrections and clarifications have been made throughout the protocol to correct identified errors:
  - Part 3c has been updated to “completed” throughout protocol, includes final enrollment numbers.
  - Table 1-2 was corrected by removing shading from the safety follow-up visit column in the AML subjects: bone marrow/aspirate/biopsy row.
  - Section 6.1.2.2 was updated to align with the formatting of Section 6.1.2.1.

  - Section 6.1.8 title was updated to indicate it is only applicable to Part 3d of the study.
  - Section 8.1.3 was updated to remove the 1-day window for the end of treatment (EOT) visit as it should occur as soon as possible after last dose and does not need a window.
  - Section 8.2.2.2.1 was updated to provide a 3-day window for collection of bone marrow smears up to 3 days prior to day 1 of cycles 2 and 3.
  - Section 8.2.9 was updated to clarify that interviews should take place as soon as possible after completion of cycle 1.
- Several sections of the protocol have been updated to include required alignments with current Amgen protocol template (Sections 6.1.6, 8.2.4.1.4, 11.2, 11.3, and 11.4):
  - Section 6.1.6 Product Complaints: Additional details have been added to clarify the types of product complaints.
  - Section 8.2.4.1.4 Serious Adverse Events After the Protocol-required Reporting Period and Section 11.4 Reporting of Serious Adverse Event: The safety monitoring language has been revised to minimally require reporting of serious adverse events (SAEs) related to the investigational product (rather than all SAEs) to be collected and reported to Amgen within 24 hours of investigator's awareness after the protocol required reporting period has ended, during the Long Term Follow-up and End of Study periods.
  - Section 11.2 Clinical Laboratory Tests: Updates related for reporting additional analyte test results and inclusion of coronavirus 2 (SARS-CoV-2) analyte testing have been added.
  - Section 11.3 Study Governance Considerations: Additional details added under subsection Regulatory and Ethical Considerations to clarify the investigator's responsibility to seek IRB/IEC approval for protocols and ICFs.
- Administrative and editorial changes (including grammatical, typographical, and formatting) have been made throughout the protocol.

Amendment 13

Protocol Title: A Phase 1 First in Human Study Evaluating the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of AMG 176 in Subjects With Relapsed or Refractory Multiple Myeloma and Subjects With Relapsed or Refractory Acute Myeloid Leukemia

Amgen Protocol Number AMG 176 20150161

Amendment Date: 20 January 2022

Rationale:

This protocol has been amended to incorporate minor changes based on the need to replace the assay used to evaluate troponin-I elevations with a new high-sensitivity assay. The current cardiac monitoring plan for AMG 176 employs testing of troponin-I with Troponin-I Ultra assay for all screening, grading, and withholding decisions. The manufacturer has decided to retire Troponin-I Ultra assay effective on end of year 2021 due to low tolerance and sensitivity issues and has recommended to transition to High-Sensitivity Troponin-I (TNIH) assay. Both assays use the ADVIA Centaur XP system which is specified on the study protocol. An assay verification study was conducted at Q2 laboratory to evaluate the accuracy and clinical performance of the new High-Sensitivity Troponin-I (TNIH) assay and to compare it to Troponin-I Ultra assay. The comparison report demonstrated consistency between the two assays and support the replacement of Troponin-I Ultra assay with High-Sensitivity Troponin-I (TNIH) assay. Based on the acceptable correlation data and the urgent need for continued cardiac monitoring, Amgen requested to replace Troponin-I Ultra assay with the new High-Sensitivity Troponin-I (TNIH) assay and continue to use the current grading criteria with the exception of increasing the male 99th percentile upper reference limit (URL) to 0.059 ng/mL per manufacturer's guideline. Since the protocol only refers to the system (ADVIA Centaur XP system) used to perform the troponin-I assay and not to the specific name of the assay, the only update made to the protocol relates to increasing the male 99th percentile upper reference limit

(URL) to 0.059 ng/mL and maintaining the URL of 0.04 ng/mL for females in relevant sections of the protocol (Sections 5.2, 6.2.1.2.1, 6.2.1.2.2, and 6.2.2.1).

Amendment 14

Protocol Title: A Phase 1 First in Human Study Evaluating the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of AMG 176 in Subjects With Relapsed or Refractory Multiple Myeloma and Subjects With Relapsed or Refractory Acute Myeloid Leukemia

Amgen Protocol Number AMG 176 20150161

NCT02675452

Amendment Date: 16 March 2022

Rationale:

The rationale for this protocol amendment is to include the following updates:

- To clarify dosing schedules of intravenous infusion of AMG 176 (ie, QW: once weekly followed by a 6-day break for 4 consecutive weeks and QD2: once daily for 2 consecutive days followed by a 5-day break for the first 3 weeks of each 4-week cycle) for different parts of the study as well as update the parts of the study that are closed to enrollment (Sections 1.1, 4.3).
- Study schema (Figure 1-7) for Acute Myeloid Leukemia (AML) Part 4 AMG 176 QW and QD2 in Combination with Azacitidine (Dose Exploration) and study schema (Figure 1-9) for Acute Myeloid Leukemia Part 5 AMG 176 QW or QD2 in Combination with Azacitidine (Dose Expansion) were updated to:
    - Define QD2 dosing schedule for intravenous administration of AMG 176 in terms of monthly cycles of treatment.
    - Clarify that lower dose levels of 120 mg/m^2 and 180 mg/m^2 may be investigated on a QD2 schedule, and that QW and QD2 combination cohorts can be conducted in parallel. The QD2 schedule will restrict AMG 176 to 3 out of 4 weeks, which may reduce the risk of hematological toxicity. Currently, the protocol only allows for the QD2 schedule to be investigated at the highest

combinational dose level of 240 mg/m^2. The rationale for this change is to allow evaluation of lower dose levels to be considered for dose optimization. The QW and QD2 combination cohorts will be gated off their respective monotherapy dose levels.

- Overview of Study Design was updated to add in Part 4 (which investigates AMG 176 in combination with azacitidine) that QD2 AMG 176 (cohort 5) dosing schedule may be conducted at the same time, in the same dose, or at a lower dose as QW AMG 176 (cohorts 1-4) dosing schedule (Table 4-1).
- Tale 1-3. Schedule of Activities: Parts 4 (Cohort 1-4 Only) and 5 (AML) AMG 176 QW in Combination with Azacitidine was updated to clarify that timepoints for the schedule of activities are relative to start of dosing of either AMG 176 or azacitidine.
- Table 1-4. Schedule of Activities: Parts 4 (Cohort 5 only) and 5 (AML) AMG 176 QD2 in Combination With Azacitidine was updated to correct cycle 1 timepoints for general and safety assessments and laboratory assessments:
    - 12-lead electrocardiogram (week 1 day 3)
    - Tumor lysis syndrome monitoring test (week 1 day 3 and week 3 day 17)
    - Cardiac monitoring test (week 1 day 3)
    - AMG 176 pharmacokinetic evaluation (week 1 day 3 and week 3 day 17)
    - [redacted]
- Table 1-5. Schedule of Activities: Part 3d (AML in United States) Drug-Drug Interaction (DDI) Assessment With Itraconazole was updated to correct an error by including a missing assessment timepoint – pre-dose for day 15 tumor lysis syndrome monitoring test.
- Table 1-6. Schedule of Activities Notes and Abbreviations Definitions was updated to clarify:
    - Neuropathy assessments, as a clinical evaluation, must be performed only for multiple myeloma subjects.

  - Timepoints for collection of pharmacokinetic samples for AMG 176 or azacitidine treatment. These timepoints are relative to start of dosing of either AMG 176 or azacitidine.

- A clarification statement was added for the use of core bone marrow biopsy/aspirate performed as standard of care to meet study screening requirements as long as it was performed within 4 weeks from enrollment and no curative anti-cancer therapy was administered during the time from biopsy to enrollment (sections 5.1, 8.1.1, 8.2.2.2.1).
- To maintain consistency, the window to accept previously conducted cardiac imaging tests to meet screening requirement was changed from 30 days of cycle 1 day 1 to 4 weeks of cycle 1 day 1 (Table 1-6 and section 8.2.3.4.2).
- Since Investigator's Brochure was recently updated, the corresponding updates were made into AMG 176 Clinical Experience and Key Benefits (sections 2.2.2.4 and 2.3.2).
- Anti-tumor therapy windows of exclusion criterion 219 were updated to remove reference to "or 5 half-lives, whichever is shorter" from the 14 days and 21 days windows of enrollment (section 5.2).
- Long-term follow up window was increase to $\pm$ 14 days to allow flexibility for these follow up visits. Multiple sections of the protocol were updated to incorporate this change (sections 4.1, 4.4.2, 8.1.5, study schemas, and Table 1-6).
- Azacitidine accountability instructions were updated to clarify that (section 6.1.2.1):
  - Only for intravenous administration of azacitidine, stop date and time is required to be recorded on each subject's case report form.
- Amgen Investigational Product: AMG 176 was updated to (section 6.2.2.1):
  - Clarify dosage adjustments guidelines for AMG 176 by changing the general format of the information.
  - Withholding criteria for elevation of cardiac troponin was modified to elevation > 0.1 ng/mL to emphasize the possibility of allowing subjects to restart AMG 176 treatment even if the elevation is a grade 3.

  - Clarify that restarting of AMG 176 dosing can be resumed if deemed safe by the site investigator instead of investigators as previously stated.

- Include updated guidance for collection/report of serious and fatal serious adverse events in alignment to current protocol template (Table 1-6, section 8.2.4.1.4).
- Include a new footnote in Table 11-1 to instruct that for local laboratory tests, all available analytes listed in the table should be recorded in the electronic case report form.
- Remove reference to central testing of troponin-I with high sensitivity Abbott ARCHITECT assay used for exploratory purposes to evaluate biological variations of troponin-I in oncology subjects (section 6.2.2.2.7).
- Administrative and editorial changes (including grammatical, typographical, abbreviations, and formatting) have been made throughout the protocol.

Amendment 15

Protocol Title: A Phase 1 First-in-Human Study Evaluating the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of AMG 176 in Subjects With Relapsed or Refractory Multiple Myeloma and Subjects With Relapsed or Refractory Acute Myeloid Leukemia

Amgen Protocol Number 20150161

EudraCT Number: 2015-004777-32
NCT Number: NCT02675452

Amendment Date: 09 February 2023

Rationale:

This protocol is being amended for the following reasons:

- The background, rationale, and benefit/risk assessments were substantially revised to include current data and more recent literature.
- Clinical results of the study were updated to reflect the current status of the study as of the most recent data cutoff of 06 September 2022.
- Details about plans for dose optimization to identify the Recommended Phase 2 Dose (RP2D) for the combination of AMG 176 with azacitidine were added, which will be estimated using the totality of data from across the first-in-human (FIH) study, including the pharmacokinetics (PK), safety, efficacy, and other results from the dose escalation and dose expansion.
- Dosing was revised and clarified for Part 5 dose confirmation/optimization (now Part 5a), and an Acute Myeloid Leukemia (AML) conventional dosing schedule was added (Part 5b) along with preclinical data and PK modeling to support investigation of this schedule.
- The dosing language was changed from on 2 consecutive days (QD2) to twice weekly (BIW) to comply with standard and accepted dosing abbreviations.
- Added further language describing that potential drug-drug interactions (DDI) between the study drugs and hormone-based contraceptives are not established. Intrauterine device for contraception methods in females was clarified to non-hormonal (ie, copper) only. The use of oral contraceptives was clarified as

prohibited for the purpose of pregnancy prevention but allowed for the treatment of menorrhagia or other abnormal menstrual bleeding at the discretion of the investigator.

- Number of subjects to be enrolled on the study was updated as follows:
  - Part 3a (closed) enrolled 17 subjects (previously: 15 subjects).
  - Part 3b (closed) enrolled 11 subjects (previously: actively enrolling, with up to 30 subjects planned).
  - Part 3d (open) will enroll up to 11 subjects (previously: up to 8 subjects).
  - Part 4 (open) will enroll approximately 60 subjects (previously: up to 50 subjects).
  - Part 4 Cohort 5 was replaced with Cohorts 5a and 5b, and the figures were updated accordingly.
  - Part 5 (open) will enroll approximately 20 subjects per cohort, approximately 60 subjects in total (previously: up to 20 subjects). It will now consist of Part 5a of 2 cohorts and the new Part 5b (conventional dosing schedule).
  - Enrollment eligibility worksheet and/or subject registration form will be completed and sent to Amgen for verification of eligibility criteria by a site representative.
- Inclusion criteria:
  - 113: Added that for Part 5a cohorts 1 and 2, enrollment will be restricted to subjects with persisting or recurring AML after 1 to 2 lines of prior therapy.
  - 114: For acute myeloid leukemia subjects, blast equivalents are now permissible for greater than or equal to 5% blasts in bone marrow requirement.
- Exclusion criteria:
  - 219, 225, 226, 228, 229: Updated language to clarify chemotherapy, antibody therapy, molecular targeted therapy, investigational agent, strong CYP3A4 inhibitors, CYP3A4 sensitive substrates, own OATP1B1, and/or OATP1B3 or BCRP substrates with a narrow therapeutic window, and any medications are

now disallowed within 5 times the $t_{½}$ of the drug, or until the relevant biological effect has resolved (whichever is longer).

- 226: Inhibitors of P-glycoprotein (P-gp) were removed from this exclusion criterion, since preliminary clinical data analysis from the Part 3d and physiologically-based pharmacokinetic (PBPK) modeling and simulation indicated weak to no drug-drug interactions.

- Observed discrepancies between the Schedule of Assessments and the electronic data capture (EDC) were addressed by updating Section 1.3 (Schedule of Activities) of the protocol accordingly. For Part 3d, Part 4, and Part 5a, timepoints of various test procedures (eg, cardiac screening, tumor lysis syndrome tests, echocardiogram, electrocardiogram, [redacted] vitals) were revised, and for Part 4 Cohorts 5a and 5b, and Part 5a (AML) Cycle 1 Week 4 procedures were added.
- The reporting period of serious adverse events was updated from “within 24 hours” to “immediately and no later than 24 hours following the investigator’s awareness of the event”.
- The exclusion of azole antifungal therapy was removed since data from Cohort 3d did not identify a DDI between AMG 176 and itraconazole.
- The drug supply information has been updated, to show that AMG 176 will be supplied as a 10 mL liquid deliverable volume in a single-use 20 cc glass vial or a 14.4 mL liquid deliverable volume in a single use 30 cc glass vial (the latter was previously under development).
- The creatinine thresholds for grades 1 through 3 in “Cairo-Bishop Clinical Tumor Lysis Syndrome Definition and Grading” table were corrected (Appendix 8).
- In addition, administrative and editorial changes (including grammatical, typographical, and formatting) have been made throughout the protocol.

Amendment 16

Protocol Title: A Phase 1 First in Human Study Evaluating the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of AMG 176 in Subjects With Relapsed or Refractory Multiple Myeloma and Subjects With Relapsed or Refractory Acute Myeloid Leukemia

Amgen Protocol Number 20150161

EudraCT Number: 2015-004777-32

NCT Number: NCT02675452

Amendment Date: 13 July 2023

Rationale:

This protocol, dated 13 July 2023, is being amended for the following reasons:

- To clarify that enrollment in Part 5B will start after Part 5A is complete (Section 1.1, Section 4.1, Section 4.1.1) and to provide the dose regimen and number of subjects to be enrolled in both Part 5A and Part 5B (Section 4.1.1, Section 4.4.1 and Section 6.1.2.1).
- To update the Simon's two-stage minimax design for Part 5A to provide interim futility criteria to minimize the number of subjects exposed to a potentially ineffective treatment. The design is based on a two-sided Type I error rate at 0.05 with 0.8 power (Section 1.1, Section 4.1, Section 4.1.1, and Section 9.4.1.1).
- To include omitted pages in Table 1-7 (Schedule of Activities: Part 5B acute myeloid leukemia [AML] Conventional Dosing – Regimen 1) and Table 1-8 (Schedule of Activities: Part 5B [AML] Conventional Dosing – Regimen 2) from amendment 15 to clarify that hospitalization is only required in the first cycle and to indicate the procedures for cycle 2 and beyond. This update allows to monitor safety without overburdening the clinical site and subject with unnecessary procedures.
- Minor updates in the list of references (Section 10).
- In addition, administrative and editorial changes (including grammatical, typographical, and formatting) have been made throughout the protocol.