Title Page

Protocol Title:		A Phase 1 Study of AMG 176 as Monotherapy and in Combination with Azacitidine in Higher-Risk Myelodysplastic Syndrome and Chronic Myelomonocytic Leukemia
Short Protocol Title:		Phase 1 Study of AMG 176 with Azacitidine in Subjects with MDS/CMML
Protocol Number:		20200392
Investigational Product:		AMG 176
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Data Elements Standards Version:	8.0

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 Study of AMG 176 as Monotherapy and in Combination with Azacitidine in Higher-Risk Myelodysplastic Syndrome and Chronic Myelomonocytic Leukemia, dated 28 April 2022, 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 sub investigators (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

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Institution Name

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Address and Telephone Number of Institution

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1. Protocol Summary

1.1 Synopsis

Protocol Title: A Phase 1 Study of AMG 176 as Monotherapy and in Combination with Azacitidine in Higher-Risk Myelodysplastic Syndrome and Chronic Myelomonocytic Leukemia

Short Protocol Title: Phase 1 Study of AMG 176 with Azacitidine in Subjects with MDS/CMML

Study Phase: 1

Indication: Higher Risk Myelodysplastic Syndrome/Chronic Myelomonocytic Leukemia (HR-MDS/CMML)

Rationale

Myeloid Leukemia Cell 1 (MCL1) is a member of the B-Cell Lymphoma 2 (BCL2) family of proteins integral to the control of apoptosis (programmed cell death) with anti-apoptotic activity that promotes cell survival. In contrast, pro-apoptotic family members, such as pro-apoptotic effector proteins BCL2 homologous antagonist/killer (BAK) and pro-apoptotic effector proteins BCL2-associated X (BAX) are critical effectors for the induction of apoptosis. Upon apoptotic stimuli, pro-apoptotic BH3 only proteins (eg, Bid) bind MCL1, and disrupt the interaction between MCL1 and BAK or BAX. This leads to the oligomerization of BAK/BAX, mitochondrial outer membrane permeabilization (MOMP), and the release of cytochrome C, caspase activation and cell death (Youle and Strasser, 2008).

The acquired resistance and evasion of apoptosis, which is central to therapeutic resistance, is an established hallmark of cancer (Hanahan and Weinberg, 2000). MCL1 is integral to the resistance of apoptosis in a substantial number of solid and hematopoietic cancers, as supported by a wealth of genetic and functional data. Internal efforts have demonstrated that knockdown of MCL1 expression by small interfering ribonucleic acid (siRNA) induces cell death in multiple cancer cell lines.

MCL1 provides a useful target for the treatment of subjects with acute myeloid leukemia (AML) as it is essential for the development and sustained growth of AML. MCL1 dependency was detected in AML mouse models (Xiang et al, 2010) and in human AML-derived cell lines. It was shown that deletion of MCL1 but not loss or pharmacological blockade of BCL-XL, BCL-2, or BCL-W induced the death of transformed AML cells and cured the disease in AML afflicted mice (Glaser et al, 2012). The upregulation of MCL1 has been described at the time of AML relapse (Kaufmann et al, 1998). In FLT3-ITD AML, upregulation of MCL1 is dependent on FLT3 signaling and an essential effector of FLT3-ITD mediated drug resistance (Bose and

Grant, 2013). Targeting MCL-1 sensitizes FLT3 ITD positive leukemia to cytotoxic therapies (Kasper et al, 2012).

The combination of AMG 176 and azacitidine in subjects with relapsed or refractory (R/R) AML is being tested in the AMG 176 phase I first in human (FIH) Study 20150161. However, this combination has yet to be investigated in patients with myelodysplastic syndrome (MDS). Given the need for improved therapies in patients with higher-risk (HR) MDS and the potential use of AMG 176 in patients who have failed chemotherapy and BCL2 inhibitors, such as venetoclax, the exploration of AMG 176 with and without azacitidine in this population, especially those with R/R disease who have progressed on hypermethylating agent (HMA) with and without venetoclax, is warranted.

Objective(s) and Endpoint(s)/Estimands

Objectives	**Endpoints**
Primary	
Part 1A – QW Monotherapy (Dose Exploration)	
• Evaluate the safety and tolerability of AMG 176 once weekly (QW) monotherapy in subjects with R/R higher risk myelodysplastic syndrome (HR-MDS)	• Incidence of dose limiting toxicities (DLTs), treatment-related, treatment-emergent adverse events and clinically significant changes in vital signs, electrocardiogram (ECGs), and clinical laboratory tests
Part 1B – QW Combination Therapy (Dose Exploration)	
• Evaluate the safety and tolerability of AMG 176 in combination with azacitidine in subjects with R/R HR-MDS and determine the Optimal Biological Dose (OBD) and Minimum Safe and Biologically Effective Dose (MSBED) of AMG 176 in combination with azacitidine	• Incidence of DLTs, treatment-related, treatment-emergent adverse events and clinically significant changes in vital signs, ECGs, and clinical laboratory tests
Part 2 – QW Combination Therapy (Dose Expansion)	
• Evaluate the preliminary efficacy of AMG 176 in combination with azacitidine in subjects with R/R HR-MDS/CMML in: – HMA Failure, Venetoclax-Naïve – HMA Failure, Venetoclax-Exposed • To assess the preliminary efficacy of AMG 176 in combination with azacitidine in subjects with Newly Diagnosed MDS/CMML	• Overall response rate (ORR), according to the Uniform Response Criteria for Myelodysplastic/ Myeloproliferative Neoplasms (MDS/MPN), including: – Complete Remission (CR) – Partial Remission (PR) – Marrow CR – Cytogenic response

Secondary	
Part 1A – QW Monotherapy (Dose Exploration)	
• Evaluate preliminary efficacy of AMG 176 QW when given as monotherapy in R/R MDS/CMML	• Overall response according to the Uniform Response Criteria for MDS/MPN, Event-Free Survival (EFS), time to response, and Duration of Response (DOR)
• Evaluate the pharmacokinetics (PK) of AMG 176 when administered as monotherapy	• 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 ($t_{1/2}$)
Part 1B – QW Combination Therapy (Dose Exploration)	
• Evaluate preliminary efficacy of AMG 176 QW in combination with azacitidine in R/R MDS/CMML	• Overall response according to the Uniform Response Criteria for MDS/MPN, EFS, time to response, and DOR
• 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 $t_{1/2}$
Part 2 – QW Combination Therapy (Dose Expansion)	
• Evaluate the preliminary efficacy of AMG 176 in combination with azacitidine in subjects with R/R HR-MDS/CMML in: – HMA Failure, Venetoclax-Naïve – HMA Failure, Venetoclax-Exposed – To assess the preliminary efficacy of AMG 176 in combination with azacitidine in subjects with Newly Diagnosed MDS/CMML	• Time to transformation to Acute Myeloid Leukemia (AML) • Duration of Response (DOR) • Overall Survival (OS) • Time to Next MDS Treatment (TTNT) • EFS
• 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 $t_{1/2}$

Overall Design

This study is a phase 1 clinical trial designed to assess the safety, tolerability, and efficacy of AMG 176 as monotherapy and in combination with the 7-day regimen of azacitidine for the treatment of HR-MDS/CMML. Subjects will be treated with Intravenous (IV) AMG 176 and IV or Subcutaneous (SC) azacitidine. The study consists of two parts.

Part 1 – Dose Escalation/Determination of Optimal Biological Dose (OBD) and Minimum Safe and Biologically Effective Dose (MSBED)

In Part 1, the modified Toxicity Probability Interval (mTPI) design will be applied for dose escalation.

Three dose levels of AMG 176 monotherapy will first be tested in Part 1A, and after the OBD or MSBED is found, three dose levels of AMG 176 in combination with azacitidine will be tested in Part 1B.

Each dose cohort will initially enroll 3 to 4 subjects and up to 10 subjects per cohort may be enrolled. After reviewing all available safety data, dose level recommendations (eg, escalation, de-escalation) will be made by the Dose Level Review Team (DLRT) using an mTPI model (Ji et al, 2010) based on all subjects that have been enrolled at the current dose. The DLRT may change the dose/dosing scheduled based on emerging data. The OBD/MSBED is defined as the minimum safe and biologically effective combination dose with a probability of DLT lower than or close to a targeted toxicity probability of 0.2.

Part 2 – Dose Expansion

Upon completion of Part 1 of the study, the dose expansion phase will begin at the OBD/MSBED and drug administration schedule with the intention of confirming the safety and tolerability and determining the efficacy of AMG 176 in combination with azacitidine in not only R/R HR - MDS/CMML, but also newly diagnosed HR- MDS/CMML. An additional 60 subjects will be enrolled in Part 2 of the study as follows:

- HMA Failure Cohort: stratified by venetoclax exposure history
  - HMA Failure, venetoclax-Naïve (n = 20)
  - HMA Failure, venetoclax-Exposed (n = 20)
- Newly diagnosed (n = 20) – subjects will not be enrolled into this cohort until all previous cohorts have been completed and the data reviewed by the Food and Drug Administration (FDA).

Toxicity will be monitored for each cohort using a Bayesian approach proposed by Thall, Simon, and Estey (1995).

The incidence of grade 3 or higher treatment-related non-hematological adverse events will be evaluated once every 5 subjects have had the chance to receive at least 1 cycle of treatment at the determined dose level for Part 2.

Number of Subjects

A total of approximately 120 subjects will be enrolled in the study:

- Part 1a: up to 30 subjects (up to 10 per cohort, 3 dose levels).
- Part 1b: up to 30 subjects (up to 10 per cohort, 3 dose levels).

Part 2: 60 subjects

Summary of Subject Eligibility Criteria

Key Inclusion Criteria:

- Age ≥ 18 years of age.
- For Part 1, patients have R/R MDS post-HMA failure, defined as prior receipt of 4 cycles of HMA therapy (including but not limited to decitabine, azacitidine,

investigational HMAs such as SGI-110, and oral HMAs such as oral decitabine and cedazuridine [ASTX727] and oral azacitidine [CC-486]) with failure to attain a response or progression of disease or relapse at any time after prior response to HMA therapy.

Note: Patients with HR-CMML (CMML-1 or 2 by World Health Organization [WHO]) are eligible. Hydroxyurea administration will be allowed on the study to lower the white cell count to ≤ 10 000/μL prior to the initiation of therapy.

- For Part 2, patients will be divided into 2 cohorts:

1. HMA Failure Cohort: patients with R/R MDS post-HMA failure (defined as prior receipt of 4 cycles of HMA therapy with failure to attain a response or progression of disease or relapse at any time after prior response to HMA therapy) are eligible. Patients who have previously received venetoclax are eligible and will be stratified accordingly in the HMA failure cohort.
2. Newly Diagnosed Cohort: patients with treatment-naïve newly diagnosed HR-MDS (revised International Prognostic Scoring System [IPSS-R] score ≥ 3.5) are eligible for enrollment only after all prior cohorts have been completed and the data reviewed by the FDA. Hydroxyurea administration will be allowed on the study to lower the white cell count to ≤ 10 000/μL prior to the initiation of therapy. Patients with HR-CMML (CMML-1 or 2 by WHO) are eligible. Hydroxyurea administration will be allowed on the study to lower the white cell count to ≤ 10000/μL prior to the initiation of therapy. Patients who have previously received venetoclax are eligible and will be stratified accordingly in the HMA Failure Cohort.

Key Exclusion Criteria:

- Patients with newly diagnosed MDS with IPSS-R lower-risk category (IPSS-R score < 3.5)
- Patients with CMML-0 by WHO
- History of other malignancy within the past 2 years prior to enrollment (with some exceptions as listed in full list of criteria)
- Excluded prior and/or concomitant therapies as listed in the full list of criteria
- Patients who are fit and deemed eligible by the investigator for intensive salvage therapy

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

Treatments

This study is a phase 1 clinical trial designed to assess the safety, tolerability, and efficacy of AMG 176 in combination with the 7-day regimen of azacitidine for the treatment of HR-MDS. Subjects will be treated with IV AMG 176 and IV or SC azacitidine. The study consists of two parts.

Part 1

Three dose levels of AMG 176 monotherapy will first be tested, and after the OBD is found, three dose levels of AMG 176 in combination with azacitidine will be tested. Each dose cohort will initially enroll 3 to 4 subjects and up to 10 subjects per cohort may be enrolled. After reviewing all available safety data, dose level recommendations (eg, escalation, de-escalation) will be made by the DLRT.

Part 2

- Upon completion of Part 1 of the study, the dose expansion phase will begin at the OBD/MSBED and drug administration schedule with the intention of confirming the safety and tolerability and determining the efficacy of AMG 176 in combination with azacitidine in not only R/R HR- MDS/CMML, but also in frontline HR-MDS/CMML. An additional 60 subjects will be enrolled in Part 2 of the study as follows:
- HMA Failure Cohort: stratified by venetoclax exposure history
    - HMA Failure, venetoclax-naïve (n = 20)
    - HMA Failure, venetoclax-exposed (n = 20)
- Newly Diagnosed (n = 20) – subjects will not be enrolled into this cohort until all previous cohorts have been completed and the data reviewed by the FDA

Toxicity will be monitored for each cohort using a Bayesian approach proposed by Thall, Simon, and Estey (1995).

Statistical Considerations

Sample Size Considerations:

It is anticipated that up to 1**2**0 subjects will be enrolled in the study, with up to **6**0 subjects in Part 1 and 60 subjects in Part 2. 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 OBD/MSBED.

Planned Analyses:

Interim Analysis and Early Stopping Guidelines

No formal interim efficacy analysis is planned. Safety data will be reviewed on an ongoing basis.

Primary Analysis

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

Final Analysis

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

Methods of Analysis:

Descriptive statistics will be provided for selected demographics, safety, Pharmacokinetics (PK), and biomarker 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. Unless otherwise specified, statistical analyses will be done using the Full Analysis Set (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.

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

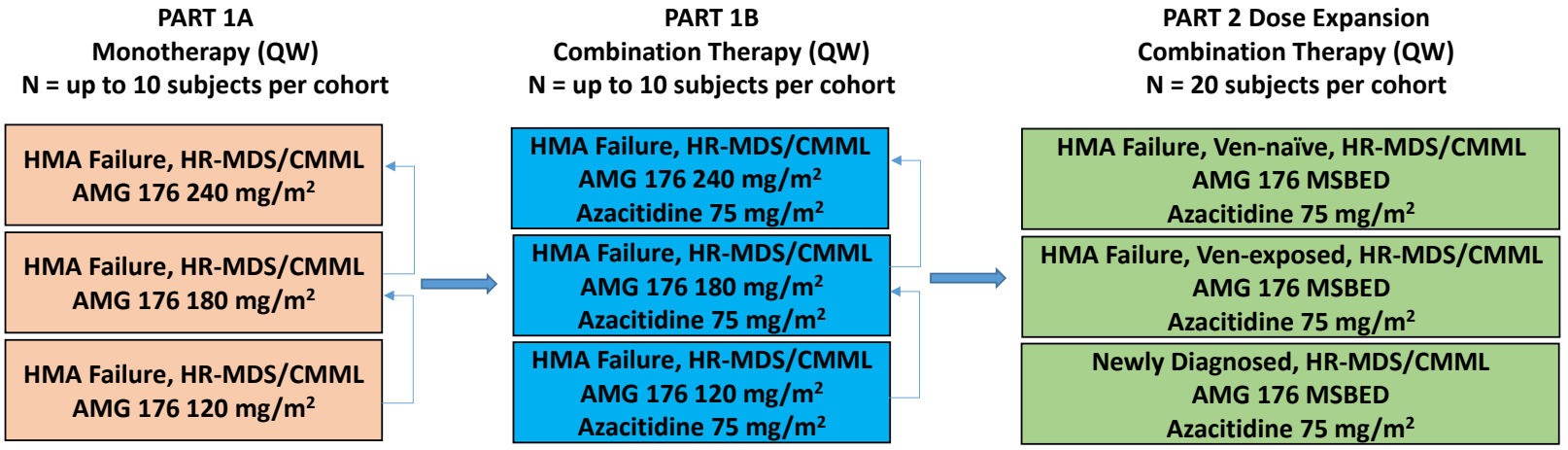
Statistical Hypotheses

The clinical hypothesis is that at least 1 dose level of AMG 176 administered in combination with azacitidine will achieve acceptable safety and tolerability in subjects with HR-MDS. No formal statistical hypothesis will be tested.

Sponsor Name: Amgen, Inc.

1.2 Study Schema

Figure 1-1. Study Schema



CMML = chronic myelomonocytic leukemia; HMA = hypomethylating agent; HR-MDS = higher-risk myelodysplastic syndrome; MSBED = minimum safe and biologically effective dose; QW = once weekly; Ven = venetoclax

1.3 Schedule of Activities (SoA)

Table 1-1. Schedule of Activities: Part 1A, AMG 176 QW, Cycle 1, All Doses

	Screen	Treatment																													
Cycle		1																													
Days	-14 to 0	1								2	8									9	15				16	22				23	
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																														
Demographics	X																														
Clinical evaluation[a]	X	X								X	X											X					X				
Vital signs	X	X		X						X	X		X									X		X			X		X		
12-lead ECG[b]	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[c]	X																														
Hospitalization[d]		Hospitalization										Hospitalization (if target dose is 180 mg/m^2 or higher only)																				
TLS prophylaxis[e]		X									X																				
Prior medications review	X																														
Concomitant therapies review		X																													
Adverse events		X																													
Serious adverse events		X																													
STUDY TREATMENT																															
AMG 176[f]			X										X										X					X			
LABORATORY ASSESSMENTS																															
Local labs																															
Safety lab tests[h]	X	X									X											X					X				
TLS monitoring[i]		X		X		X			X	X	X	X		X		X			X	X	X	X				X	X				X
Cardiac monitoring tests[j]	X	X							X		X	X							X		X	X			X	X	X			X	X
Pregnancy test[k]	X	X																													
Hepatitis serology	X																														

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See end of Table 1-4 for assessment notes and abbreviation definitions

Table 1-1. Schedule of Activities: Part 1A, AMG 176 QW, Cycle 1, All Doses

	Screen	Treatment																														
Cycle		1																														
Days	-14 to 0	1								2	8									9	15				16	22				23		
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	
Local labs (continued)																																
HIV testing[l]	X																															
Central labs																																
AMG 176 PK[m,n]		X		X	X		X	X	X		X	X		X	X		X	X	X	X	X	X		X	X	X	X		X	X	X
DISEASE AND IMAGING ASSESSMENTS																																
Bone marrow aspirate/biopsy[p]	X																															
[redacted]		X										X										X					X				

See end of Table 1-4 for assessment notes and abbreviation definitions

Table 1-2. Schedule of Activities: Part 1A, AMG 176 QW, Cycles 2 and Beyond, All Doses

	Treatment																									
Cycle	2 through 4											≥ 5														
Days	1			2	8 & 15		9	16	22		23	1		2	8		15		9	16	22		23			
Hours (relative to start of dosing)	Pre-dose	0	EOI	24h after D1	Pre-dose	0	24h after D8	24h after D15	Pre-dose	0	24h after D22	Pre-dose	0	24h after D1	Pre-dose	0	Pre-dose	0	24h after D8	24h after D1	Pre-dose	0	24h after D15	EOT[q]	SFU[q]	LTFU/EOS[r,s]
GENERAL ASSESSMENTS																										
Clinical evaluation[a]	X				X				X			X			X		X				X			X	X	
Vital signs	X		X		X				X			X			X		X				X			X	X	
12-lead ECG[b]	X		X	X	X		X	X	X		X	X		X	X		X		X	X	X		X	X	X	
ECHO/MUGA[c]																								X		X
Concomitant therapies review														X												
Adverse events														X												
Serious adverse events[s]														X												
Subsequent anti-cancer therapy and survival																										X
STUDY TREATMENT																										
AMG 176[f]		X				X				X			X			X		X				X				
LABORATORY ASSESSMENTS																										
Local labs																										
Safety lab tests[h]	X				X				X			X			X		X				X			X	X	
Cardiac monitoring tests[j]	X			X	X		X	X	X		X	X		X	X		X		X	X	X		X	X	X	
Pregnancy test[k]	X											X												X	X	

See end of Table 1-4 for assessment notes and abbreviation definitions

Table 1-2. Schedule of Activities: Part 1A, AMG 176 QW, Cycles 2 and Beyond, All Doses

	Treatment																							EOT[q]	SFU[q]	LTFU/EOS[r,s]
Cycle	2 through 4											≥ 5														
Days	1			2	8 & 15		9	16	22		23	1		2	8		15		9	16	22		23			
Hours (relative to start of dosing)	Pre-dose	0	EOI	24h after D1	Pre-dose	0	24h after D8	24h after D15	Pre-dose	0	24h after D22	Pre-dose	0	24h after D1	Pre-dose	0	Pre-dose	0	24h after D8	24h after D1	Pre-dose	0	24h after D15			
Central labs																										
AMG 176 PK[m,n]	X		X	X																						
DISEASE AND IMAGING ASSESSMENTS																										
Bone marrow aspirate/biopsy[p]	C2D1, C3D1, and thereafter prior to every other cycle or when clinically indicated until disease progression and to confirm CR and MRD status																									
[redacted]	X				X				X			X			X		X				X			X		
[redacted]	[redacted]																									
[redacted]	[redacted]																									
[redacted]	[redacted]																									
[redacted]	Assessed and documented at every cycle and at time of disease progression																									

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See end of Table 1-4 for assessment notes and abbreviation definitions

Table 1-3. Schedule of Activities: Part 1B and Part 2, Combination Therapy Cycle 1, All Doses

	Screen	Treatment																																
Cycle		1																																
Days	-14 to 0	1												2	3 to 7	8										9	15				16	22				23
Hours (relative to start of dosing)		Pre-dose	0	5 minutes	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 ASSESSMENTS																																		
Informed consent	X																																	
Demographics	X																																	
Clinical evaluation[a]	X	X												X		X											X				X				
Vital signs	X	X			X									X		X		X									X		X			X		X	
12-lead ECG[b]	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[c]	X																																	
Hospitalization[d]		Hospitalization														Hospitalization (if target dose is 180 mg/m^2 or higher only)																				
TLS prophylaxis[e]		X														X																			
Prior medications review	X																																	
Concomitant therapies review		X																																
Adverse events		X																																
Serious adverse events		X																																
STUDY TREATMENT																																		
AMG 176[f]			X														X										X					X			
Azacitidine[g]			X											X	X																				
LABORATORY ASSESSMENTS																																		
Local labs																																		
Safety lab tests[h]	X	X														X										X					X			
TLS monitoring[i]		X			X				X			X	X	X		X		X		X			X	X	X	X				X	X			X
Cardiac monitoring tests[j]	X	X										X		X		X							X		X	X			X	X	X		X	X
Pregnancy test[k]	X	X																																
Hepatitis serology	X																																	

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See end of Table 1-4 for assessment notes and abbreviation definitions

Table 1-3. Schedule of Activities: Part 1B and Part 2, Combination Therapy Cycle 1, All Doses

	Screen	Treatment																																		
Cycle		1																																			
Days	-14 to 0	1											2	3 to 7	8									9	15				16	22				23		
Hours (relative to start of dosing)		Pre-dose	0	5 minutes	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		
Local labs (continued)																																				
HIV testing[l]	X																																			
Central labs																																				
AMG 176 PK[m,n]		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[m,o]		X		X	X	X	X		X			X																									
DISEASE AND IMAGING ASSESSMENTS																																				
Bone marrow aspirate/biopsy[p]	X																																			
Peripheral blood count	X	X														X										X					X					
[redacted]																																				

See end of Table 1-4 for assessment notes and abbreviation definitions

Table 1-4. Schedule of Activities: Part 1B and Part 2, Combination Therapy Cycles 2 and Beyond, All Doses

Cycle	Treatment																										
	2								3 and 4								≥ 5										
Days	1			2, 9, 16, & 23	3 to 7	8, 15, & 22			1			2, 9, 16, & 23	3 to 7	8, 15, & 22			1		2, 9, 16, & 23	3 to 7	8, 15, & 22			EOT[q]	SFU[q]	LTFU/EOS[r,s]
Hours (relative to start of dosing)	Pre-dose	0	EOI	24h after dose		Pre-dose	0	EOI	Pre-dose	0	EOI	24h after dose		Pre-dose	0	EOI	Pre-dose	0	24h after dose		Pre-dose	0	EOI			
Clinical evaluation[a]	X					X			X					X			X				X			X	X	
Vital signs	X		X			X			X		X			X			X				X			X	X	
12-lead ECG[b]	X		X	X		X			X		X	X		X			X		X		X			X	X	
ECHO/MUGA[c]																								X		X
Concomitant therapies review	X																									
Adverse events	X																									
Serious adverse events[s]	X																									
Subsequent anti-cancer therapy and survival																										X
STUDY TREATMENT																										
AMG 176[f]		X					X			X					X			X				X				
Azacitidine[g]		X		D2	X					X		D2	X					X	D2	X						
LABORATORY ASSESSMENTS																										
Local labs																										
Safety lab tests[h]	X					X			X					X			X				X			X	X	
Cardiac monitoring tests[j]	X			X		X			X			X		X			X		X		X			X	X	
Pregnancy test[k]	X								X								X							X	X	
Central Labs																										
AMG 176 PK[m,n]	X		X	D2					X		X	D2														

See end of Table 1-4 for assessment notes and abbreviation definitions

Table 1-4. Schedule of Activities: Part 1B and Part 2, Combination Therapy Cycles 2 and Beyond, All Doses

Cycle	**Treatment**																							EOT[q]	SFU[q]	LTFU/EOS[r,s]
	2								3 and 4								≥ 5									
Days	1			2, 9, 16, & 23	3 to 7	8, 15, & 22			1			2, 9, 16, & 23	3 to 7	8, 15, & 22			1		2, 9, 16, & 23	3 to 7	8, 15, & 22					
Hours (relative to start of dosing)	Pre-dose	0	EOI	24h after dose		Pre-dose	0	EOI	Pre-dose	0	EOI	24h after dose		Pre-dose	0	EOI	Pre-dose	0	24h after dose		Pre-dose	0	EOI			
DISEASE AND IMAGING ASSESSMENTS																										
Bone marrow aspirate/biopsy[p]	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	X					X			X					X			X				X			X		
[redacted]	[redacted]																									
Overall disease response	Assessed and documented at every cycle and at the time of disease progression																									

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AE = adverse event; ALT = alanine aminotransferase; BNP = B-type natriuretic protein; BSA = body surface area; C = cycle; CBC = complete blood count; CR = complete remission; CXDX = cycle X day X; D = day; ECG = electrocardiogram; ECHO = echocardiogram; ECOG PS = Eastern Cooperative Oncology Group Performance Status; EOI = end of infusion; EOS = end of study; EOT = end of treatment; FDG = fluorodeoxyglucose; h= hour; HIV = human immunodeficiency virus; IV = intravenous; LTFU = long-term follow-up; min = minute; MRD = minimal residual disease; MUGA = multigated acquisition scan; NT-pro-BNP = N-terminal prohormone of brain natriuretic peptide PBMC = peripheral blood mononuclear cell; PK = pharmacokinetics; QW = weekly; SAE = serious adverse event; SC = subcutaneous; SCR = screening; SFU = safety follow-up; SOA = schedule of activities; SOC = standard of care; TLS = tumor lysis syndrome; W = week; WBC = white blood cell.

[a] Clinical evaluations: (ie, physical exam, ECOG PS, and weight) When collected on dosing days, will be collected pre-dose. Medical and surgical history, neurological assessment and height need only be collected at the screening visit. Prior to dosing on day 1 of every cycle, weight must be collected and BSA must be calculated. Physical examination (including ECOG PS and concomitant medications) every 28 days (± 7 days) for the first 3 cycles, then every 3 cycles until 12 cycles from the start of therapy; then every 6 cycles (±2 months).

[b] 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 ≥ 5 minutes apart, with each baseline ECG performed in triplicate, and with at least 5 minutes between the end of each triplicate and the start of the next (total 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

[c] 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 30 days of C1D1 as part of SOC, then it does not have to be repeated during screening as long as the same modality is used throughout the study.

[d] 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. If the target dose is 180 mg/m^2 or higher, hospitalization will also be required within 24 hours before administration of the target dose on day 8 and will continue until 24 hours post administration. Hospitalization period can be increased per institutional standards or investigators discretion. Hospitalization for the purpose of TLS prophylaxis will not be captured as an SAE.

[e] TLS Prophylaxis: See Protocol for prophylaxis requirements (see Section 11.9) including additional serum chemistry and hematology laboratory samples that must be collected within 24 hours prior to the first dose (see Section 8.4.3.2). Electrolyte values must be within normal range prior to AMG 176 dosing.

[f] AMG 176 dosing: AMG 176 will be administered QW IV on days 1, 8, 15, and 22 on a 28-day cycle. A lead in dose of 120 mg/m^2 will be required if the target dose is 180 mg/m^2 or higher. AMG 176 will be infused over 2 hours (± 5 minutes). Clinical visits on dosing days can be scheduled ± 1 day; however, safety and PK evaluations must occur at indicated time points, including a return to clinic 24 hours after dosing for safety and PK evaluations.

[g] Azacitidine dosing: refer to the prescribing information for full details. The standard dose and schedule for azacitidine is as follows: Azacitidine will be administered at a dose of 75 mg/m^2 IV or SC daily on days 1 to 7 of each 4-week cycle.

[h] Safety Labs: Safety labs include chemistry, hematology, urinalysis, and coagulation analytes. See Protocol for the list of analytes (Table 11-1). 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).

- CBC with differential (differential not required if WBC ≤ 0.5 k/μL), at least once weekly for the 1st cycle, then every 2 to 4 weeks during cycles 2 to 6, and then every 4 weeks (± 14 days) thereafter as long as they are on study.
- Serum chemistry profile at least once weekly for the 1st cycle, then every 2 to 4 weeks during cycles 2 to 6, and then at least every 4 weeks (± 14 days) during active treatment.

[i] 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.

[j] 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.

[k] 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. Additional on-treatment pregnancy testing may be performed at the investigator's discretion if there is suspicion that a female subject is pregnant or per local laws and regulations.

[l] HIV: to be performed only if required by local regulatory authorities.

[m] PK: PK samples should be collected at the exact nominal time point as noted. 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.

[n] AMG 176 PK: samples collected and analyzed for AMG 176 at the timepoints indicated. All AMG 176 timepoints are relative to start of infusion.

[o] Azacitidine PK: samples collected and analyzed for azacitidine at the timepoints indicated. All azacitidine timepoints are relative to azacitidine administration.

[p] Cytomorphology: bone marrow smears (slides) at screening, pre-dose on day 1 of cycle 2 and cycle 3 and thereafter prior to every other cycle or when clinically indicated until disease progression. Bone marrow biopsies/aspirates may be performed with a ± 3 day window.

[q] 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 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 subject's medical records.

[r] LTFU/EOS: Long-term follow-up (LTFU) visits will occur every 3 months 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.
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 subject's medical records.

[s] **During** the **Long-term follow-up phase, serious adverse event(s) suspected to be related to Investigational Product will be reported to Amgen. After end of study serious adverse event(s) suspected to be related to Investigational Product will be reported to Amgen**. **Please refer to Section 8.4.6.1.3 for additional details.**

[redacted]

2. Introduction

2.1 Study Rationale

Programmed cell death or apoptosis is a survival mechanism utilized by different types of cancer, with evasion of apoptosis leading to malignant transformation (Fouad and Aanei, 2017; Hanahan and Weinberg, 2000). The process of apoptosis is regulated by complex protein-protein interactions between subgroups of the B-cell lymphoma/leukemia 2 (BCL2) protein family (Strasser et al, 2011; Czabotar et al, 2014). Myeloid Cell Leukemia 1 (MCL1) is an anti-apoptotic member of this protein family that promotes cell survival (Kozopas et al, 1993). With apoptotic stimuli, pro-apoptotic BCL2 homology 3 (BH3)-only proteins, such as BCL2-Interacting Mediator of cell death (BIM) and p53-Upregulated Modulator of Apoptosis (PUMA), bind MCL1 and other pro-survival BCL2 family members, thus disrupting interactions between MCL1 and BAK and BAX. This disruption leads to the activation and oligomerization of BAK and BAX, Mitochondrial Outer Membrane Permeabilization (MOMP), release of cytochrome C, caspase activation, and ultimately cell death (Youle and Strasser, 2008). MCL1 is expressed in a range of human and mouse tissues (Strasser et al, 2011; Thomas et al, 2013; Wang et al, 2013), and overexpression of MCL1 has been implicated in the development of numerous solid and hematopoietic malignancies (Glaser et al, 2012; Kotschy et al, 2016; Ashkenazi et al, 2017; Merino et al, 2017), as well as in resistance to chemotherapy and to BCL2/BCL-XL inhibitors (van Delft et al, 2006; Wertz et al, 2011). These findings suggest that the inhibition of MCL1 is a novel and compelling therapeutic strategy for the treatment of malignancies.

2.2 Background

2.2.1 Disease

Myelodysplastic Syndromes (MDS) are malignant clonal disorders characterized by ineffective hematopoiesis; bone marrow dysplasia; peripheral cytopenias, including neutropenia, anemia, and/or thrombocytopenia; and a propensity to transform into acute myeloid leukemia (AML) (Albitar et al, 2002; Doll and List, 1989). The incidence of MDS in the United States is increasing, with approximately 20 000 to 30 000 new cases diagnosed annually and a median age of diagnosis approximately 70 years (Kadia et al, 2011; List 2005; Ma et al, 2007). By the International Prognostic Scoring System (IPSS) and Revised IPSS (IPSS-R), MDS patients are divided into two major risk groups: lower-risk and HR-MDS (Greenberg et al, 1997; Greenberg et al, 2012). Patients who

present to HR-MDS have a median OS of less than one year with best supportive care (Fenaux et al, 2009).

The selection of therapy for MDS is based on the patient IPSS risk category, age, and performance status. Treatment goals range from managing cytopenias and improving quality of life in lower-risk MDS to prolonging survival in HR- MDS (Cheson et al, 2006). Current treatment options for patients with MDS range from growth factor support or lenalidomide in low risk patients, to intensive chemotherapy and allogeneic hematopoietic stem cell transplantation (HSCT) for patients with high-risk disease. The use of lenalidomide has demonstrated significant clinical activity in patients with anemia and a chromosome 5q deletion (del [5q]), with response rates as high at 35% to 60% (Cheson et al, 2006). However, the only potentially curative therapy for MDS remains allogeneic HSCT. Yet, due to the high risk of HSCT-associated morbidity and mortality, less than 1000 patients with MDS currently undergo an HSCT in the US each year (Bejar and Steensma, 2014).

Therapeutic options for MDS remain limited despite some advances. A small percentage of patients with minimal comorbidities and good performance statuses are candidates for curative therapies, such as allogeneic stem cell transplantation. For the vast majority of patients, the lack of acceptable donors, advanced age, and/or serious comorbid medical conditions and organ dysfunction prevent access to curative options. For similar reasons, AML therapy-based intensive chemotherapy regimens present an unacceptable risk-benefit ratio for many patients. The Standard of Care (SOC) in MDS has generally been accepted as supportive in nature.

Over the past 15 years, clinical use of HMA, including azacitidine (Vidaza), have been shown to improve patient quality of life, decrease transfusion requirements, and improve outcome parameters in MDS patients and has become the SOC for patients with MDS requiring treatment (Fenaux et al, 2009; Kantarjian et al, 2006). Only azacitidine has demonstrated a survival advantage compared to conventional care regimens with best supportive care, low-dose cytarabine, or intensive chemotherapy with a median OS of 24.5 months versus 15.0 months respectively (Fenaux et al, 2009). However, not all patients respond to HMA therapy and, unfortunately, patients will ultimately progress on HMAs. Current research demonstrates overall response rate (ORR) of 28% to 48%, Complete Response rates of 6% to 34%, and median DOR of 8 to 10 months in all patients treated with HMAs (Kadia et al, 2011; Prebet et al, 2011). Patients who have failed HMA therapy have extremely poor prognoses with a median OS of 4 to 6 months

(Prebet et al, 2011; Jabbour et al, 2010). There are currently no Food and Drug Administration (FDA)-approved agents in the setting of HMA failure MDS patients, and there are limited therapeutic options, especially given the increased age and frequent comorbidities of this patient population. Because azacitidine is the only drug that has been shown to have a survival advantage for MDS patients, combination strategies with azacitidine-based therapy have become a major focus of clinical research (Steensma 2012).

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 BAK, BAX, or the BH3-only protein family members, such as BIM and PUMA, are critical effectors for the induction of apoptosis. Upon the induction of apoptotic stimuli, pro-apoptotic BH3 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, 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 multiple myeloma (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/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.

The MCL1 inhibitor AMG 176 is a first in class, small molecule therapeutic candidate with novel Mechanism of Action (MOA) (disruption of protein-protein interactions) with the potential to directly induce apoptosis in cells dependent on MCL1 for survival. Furthermore, the activity of AMG 176 in pre-clinical models suggests that AMG 176 may have utility in hematological malignancies, particularly MM and AML.

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 inhibitory constant (Ki) of 0.00006 μmol/L (Caenepeel et al, 2018). 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 (Caenepeel et al, 2018). The profiling of a large and diverse panel of tumor cell lines revealed that AML cell lines were sensitive to MCL1 inhibition in vitro. This observation led us to test the hypothesis that the combinations of MCL1 inhibition with SOC agents may further sensitize AML tumors to treatment with an MCL1 inhibitor. We characterized the effects of MCL1 inhibition when combined with the BCL2 inhibitor venetoclax, cytarabine, decitabine, and doxorubicin in AML cell lines. A synergistic interaction was observed with all 4 combinations highlighting the potential for combining MCL1 inhibitors with SOC agents in AML (Caenepeel et al, 2018).

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 (Every 2 Weeks [Q2W]) schedule (Caenepeel et al, 2018). The combination of AMG 176 and the HMA 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, 2018). We also tested the combination of AMG 176 and venetoclax in the MOLM13 orthotopic AML xenograft model. Mice harboring MOLM13 tumors were treated twice weekly with AMG 176 (30 mg/kg) and daily with venetoclax (50 mg/kg). Whereas both single agents achieved significant reductions in tumor burden (55% and 23%, respectively), the combination exhibited complete inhibition of tumor burden and achieved regression relative to the first day of dosing (Caenepeel et al, 2018). In summary, these data highlight the promise of AMG 176 as a novel therapeutic for the treatment of AML, and also illustrate the potential of AMG 176 to be combined with AML SOC to improve clinical outcomes.

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 drug 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 Pharmacokinetics (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 rate of enzyme inactivation [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 (concentration of drug producing 50% inhibition [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 Drug-Drug Interactions (DDIs) by inhibition (eg, inhibition of CYP3A4 substrates), CYP3A4 induction and transporter mediated DDIs.

2.2.2.3 AMG 176 Preclinical 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 [IB]). 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 IB).

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. While no preclinical safety data exist for Once Weekly (QW) dosing, the twice weekly 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 2 ongoing clinical studies: Study 20150161, a phase 1, FIH, multicenter, nonrandomized, open-label, dose-exploration study in

subjects with R/R multiple myeloma and in subjects with R/R AML; and Study M16-785, a phase 1b study of venetoclax and AMG 176 in patients with R/R hematologic malignancies.

A phase 1, FIH study of AMG 176 (Study 20150161) is ongoing. As of 15 June 2021, preliminary data were available for 48 subjects with MM who had received at least 1 dose of AMG 176:

- Thirty-six subjects in Part 1a (once daily for two consecutive days [QD2] dosing schedule)
  - In Part 1a:
    - Four subjects in the 50 mg/m^2 cohort;
    - Three subjects each in the 30, 40, 60, and 120 mg/m^2 cohorts,
    - Two subjects in the 240 mg/m^2 cohort,
    - Four subjects each in the 120/180 mg/m^2 and 120/240 mg/m^2 cohorts, and
    - Five subjects each in the 120/360 mg/m^2 and 120/480 mg/m^2 cohorts.
- Twelve subjects in Part 1b (QW dosing schedule)
  - In Part 1b, 3 subjects each in 120/180, 120/240, 120/360, and 120/480 mg/m^2 cohorts.

Preliminary data were also available for 37 subjects with AML who had received at least 1 dose of AMG 176 (see also Section 2.3.1 for efficacy data):

- Fifteen subjects in Part 3a (QD2 dosing schedule)
  - In Part 3a, 5 subjects each treated in the 60, 120, and 120/180 mg/m^2 cohorts.
- Two subjects in Part 3 QW Japan (a dose cohort described in a country-specific supplement)
  - In Part 3 QW Japan, 2 subjects were in 120/180 mg/m^2 cohort
- Eight subjects in Part 3b (QW dosing schedule monotherapy at 120 mg/m^2)
- Four subjects in Part 3c (QW dosing schedule monotherapy at 120 mg/m^2 in Japan)
- Eight subjects in Part 4 (QW dosing schedule in combination at 60 mg/m^2 with azacitidine).

Since the safety cutoff, 5 Dose Level Review Meetings (DLRMs) have been held on Study 20150161 at the 120 mg/m^2 and 180 mg/m^2 monotherapy doses (Part 3b) and the 60 mg/m^2 and 120 mg/m^2 combination doses (Part 4); no concerning safety events (including elevations of troponin) and no DLTs were observed. Evaluation of the Part 4 180 mg/m^2 combination will be completed and results reviewed prior to opening enrollment at that dose level on this study.

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

2.2.3 Non-Amgen Non-Investigational Product Background: Azacitidine

2.2.3.1 Azacitidine Pharmacokinetics

The pharmacokinetics of azacitidine were studied following a single 75 mg/m^2 Subcutaneous (SC) dose and a single 75 mg/m^2 IV dose. Azacitidine is rapidly absorbed after SC administration, with peak plasma concentrations achieved in 0.5 hour. Mean half-life ($t_{1/2}$) after SC administration is 41 $\pm$ 8 minutes.

Urinary excretion is the primary route of elimination of azacitidine and its metabolites. In vitro studies indicate azacitidine may be metabolized in the liver. No formal clinical DDI studies with azacitidine have been conducted. In vitro studies indicate that azacitidine did not cause any inhibition of CYP2B6 and CYP2C8 or induction of CYP1A2, CYP2C19 or CYP3A4/5. Refer to the United States Prescribing Information (USPI) for additional information.

2.2.3.2 Azacitidine Clinical Experience

A randomized, open-label, controlled trial carried out in 53 U.S. sites compared the safety and efficacy of SC azacitidine plus supportive care with supportive care alone ("observation") in subjects with any of the 5 French – American – British subtypes (FAB) of MDS: Refractory Anemia (RA), RA with Ringed Sideroblasts (RARS), RA with Excess Blasts (RAEB), RAEB in Transformation (RAEB-T), and Chronic Myelomonocytic Leukemia (CMMoL). Subjects with acute myelogenous leukemia were not intended to be included. Baseline patient and disease characteristics of the 2 groups were similar. Azacitidine was administered at a SC dose of 75 mg/m^2 daily for 7 days every 4 weeks. The dose was increased to 100 mg/m^2 if no beneficial effect was seen after 2 treatment cycles. The dose was decreased and/or delayed based on hematologic response or evidence of renal toxicity.

The ORR (CR + Partial Remission [PR]) of 15.7% (14 out of 89) in azacitidine-treated subjects without AML (16.2% for all azacitidine randomized subjects including AML) was statistically significantly higher than the response rate of 0% in the observation group ($p < 0.0001$). The majority of subjects who achieved either CR or PR had either 2 or 3 cell line abnormalities at baseline (79%; 11 out of 14) and had elevated bone marrow blasts or were transfusion dependent at baseline.

Subjects in the observation group who crossed over to receive azacitidine treatment (47 subjects) had a response rate of 12.8%.

Additionally, a multi-center, open-label, single-arm study of 72 subjects with RAEB, RAEB-T, CMMoL, or AML was also carried out. Treatment with SC azacitidine resulted in a response rate (CR + PR) of 13.9%, using criteria similar to those described above. The mean and median duration of clinical response of PR or better was estimated as 810 and 430 days, respectively; 80% of the responding subjects were still in PR or better at the time of completion of study involvement.

In another open-label, single-arm study of 48 subjects with RAEB, RAEB-T, or AML, treatment with IV azacitidine resulted in a response rate of 18.8%, again using criteria similar to those described above. The mean and median duration of clinical response of PR or better was estimated as 389 and 281 days, respectively; 67% of the responding subjects were still in PR or better at the time of completion of treatment. Response occurred in all MDS subtypes as well as in subjects with adjudicated baseline diagnosis of AML in both of these studies. Azacitidine dosage regimens in these 2 studies were similar to the regimen used in the controlled study.

Benefit was seen in subjects who did not meet the criteria for PR or better but were considered "improved". About 24% of azacitidine-treated subjects were considered improved, and about 2/3 of those lost transfusion dependences. In the observation group, only 5 out of 83 subjects met criteria for improvement; none lost transfusion dependence. In all 3 studies, about 19% of subjects met criteria for improvement, with a median duration of 195 days. Response rate estimates were similar regardless of age or gender.

Azacitidine is commercial grade; refer to USPI for additional information.

Refer to the regional manufacturer package insert for additional information.

2.3 Benefit/Risk Assessment

Based on early evidence of clinical activity from the FIH study (20150161), nonclinical toxicity studies in AMG 176, and clinical safety experience, the overall benefit/risk profile supports the further clinical development of AMG 176 in combination therapy for subjects with HR-MDS/CMML. 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.

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. As of 23 April 2020, 17 subjects with R/R AML were enrolled in Part 3. Of these 17 subjects, 2 subjects in dose escalation have achieved incomplete Count Recovery (CRi), with AMG 176 treatment at the 60 mg/m^2 and 120 mg/m^2 QD2 dose levels. One subject achieved a PR at the 60 mg/m^2 QD2 dose. Since the 23 April 2020 data cut-off, additional subjects have been enrolled and analysis is ongoing. There have been no additional risks identified.

Preclinical data identified a synergistic effect with AMG 176 when given in combination with the HMA decitabine or venetoclax that resulted in an increase in anti-leukemic activity (see Section 2.2.2.1). Based on preclinical data, AMG 176 in combination with azacitidine therapy, a similar HMA, is anticipated to provide a new treatment option with the potential for better disease control with more Durable Responses (DR) that will lead to improved clinical outcomes for subjects with MDS/CMML.

2.3.2 Key Risks

At this time, there is limited clinical experience with AMG 176 in humans. Based on biological plausibility, nonclinical toxicity studies of AMG 176, and clinical safety experience, Tumor Lysis Syndrome (TLS), increased troponins, neutropenia, nausea, vomiting, and diarrhea have been determined to be identified risks.

Tumor Lysis Syndrome

Administration of AMG 176 has been associated with TLS with a fatal outcome. Subjects with a high tumor burden or compromised renal function (eg, International Staging System [ISS] Stage II/III) may be at elevated risk for TLS. The risk of TLS may increase in the setting of combinational therapy with azacitidine due to the anticipated increase in anti-leukemic 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 (Appendix 9) for specific recommendations regarding the mitigation and management of TLS.

Increased Troponin

Administration of AMG 176 has led to elevations of serum troponins. The exact cause and clinical effects of troponin increases observed during the use of AMG 176 are not

known. A cardiac monitoring plan has been implemented to mitigate the risk of troponin elevations and potential for cardiac toxicity. Refer to Section 11.10 (Appendix 10) and Section 11.11 (Appendix 11) for specific information regarding the cardiac monitoring plan and dose modification guidelines, respectively.

Potential Risks

In addition to the identified risks listed above, potential risks for AMG 176 based on nonclinical findings **include** reproductive toxicity-male, hepatobiliary toxicity, and cardiovascular toxicity (for details, see Section 2.2.2.3). In addition, bone marrow toxicity has been observed in non-clinical studies. While neutropenia has been identified as a risk, anemia and thrombocytopenia due to bone marrow toxicity remain a potential risk. Additional DDI risk is unknown at this time. 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 Investigator's Brochure for further description of potential risks.

There is significant clinical experience with azacitidine and it has an acceptable safety profile. Hematological toxicity, hepatotoxicity, and TLS are associated with azacitidine. Tumor Lysis syndrome is an identified risk and bone marrow toxicity and hepatobiliary toxicity are potential risks for AMG 176. The incidence and/or severity of these risks may increase when azacitidine and AMG 176 are given in combination. Refer to Section 6.2 for dose modification guidelines for both AMG 176 and azacitidine, as well as the approved product label of azacitidine.

Co-administration of AMG 176 with azacitidine is unlikely to result in DDIs based on in vitro studies (refer to azacitidine USPI and AMG 176 Investigators Brochure).

The above 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, and the respective Prescribing Information for further data on azacitidine.

3. Objectives and Endpoints/Estimands

Objectives	Endpoints
Primary	
Part 1A – QW Monotherapy (Dose Exploration)	

• Evaluate the safety and tolerability of AMG 176 once weekly (QW) monotherapy in subjects with R/R higher risk myelodysplastic syndrome (HR-MDS)	• Incidence of dose limiting toxicities (DLTs), treatment-related, treatment-emergent adverse events and clinically significant changes in vital signs, electrocardiogram (ECGs), and clinical laboratory tests
Part 1B – QW Combination Therapy (Dose Exploration)	
• Evaluate the safety and tolerability of AMG 176 in combination with azacitidine in subjects with R/R HR-MDS and determine the Optimal Biological Dose (OBD) and Minimum Safe and Biologically Effective Dose (MSBED) of AMG 176 in combination with azacitidine	• Incidence of DLTs, treatment-related, treatment-emergent adverse events and clinically significant changes in vital signs, ECGs, and clinical laboratory tests
Part 2 – QW Combination Therapy (Dose Expansion)	
• Evaluate the preliminary efficacy of AMG 176 in combination with azacitidine in subjects with R/R HR-MDS/CMML in: – HMA Failure, Venetoclax-Naïve – HMA Failure, Venetoclax-Exposed • To assess the preliminary efficacy of AMG 176 in combination with azacitidine in subjects with Newly Diagnosed MDS/CMML	• Overall response rate (ORR), according to the Uniform Response Criteria for Myelodysplastic/ Myeloproliferative Neoplasms (MDS/MPN), including: – Complete Remission (CR) – Partial Remission (PR) – Marrow CR – Cytogenic response
Secondary	
Part 1A – QW Monotherapy (Dose Exploration)	
• Evaluate preliminary efficacy of AMG 176 QW when given as monotherapy in R/R MDS/CMML	• Overall response according to the Uniform Response Criteria for MDS/MPN, Event-Free Survival (EFS), time to response, and Duration of Response (DOR)
• Evaluate the pharmacokinetics (PK) of AMG 176 when administered as monotherapy	• 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 ($t_{1/2}$)
Part 1B – QW Combination Therapy (Dose Exploration)	
• Evaluate preliminary efficacy of AMG 176 QW in combination with azacitidine in R/R MDS/CMML	• Overall response according to the Uniform Response Criteria for MDS/MPN, EFS, time to response, and DOR

• 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 $t_{1/2}$
Part 2 – QW Combination Therapy (Dose Expansion)	
• Evaluate the preliminary efficacy of AMG 176 in combination with azacitidine in subjects with R/R HR-MDS/CMML in: – HMA Failure, Venetoclax-Naïve – HMA Failure, Venetoclax-Exposed – To assess the preliminary efficacy of AMG 176 in combination with azacitidine in subjects with Newly Diagnosed MDS/CMML	• Time to transformation to Acute Myeloid Leukemia (AML) • Duration of Response (DOR) • Overall Survival (OS) • Time to Next MDS Treatment (TTNT) • EFS
• 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 $t_{1/2}$

4. Study Design

4.1 Overall Design

This study is a phase 1 clinical trial designed to assess the safety, tolerability, and efficacy of AMG 176 in combination with the 7-day regimen of azacitidine for the treatment of HR-MDS/CMML. Subjects will be treated with IV AMG 176 and IV or SC azacitidine. The study consists of 2 parts.

4.1.1 Part 1 – Dose Escalation/Determination of Optimal Biological Dose (OBD) and Minimal Safe and Biologically Effective Dose (MSBED)

In Part 1, the modified Toxicity Probability Interval (mTPI) design will be applied for dose escalation. Three dose levels of AMG 176 monotherapy will first be tested, and after the OBD is found, three dose levels of AMG 176 in combination with azacitidine will be tested.

After obtaining the monotherapy data from Part 1A, available data for monotherapy and combination therapy (with azacitidine) from the FIH study (Study 20150161) will also be leveraged to identify the MSBED for AMG 176. Dose exploration for AMG 176 in combination with azacitidine in Part 1B will then begin at the monotherapy MSBED -1 for AMG 176. The combination MSBED in Part 1B will be selected after an integrated assessment of all available clinical safety, efficacy, PK, and pharmacodynamic (PD) data for AMG 176 is performed, in order to select doses of AMG 176 that are likely to achieve the optimal benefit-risk profile.

Each dose cohort will initially enroll 3 to 4 subjects and up to 10 subjects per cohort may be enrolled. After reviewing all available safety data, dose level decisions (eg, escalation, de-escalation) will be made by the DLRT using mTPI model (Ji et al, 2010) based on all subjects that have been enrolled at the current dose. The DLRT may change the dose/dosing scheduled based on emerging data. The OBD/MSBED is defined as the minimum safe and biologically effective combination dose with a probability of DLT lower than or close to a targeted toxicity probability of 0.2.

Dose escalation is considered complete if one of the following rules is met:

1. The highest planned dose level is evaluated, OBD has not been defined, and no DLTs occur at any dose level. In this case, the Maximum Administered Dose (MAD) may be used for Part 2.
2. An OBD is identified.

Guidelines for dose level decisions can be found in Table 4-1. Details regarding the mTPI model are described in Appendix 14 (see Section 11.14).

Table 4-1. Guidelines for Dose Level Decisions in Part 1

	Number of DLTs		
No. of DLT-evaluable[a] subjects treated at current dose	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 100% of the planned doses of azacitidine, 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.

4.1.2 Part 2 – Dose Expansion

Upon completion of Part 1 of the study, the dose expansion phase will begin at the OBD/MSBED and drug administration schedule with the intention of confirming the safety and tolerability and determining the efficacy of AMG 176 in combination with azacitidine in not only R/R HR- MDS/CMML, but also in frontline HR-MDS/CMML. An additional 60 subjects will be enrolled in Part 2 of the study as follows:

- HMA Failure Cohort: stratified by venetoclax exposure history
    - HMA Failure, venetoclax-Naïve (n = 20)

  - HMA Failure, venetoclax-Exposed (n = 20)
- Newly Diagnosed (n = 20) – subjects will not be enrolled into this cohort until all previous cohorts have been completed and the data reviewed by the FDA.
  Toxicity will be monitored for each cohort using a Bayesian approach proposed by Thall, Simon, and Estey (1995).

The incidence of grade 3 or higher treatment-related non-hematological adverse events will be evaluated once every 5 subjects have had the chance to receive at least 1 cycle of treatment at the determined dose level for Part 2. Assuming a prior distribution of beta (1, 1), if the posterior probability that the incidence is greater than 20% is > 80% at these interim analyses, the study will stop early. The purpose of the safety interim analyses is to assess if the threshold for early termination has been reached. The stopping rules and operating characteristics are described in Table 4-2 and Table 4-3.

Table 4-2. Stopping Boundary for Each Cohort in Part 2

Number of subjects	Stop study if observing this number of subjects with grade 3 or higher treatment-related non-hematological adverse event
5 ~ 6	≥ 2
7 ~ 10	≥ 3
11 ~ 14	≥ 4
15 ~ 19	≥ 5
20	Completes

Table 4-3. Operating Characteristics in Part 2

True grade 3 or higher treatment-related non-hematological adverse event rate	Probability of early stopping
0.10	15%
0.15	32%
0.20	51%
0.25	69%
0.30	82%

Duration of Therapy

In the absence of treatment delays due to clinically significant study drug-related adverse events, treatment may continue until one of the following criteria applies:

- Clinically significant progressive disease. Subjects may continue therapy with either or both AMG 176 and azacitidine as long as they have stable disease, as long as, in the opinion of the treating physician and/or Principal Investigator (PI), the subject continues to derive clinical benefit and has otherwise not had an event requiring permanent discontinuation.
- Inter-current illness that prevents further administration of treatment.

- Subject decides to withdraw from the study.
- Excess toxicity that in the opinion of the PI would present a safety risk for further participation on the study.

Subjects may receive further courses of therapy not earlier than 4 weeks from the previous course, provided the subject has recovered from myelosuppression considered to be related to chemotherapy.

A minimum of one full course (or 4 weeks from the start of therapy) will be required for a subject to be considered as having received an adequate trial to evaluate efficacy. All subjects receiving at least one dose of any of the two drugs will be considered evaluable for toxicity. Subjects achieving a partial remission or with stable disease may continue on therapy until definite evidence of disease progression.

4.2 Patient Input into the Study Design

The overall study design is described by a study schema in Section 1.2. The endpoints are defined in Section 3.

Approximately 120 subjects will be enrolled in the study, with up to 60 subjects in Part 1 and up to 60 subjects in Part 2.

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

4.3 Justification for Dose

4.3.1 Justification for Investigational Product Dose

The starting dose of AMG 176 will be 120 mg/m^2 QW, which is based on prior clinical experience that demonstrated significant clinical safety and efficacy in subjects with AML (Section 2.2.2.4). Increased troponin is an identified risk with AMG 176 (Section 2.3.2). Troponin elevations in AML and MM subjects studied to date (Study 20150161) were reported primarily at higher dose levels of AMG 176 of 360 and 480 mg/m^2 as monotherapy when administered twice weekly using high sensitivity assays (Abbott Architect hs-cTnI) but were not observed for dose levels of 120 and 180 mg/m^2 administered weekly on a 3 out of 4 week dosing schedule. Additionally, AMG 176 was well-tolerated with no DLTs reported in subjects treated with 120 mg/m^2 monotherapy and 60 mg/m^2 in combination with azacitidine when administered weekly for 4 consecutive weeks each cycle. In this study, AMG 176 will be administered QW for 4 consecutive weeks each cycle. This 28-day duration is considered 1 cycle. Lead in dosing of 120 mg/m^2 will be utilized whenever the target dose level is at 180 mg/m^2 or higher.

4.3.2 Justification for Non-investigational Product Dose

The dose of azacitidine for the first treatment cycle, for all subjects regardless of baseline hematology laboratory values, is 75 mg/m^2 subcutaneously or intravenously, daily for the first 7 days of a 4-week cycle (as per local prescribing information). Prophylactic treatment to mitigate nausea and vomiting will be administered.

4.4 End of Study

An individual subject is considered to have completed the study if he/she has completed the last visit or the last scheduled procedure shown in the Schedule of Activities. The total study duration for an individual subject is 7.5 months from screening through the safety follow-up visit.

The end of study (EOS) 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), including any additional parts in the study (eg, long-term follow-up, additional antibody testing), as applicable.

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).

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions will not be provided.

5.1 Inclusion Criteria

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

101 Age ≥ 18 years of age.

102 Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2. Refer to Section 11.11.1 for more details.

103 For Part 1, patients have R/R MDS post-HMA failure, defined as prior receipt of 4 cycles of HMA therapy (including but not limited to decitabine, azacitidine, investigational HMAs such as SGI-110, and oral HMAs such as ASTX727 and CC-486) with failure to attain a response or progression of disease or relapse at any time after prior response to HMA therapy.

Note:

1) Patients with HR-CMML (CMML, CMML-1 or 2 by World Health Organization [WHO]) are eligible.

2) Hydroxyurea administration will be allowed on the study to lower the white cell count to ≤ 10 000/μL prior to the initiation of therapy.

104 For Part 2, patients will be divided into 2 cohorts:

a. HMA Failure Cohort: patients with R/R MDS post-HMA failure (defined as prior receipt of 4 cycles of HMA therapy with failure to attain a response or progression of disease or relapse at any time after prior response to HMA therapy) are eligible. Patients who have previously received venetoclax are eligible and will be stratified accordingly in the HMA Failure Cohort.

b. Newly Diagnosed Cohort: patients with treatment-naïve newly diagnosed HR-MDS (IPSS score ≥ 3.5) are eligible.

Note:

1) Patients with HR-CMML (CMML-1 or 2 by WHO) are eligible.

2) Hydroxyurea administration will be allowed on the study to lower the white cell count to ≤ 10 000/μL prior to the initiation of therapy.

3) Patients who have previously received venetoclax are eligible and will be stratified accordingly in the HMA Failure Cohort.

105 Must be willing and able to undergo bone marrow aspirate at screening.

106 Life expectancy of > 3 months, in the opinion of the investigator.

107 Hepatic function, as follows**:** AST, and Alanine Aminotransferase (ALT) < 3 X ULN, total bilirubin < 1.5 X ULN (except subjects with Gilbert's syndrome).

108 Cardiac function, as follows; Left Ventricular Ejection Fraction (LVEF) > 50% 2D transthoracic ECHO is the preferred method of evaluation. Multigated Acquisition (MUGA) scan is acceptable if ECHO is not available.

109 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.

110 Females must be surgically or biologically sterile or postmenopausal (amenorrheic for at least 12 months) or if of childbearing potential, must have a negative serum or urine pregnancy test within 72 hours before the start of the treatment. Female subjects of childbearing potential must agree to use highly effective methods of contraception (see Section 11.5) an adequate method of contraception during treatment and until 3 months after the last treatment.

111 Males must be surgically or biologically sterile or agree to use an adequate method of contraception during the study until 3 months after the last treatment.

5.2 Exclusion Criteria

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

Disease Related

201 Patients with newly diagnosed MDS with IPSS-R lower-risk category (IPSS score <3.5).

202 Patients with CMML-0 by WHO.

Other Medical Conditions

203 Myocardial infarction within 6 months of enrollment

204 Moderate to severe heart failure (New York Heart Association [NYHA] Functional Classification III, IV at baseline).

205 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.

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

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

208 Known or suspected Human Immunodeficiency Virus (HIV) infection or subjects who are HIV seropositive. Testing will be performed if required by local regulatory authorities.

209 Patient has chronic respiratory disease that requires continuous oxygen, or significant history of renal, neurologic, psychiatric, endocrinologic, metabolic, or immunologic condition.

210 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: 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.

Prior/Concomitant Therapy

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

212 Anti-tumor therapy: chemotherapy within 14 days (or 5 half-lives, whichever is shorter) of enrollment, antibody therapy, molecular targeted therapy, or investigational agent within 21 days (or 5 half-lives, whichever is shorter) of

enrollment. Exceptions: hydroxyurea to control peripheral blood leukemic cell counts is allowed until prior to receiving the first dose of AMG 176.

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

214 Patient has received a live attenuated vaccine within 4 weeks prior to the first dose of study drug. Patients who have received coronavirus disease 2019 (COVID-19) vaccine within **14** days prior to dosing, or plan to receive a COVID-19 vaccine within 28 days postdose; from 29 days postdose through EOS, vaccination for COVID-19 may be deemed acceptable for a subject following discussion and agreement between the sponsor and the investigator.

215 Use of any medications (except anti-tumor medications), including herbal medicines (eg, St. John's wort), vitamins, or supplements consumed by the subject within the 30 days prior to enrollment, and continuing use if applicable, that was not reviewed and approved by the PI and the Amgen Medical Monitor prior to enrollment. Written documentation of this review and Amgen acknowledgment is required for subject participation.

216 Use of known strong inhibitors of CYP3A4/P-gp within the 14 days or 5 half-lives (whichever is longer) or products containing grapefruit juice, Seville oranges, or St. John's wort within 7 days, 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.

217 Use of known CYP3A4 sensitive 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 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.

218 Use of known OATP1B1 and/or OATP1B3 or 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 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.

219 Major surgery within 28 days of enrollment.

Prior/Concurrent Clinical Study Experience

220 Currently receiving treatment in another investigational device or drug study, or less than 30 days since ending treatment on another investigational device or drug study(ies). Other investigational procedures while participating in this study are excluded.

Diagnostic Assessments

221 Subjects with elevated cardiac troponin above the manufacturer's 99th percentile upper reference limit for ADVIA Centaur XP TnI assay at screening performed by the central laboratory.

222 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.

223 Patient has a white blood cell count $> 10 \times 10^9$/L. Hydroxyurea or leukapheresis are permitted to meet this criterion.

Other Exclusions

224 Female subjects of childbearing potential unwilling to use highly effective methods of contraception (see Section 11.5) during treatment and for an additional 3 months after the last dose of investigational product.

225 Female subjects who are breastfeeding or who plan to breastfeed while on study through 3 months after the last dose of investigational product.

226 Female subjects planning to become pregnant while on study through 3 months after the last dose of investigational product.

227 Female subjects of childbearing potential with a positive pregnancy test assessed at Screening and/or day 1 by a highly sensitive urine or serum pregnancy test.

228 Male subjects with a female partner of childbearing potential who are unwilling to practice sexual abstinence (refrain from heterosexual intercourse) or use contraception during treatment and for an additional 4 months after the last dose of investigational product. Refer to Section 11.5 for additional contraceptive information.

229 Male subjects with a pregnant partner who are unwilling to practice abstinence or use a condom during treatment and for an additional 4 months after the last dose of investigational product.

230 Male subjects unwilling to abstain from donating sperm during treatment and for an additional 4 months after the last dose of investigational product.

231 Subject is fit and deemed eligible by the investigator for intensive salvage therapy.

232 Subject is eligible for HSCT.

233 Subject has known sensitivity to any of the products or components to be administered during dosing.

234 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, Clinical Outcome Assessments) to the best of the subject and investigator's knowledge.

235 History or evidence of any other clinically significant disorder, condition**,** or disease (with the exception of those outlined above) 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.

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.

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 Subject Enrollment Case Report Form (CRF).

Each subject who enters into the screening period for the study 14 days prior to day 1 receives a unique subject identification number before any study-related activities/procedures are performed. The subject identification number will be assigned manually. 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 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 enrolled in the study. A minimal set of screen failure information will be collected that includes demography, screen failure details, eligibility criteria, medical history, prior and concomitant (if subject experienced a serious adverse event) therapies, 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. Study Intervention

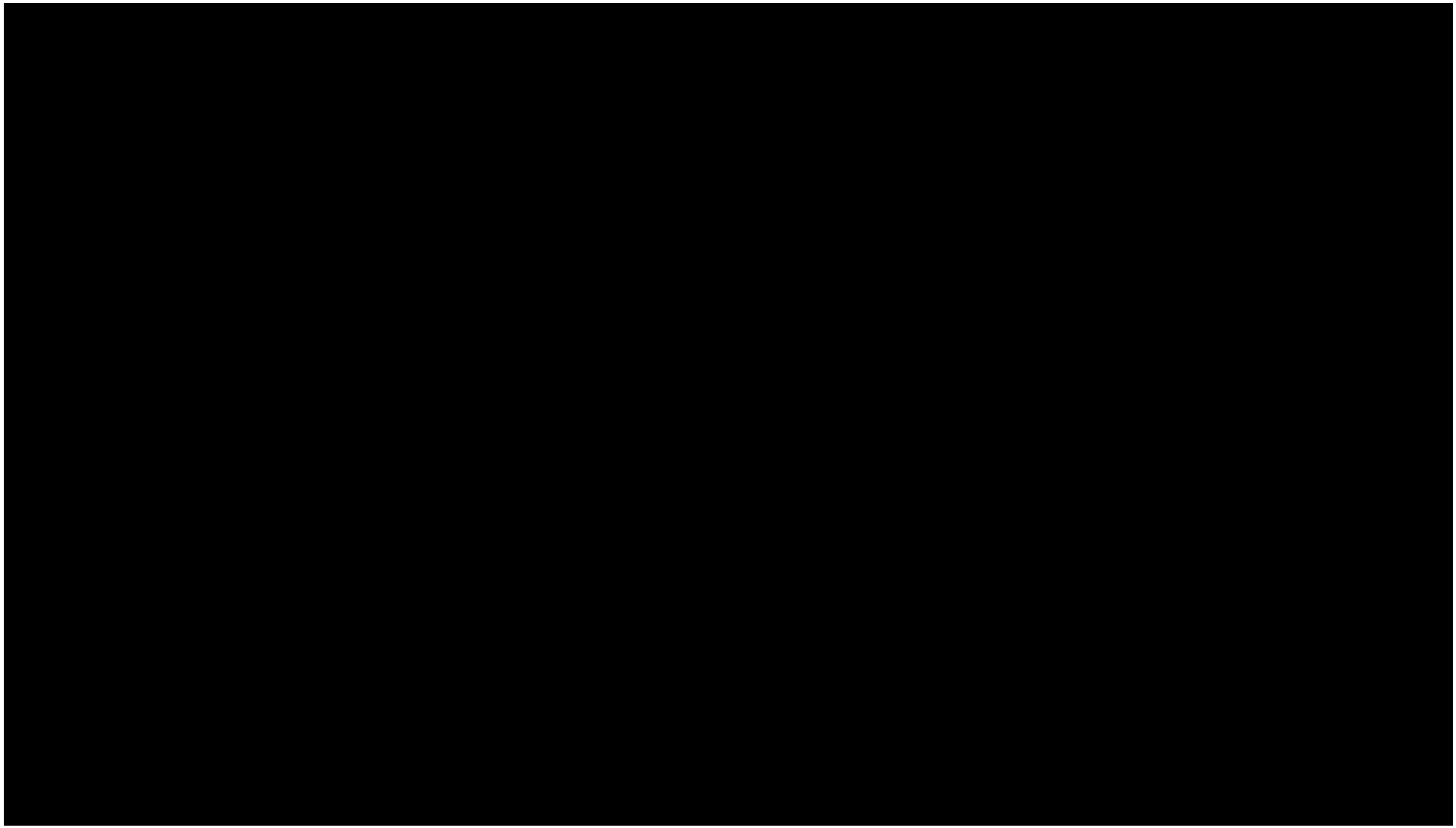
Study intervention is defined as any investigational product(s), non-investigational product(s), placebo, combination product(s), or medical device(s) intended to be administered to a study subject according to the study protocol.

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

A summary of the dosing and administration of each treatment is shown in Table 6-1 below.

6.1 Study Interventions Administered

6.1.1 Investigational Products



6.1.2 Non-investigational Products

The non-investigational product used in this study (azacitidine) may be considered investigational in some countries. Refer to regional prescribing information for full details.

Decisions regarding the AMG 176 lead-in dosing period regimen, lead-in period starting dose, dosing increments, will be made by DLRT and communicated to the IRB/IEC, as appropriate (see Section 11.3).

Azacitidine will be administered at 75 mg/m^2 IV over approximately 15 minutes or via subcutaneous injection daily for 7 days on days 1 to 7 of each treatment cycle. Treatment cycles will begin on day 1 of each new azacitidine cycle.

Azacitidine will be dosed based on actual body weight. However, at the treating physician's discretion, an adjusted body weight may be used, if the actual body weight is greater than 40% over the ideal body weight.

$$Adjusted\ body\ weight = 0.4(actual\ body\ weight - ideal\ body\ weight) + ideal\ body\ weight$$

The patient's baseline body weight will be used throughout treatment with consideration given to update the dosing weight for a weight change of greater than 10%.

After cycle 1, azacitidine may be subsequently administered at any of the Houston Area Locations (HALs) or at the patients' local oncologists' offices, and a schedule of 7 azacitidine doses within 9 days is allowed due to possible weekend closure of local offices. Patients will receive one course every 4 to 8 weeks; however, delays of more than 8 weeks may be allowed if determined by the investigator to be in the best interest of the patient after discussion with the PI and the discussion documented in the patient's medical record.

Azacitidine will be obtained from commercial sources. Please refer to the FDA prescribing information for azacitidine for further details.

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-Amgen 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 lead-in dosing (see Section 6.1.1) will be used and TLS prophylaxis must be initiated in all subjects prior to all lead-in dosing of AMG 176 and prior to all subsequent dose escalations (ie, first dose on the targeted cohort dose level). 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 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.

All subjects will be hospitalized to monitor for TLS and all TLS monitoring assessments will be performed as outlined in the Schedule of Activities (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.

- Hospitalization and monitoring, beginning the night before AMG 176 administration until at least 24 hours post-first AMG 176 dose.
- IV hydration must be started the night before AMG 176 administration and to be continued until at least 24 hours post–dose during hospitalization as clinically tolerated (refer to Section 11.9.3 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 lead-in 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.

All 24-hour laboratory assessments may be taken $\pm$ 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 Intervention 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, combination product, or device 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/non-investigational product provisioned and/or repackaged/modified by Amgen: AMG 176.

Any product complaint(s) associated with an investigational product or non-investigational product supplied by Amgen are to be reported.

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.
- 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 half-lives (whichever is longer) or products containing grapefruit, Seville oranges, or St. John's wort within 7 days, prior to enrollment.
- 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.
- Oral contraceptives (either combined or progesterone only), estrogenic vaginal ring/percutaneous contraceptive patches, or implants of levonorgestrel/injectable progesterone 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.

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.

6.2 Dose Modification

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

Dose Level Determination

A recommendation to escalate to a higher dose cohort will only occur when the previous dose regimen(s) has/have been found to be reasonably tolerated based on available study data through study day 28 for all subjects and upon unanimous agreement of the DLRT members. Available data from previous cohorts will also be considered. Dose level recommendations will be made on a treatment cohort basis (not on an individual basis). After receiving the DLRT recommendation, Amgen will render a final decision

and will issue a written notification of the dose change decision to investigators. Further information on DLRM is provided in Appendix 3 (Section 11.3).

6.2.1.1 Dose-limiting Toxicity Evaluation Period

The minimum DLT evaluation period is defined as 28-days 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 2) and completed the DLT evaluation period.

Subjects who do not complete 75% of the planned doses of AMG 176 (and 100% of the planned doses of azacitidine) 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 OBD/MSBED 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 MSBED determination and replaced at the discretion of the Medical Monitor.

6.2.1.2 Definition of Dose 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 Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 (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 5.0. 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 Part 1 unless clearly attributable to causes other than AMG 176 treatment.

If a DLT of TLS is observed during the lead-in period, it will be attributed to the lead-in period and a modification may be made to the lead-in period regimen for subsequent groups. Any other DLTs observed during the lead-in and/or designated group dosing period may require a modification of the designated cohort dose (and/or lead-in 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 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 6-2. DLT Criteria

	All Subjects
DLT Criteria	• 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 • Hematological adverse events: - Any grade 4 neutropenia and/or thrombocytopenia lasting ≥ 28 days from the start of cycle in the absence of active MDS or CMML • Any treatment-related death • Clinical TLS per Cairo-Bishop criteria (see Section 11.9.1) grade ≥ 3 not resolved to grade ≤ 2 within 7 days without end-organ damage • Severe DILI per the Hy's Law criteria (ie, AST or ALT ≥ 3 x ULN and serum bilirubin > 2 x 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] • QTcF interval ≥ 501 ms or an increase of > 60 ms from baseline on at least 2 separate ECG assessments • Asymptomatic, absolute decrease in LVEF of ≥ 10% from baseline AND LVEF < 50% • Asymptomatic, absolute decrease in LVEF of ≥ 20% from baseline • Symptomatic congestive heart failure

Footnotes defined on last page of the table

Table 6 2. DLT Criteria

	All Subjects
Exceptions	• 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

AE = adverse event; AML = acute myeloid leukemia; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CMML = chronic myelomonocytic leukemia; DILI = drug-induced liver injury; DLT = dose limiting toxicity; ECG = electrocardiogram; LVEF = left ventricular ejection fraction; MDS = myelodysplastic syndrome; QTcF = QT interval with Fridericia's correction; TLS = tumor lysis syndrome; ULN = upper limit of normal.

[a] Further treatment with AMG 176 may be considered for grade 1 elevations of troponin-I 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 determination, grading, and withholding decisions. The following criteria is developed based on CTCAE 5.0 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 Upper Reference Limit (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

Dose Cohort Stopping Rules

The DLRT will recommend stopping or modifying dosing if suspected adverse drug reactions, changes in vital signs, ECG, or clinical laboratory results are observed and these changes pose a significant health risk. The Amgen Medical Monitor may suspend dosing and convene a DLRM at any time based on emerging safety data.

Clinically or medically significant suspected adverse drug reactions, and serious adverse events considered to be related to study procedures will be followed until resolved or considered stable.

The study may be terminated at any point at the discretion of the sponsor.

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

For Hematologic Drug-Related Adverse Events (AE)

Dose reduction/interruption/discontinuation decisions should be based on the National Cancer Institute (NCI) CTCAE version 5.0 of the toxicity and the guidelines provided below. Dose modifications outside of those provided in Table 6-3 are allowable after discussion with the PI and documentation in the medical record, if in the best interest of the patient.

Patients with HR- MDS usually present with abnormal peripheral blood counts at the time therapy is started, and myelosuppression is an expected event during the course of therapy. Thus, no dose adjustments or treatment interruptions for myelosuppression will be planned in the presence of residual MDS. Dose-interruptions of azacitidine and AMG 176 in these patients should be considered on an individual case and discussed with the PI.

Patients with a response (with decline in blasts < 5%) who have prolonged (> 28 days) count recovery, may have the treatment with azacitidine and AMG 176 interrupted at the discretion of the treating physician after discussing with the PI until neutrophils recover to Absolute Neutrophil Count (ANC) is ≥ 500/µL and PLT to > 50 x10^9/L. Investigators should, whenever possible, determine which medication is causing the toxicity and interrupt or dose reduce azacitidine and/or AMG 176, as applicable. After interruption, dose adjustment for azacitidine, AMG 176, or both can be made as follows:

- A reduction of two dose levels or holding of AMG 176 on day 22 may be considered if the myelosuppression or was deemed severe and life threatening by the treating physician, and if it is in the patient's best interest.
- If additional dose reductions are thought to be necessary by the investigator, a discussion with the PI or co-PI is required on an individual case.

For Non-Hematologic Drug-Related AEs

Investigators should, whenever possible, determine which medication is causing the toxicity and interrupt or dose reduce azacitidine and/or AMG 176, as applicable. Dose reductions will be as per Table 6-3 recommendations. Dose reductions different than Table 6-3 are allowed if determined to be in the patient's best interest and rationale documented in patient record. The investigators will use their clinical judgment to determine whether toxicity is caused by azacitidine, AMG 176, or both. Dose reductions of one of the agents, or both, are allowed after discussion with the PI or co-PI and documentation in the medical record.

Table 6-3. Dose Adjustments for Non-hematologic AEs That Are at Least Possibly Related

Grade	Occurrence	Dose Modification
1 or 2	Anytime	No dose reduction
3 or 4 Persistent grade 2: consider similar dose adjustments if persistent and not responding to optimal management in the opinion of PI and treating physician	First and second time	• Hold AMG 176 ± azacitidine. • Resume AMG 176 ± azacitidine at prior dose if recovery to ≤ grade 1 occurs within 14 days. • If toxicity persists for 15 to 28 days, hold therapy and resume azacitidine and AMG 176 at prior dose if recovery to ≤ grade 1 or resume AMG 176 ± azacitidine at ONE dose level below current dose if recovery to ≤ grade 2.
	Third and fourth time	• Hold AMG 176 ± azacitidine. • Follow until toxicity ≤ grade 2. • Resume AMG 176 ± azacitidine at ONE dose level below current dose.
	Fifth time	• Hold AMG 176 ± azacitidine. • Follow until toxicity ≤ grade 2. • Resume AMG 176 ± azacitidine at TWO dose levels below current dose.

PI = Principal Investigator.

Other Modifications of Dose Schedules

- Further dose reductions can be made to prevent adverse events and keep clinically significant toxicities grade ≤ 2.
- Dose adjustments by more than one dose level at a time can be considered when judged in the best interest of the patient (eg, severe myelosuppression) when toxicity has resolved. The reason for this reduction will be discussed with the PI or co-PI and documented in the medical record.
- Treatment interruptions and dose modifications other than the ones mentioned above can be considered after discussion with the PI and proper documentation of the rationale. Dose adjustment/delay of only one of the agents is permissible if the toxicity is most likely judged to be related to one of the agents by the investigator.

Supportive Care

Supportive care measures including blood products, infection prophylaxis, and growth factors will be administered according to institutional and Leukemia Department guidelines.

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).

6.2.2.1.1 Dosage Adjustments

Upon completion of the lead-in 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 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 as a result of an adverse event. 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 Investigator and Amgen's medical monitor.
- For 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 to $<$ 0.78 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 (see Section 11.7)
- 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.

6.2.2.1.2 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.

6.2.2.1.3 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 x ULN or total bilirubin greater than 1.5 x 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 TnI manufacturer's prognostic cut-off) and $<$ 0.78 ng/mL, OR any change in the clinical status, above lab analytes (central or locally obtained), ECHO, 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 to $\leq$ 0.1 ng/mL do not require withholding or dose reductions, though troponins should be monitored with subsequent doses.
- Elevations from $>$ 0.1 to $<$ 0.78 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.
- Permanently discontinue AMG 176 for elevations $\geq$ 0.78 ng/mL.
  - 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.

6.2.2.1.4 Rules for Restarting

AMG 176 dosing can be resumed:

- If the adverse event resolves to grade $\leq$ 1 or return to subjects' baseline values.
  - For subjects meeting the withholding criteria for elevation of cardiac troponin ($>$ 0.1 to $<$ 0.78 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 investigators and Amgen's Medical Monitor.

6.2.2.1.5 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 arrhythmia possibly associated with AMG 176.
- Symptoms of clinically significant cardiac dysfunction (defined in Table 6-2), 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 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 (eg, treatment with ciprofloxacin) and antifungal (treatment with amphotericin B or echinocandins).

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.

6.2.2.2.2 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 Activities (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 arrhythmia related to AMG 176 administration, AMG 176 should be permanently discontinued.

6.2.2.2.3 Management of Gastrointestinal Toxicities

Nausea, vomiting, and diarrhea have been observed in a phase 1 FIH dose finding study (Study 20150161). 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.

6.2.2.2.4 Prophylaxis and Management of Tumor Lysis Syndrome

Refer to Section 11.9 for guidance.

6.2.2.2.5 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 TnI assay will be performed for all screening, grading, and withholding decisions.

6.2.2.3 Amgen/Non-Amgen Non-Investigational Product: Azacitidine

The reason for dose change of azacitidine 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.

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 x [baseline count - nadir count]).
- Subjects without reduced baseline blood counts (ie, White Blood Cells [WBC] $\geq 3.0 \times 10^9$/L and ANC $\geq 1.5 \times 10^9$/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 PLT $\geq 75.0 \times 10^9$/L, adjust the dose as follows, based on nadir counts for any given cycle (see Table 6-4):

Table 6-4. Azacitidine Hematology Dose Reduction Guidance

Nadir counts		
ANC (x 10^9/L)	Platelets (x 10^9/L)	% Dose in the Next Cycle
< 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 < 3.0×10^9/L, ANC < 1.5×10^9/L, or platelets < 75.0×10^9/L, dose adjustments should be based on nadir counts and bone marrow biopsy cellularity at the time of the nadir as noted below (see Table 6-5), 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 6-5. 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 Blood Urea Nitrogen (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.

6.2.3 Hepatotoxicity Stopping and Rechallenge Rules

Refer to Section 11.7 for details regarding DILI 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 drug accountability for the investigational product and/or other protocol-required therapies and/or devices will be provided to the site.

6.4 Measures to Minimize Bias: Randomization and Blinding

6.4.1 Method of Treatment Assignment

Subjects who meet eligibility criteria will be assigned to treatment with AMG 176.

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 directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the 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 Sections 6.2.2.1 and 6.2.2.2.5.

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

Prior therapies that were being taken from 2 years prior to enrollment through the informed consent should be collected. For prior therapies being taken for the disease under study (eg, steroids, chemotherapy on oncology studies), collect therapy name, indication, dose, unit, frequency, start date, and stop date. For all other prior therapies, collect therapy name, indication, dose, unit, frequency, route, start date, and stop date.

6.7.2 Concomitant Treatment

Throughout the study, investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care except for those listed in Section 6.1.7.

Concomitant therapies are to be collected from informed consent through the 30 days (+ 3 days) after the last dose of protocol-required therapies. For concomitant therapies being taken for the disease under study (eg, steroids, chemotherapy on oncology studies), assist in the evaluation of efficacy or safety endpoints, in a specific class, collect therapy name, indication, dose, unit, frequency, start date, and stop date.

For all other concomitant 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 electronic Case Report Form (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.

6.7.2.1 Antifungal Prophylaxis

Use of micafungin and amphotericin B for antifungal prophylaxis is allowed for neutropenic subjects.

6.7.2.2 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.

7. Discontinuation of Study Treatment and Subject Discontinuation/Withdrawal

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.

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 and/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 Table 1-1) 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 and/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.

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

- Decision by Sponsor
- Lost to follow-up
- Death
- Adverse event
- Subject request
- Ineligibility determined
- Protocol deviation
- Non-compliance (eg, procedural or dosing as defined in Section 6.1.1)
- Disease progression according to the Uniform Response Criteria for MDS/MPN, and/or per institutional guidelines as applicable
- Requirement for alternative therapy
- Pregnancy

7.2 Subject Discontinuation/Withdrawal 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 (Table 1-1) 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 should 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 Table 1-1).

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

8.1.1 Screening, Enrollment and/or Randomization

Informed consent must be obtained before completing any screening procedure or discontinuation of standard therapy for any disallowed therapy. After the subject has signed the informed consent form, the site will register the subject in the Interactive Response Technology (IRT) and screen the subject in order to assess eligibility for participation. The screening window is up to 14 days.

All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. The investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure, (see Section 5.4) as applicable.

If a subject has not met all eligibility criteria at the end of the screening period, the subject will be registered as a screen fail. Screen fail subjects may be eligible for re-screening 2 times.

Rescreen subjects must first be registered as screen failures in IRT and subsequently registered as rescreens. Once the subject is registered as rescreened, a new 14 day screening window will begin. Subjects will retain the same subject identification number assigned at the original screening. If the rescreening period begins more than 30 days after the original signing of the informed consent form, all screening procedures, including informed consent, must be repeated.

8.1.2 Treatment Period

Visits will occur per the Schedule of Activities (Table 1-1). On-study visits during cycles 1 and 2 should be done on the days specified, if possible. All subsequent visits beginning on cycle 3 may be completed within ± 1 day unless otherwise specified. The date of the first dose of AMG 176 is defined as day 1. All subsequent doses and study visits will be scheduled based on the day 1 date. Administration of AMG 176 is to be administered after all protocol-specific pre-dose assessments have been performed during each visit that it is required.

8.1.3 End of Treatment

The End of Treatment (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 (± 1 day). 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 (+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 (LTFU) assessments will occur every 3 months 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 LTFU visit will require an ECHO (see Section 8.4.5.1).

8.1.6 End of Study

A subject is considered to have completed the study if he/she has completed all phases of the study including the last LTFU visit shown in the Schedule of Activities or dies, whichever occurs first.

8.2 General Assessments

8.2.1 Informed Consent

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

8.2.2 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 biomarkers variability and pharmacokinetics of the protocol-required therapies.

8.2.3 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.

8.2.4 Physical Examination

Physical examination will be performed as per SOC. Physical examination findings should be recorded on the appropriate CRF (eg, medical history, event).

8.2.5 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).

8.2.6 Eastern Cooperative Oncology Group Performance Status

Eastern Cooperative Oncology Group Performance Status (ECOG PS) (Section 11.11) assessments will occur at time points specified in the Schedule of Activities (see Section 1.3).

8.3 Efficacy Assessments

8.3.1 Bone Marrow

Bone marrow aspirate will be performed for the following:

1. Hematocytology and cytochemistry to establish WHO subtype of MDS – local site laboratory according to local procedures using slides of bone marrow and peripheral blood.
2. Immunological phenotyping to verify myeloid leukemia. Additional immunological phenotyping and/or Minimum Residual Disease (MRD) will be performed/done at the investigator's discretion, for relapsed and/or for response confirmation.
3. Cytogenetics (gene expressions, gene mutations, cell culture and banding analysis) - a local laboratory may perform cytogenetics to determine eligibility at screening. Previous bone marrow aspirate or biopsy performed within 6 months of day 1 may be used to determine eligibility for subjects. A bone marrow biopsy or aspirate will still be required during screening for all subjects.
4. Additional cytogenetics will be performed/done at the investigator's discretion, for relapsed and/or for response confirmation.

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 results will be captured in the respective eCRFs.

8.3.2 Peripheral Blood

Blood samples will be collected for peripheral blood counts as per the Schedule of Activities (Section 1.3). Peripheral blood counts will include ANC, platelets, blasts, and hemoglobin (Hgb).

8.3.3 Disease Response

Disease response assessments will be based upon review of bone marrow aspirates, and peripheral blood count. Refer to the Uniform Response Criteria for MDS/MPN in Section 11.12 for additional details. Complete remission/CRi must be established from a bone marrow sample 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.

8.4 Safety Assessments

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

8.4.1 Vital Signs

The following measurements must be performed: systolic/diastolic blood pressure, heart rate, respiratory rate, pulse oximetry and temperature. Subject must be in a supine position in a rested and calm state for at least 5 minutes before blood pressure and pulse oximetry assessments are conducted. If the subject is unable to be in the supine position, the subject should be in most recumbent position as possible. The position selected for a subject should be the same that is used throughout the study and documented on the vital sign CRF. Oxygen saturation will be measured using a standard pulse oximeter. The temperature location selected for a subject should be the

same that is used throughout the study and documented on the vital signs CRF. Record all measurements on the vital signs CRF.

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.

8.4.2 Electrocardiograms (ECGs)

Subject must be in supine position in a rested and calm state for at least 5 minutes before ECG assessment is conducted. If the subject is unable to be in the supine position, the subject should be in most recumbent position as possible. Electrocardiograms should be performed in a standardized method, in triplicate, and run consecutively. Each triplicate, which consists of three 10-second tracings, should be completed within a total of five minutes from the start of the first to the completion of the third, prior to blood draws or other invasive procedures. Each ECG must include the following measurements: QRS interval (QRS), QT interval (QT), QTc, RR, and PR intervals (PR).

- Baseline ECGs should be collected at 3 timepoints ≥ 5 minutes apart, with each baseline ECG performed in triplicate, and with at least 5 minutes between the end of each triplicate and the start of the next (total 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: single ECG

The PI or designated site physician will review all ECGs. ECGs will be transferred electronically to an ECG central vendor for storage or for analysis per Amgen instructions. Once signed, the original ECG tracing will be retained with the subject's source documents. At the request of the sponsor, a copy of the original ECG will be made available to Amgen. 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.

8.4.3 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).

8.4.3.1 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.

8.4.3.2 Tumor Lysis Syndrome Laboratory Monitoring

Tumor lysis syndrome prophylaxis must be initiated prior to all lead-in 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. 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.

8.4.3.3 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.

8.4.4 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.

8.4.5 Other Safety

8.4.5.1 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 Magnetic Resonance Imaging (MRI) at baseline, EOT, and the first long-term follow-up visit is recommended. If cardiac imaging was performed within 30 days of C1D1, one does not need to be performed again at screening as long as the same modality is used throughout the study.

8.4.6 Adverse Events and Serious Adverse Events

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

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

8.4.6.1.1 Adverse Events

The adverse event grading scale to be used for this study will be the Common Terminology Criteria for Adverse Events (CTCAE) 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 the first dose of investigational product through the LTFU/EOS visit are reported using the Events CRF.

8.4.6.1.2 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 the **safety follow-up visit or 30 days after last day of dosing interval of investigational product(s)/protocol-required therapies, whichever is later,** are reported using the Events CRF.

All serious adverse events will be collected, recorded, and reported to the sponsor or designee within 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 within 24 hours of it being available.

Since the criteria of the CTCAE grading scale differs from the regulatory criteria for serious adverse events, if adverse events correspond to grade 4 CTCAE toxicity grading scale criteria (eg, laboratory abnormality reported as grade 4 without manifestation of life-threatening status), it will be left to the investigator's judgment to also report these abnormalities as serious adverse events. For any adverse event that applies to this situation, comprehensive documentation of the event's severity must be recorded in the subject medical records.

8.4.6.1.3 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 8.4.6.1.2) is complete, then these serious adverse events will be reported to Amgen within 24 hours following the investigator's awareness of the event on the Events CRF.

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 within 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.

8.4.6.2 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.

8.4.6.3 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 within 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.

8.4.6.4 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.

8.4.6.5 Safety Monitoring Plan

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

8.4.6.6 Pregnancy and Lactation

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

Details of all pregnancies and/or lactation in female partners of male subjects will be collected after the start of study treatment and until 4 months after the last dose of investigational product.

If a pregnancy is reported, the investigator is to inform Amgen within 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.

Pregnancy Testing

A highly sensitive (urine or serum) pregnancy test should be completed at screening and within 7 days of initiation of investigational product for females of childbearing potential.

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.

A pregnancy test should be performed should be performed as indicated in the Schedule of Activities (Section 1.3).

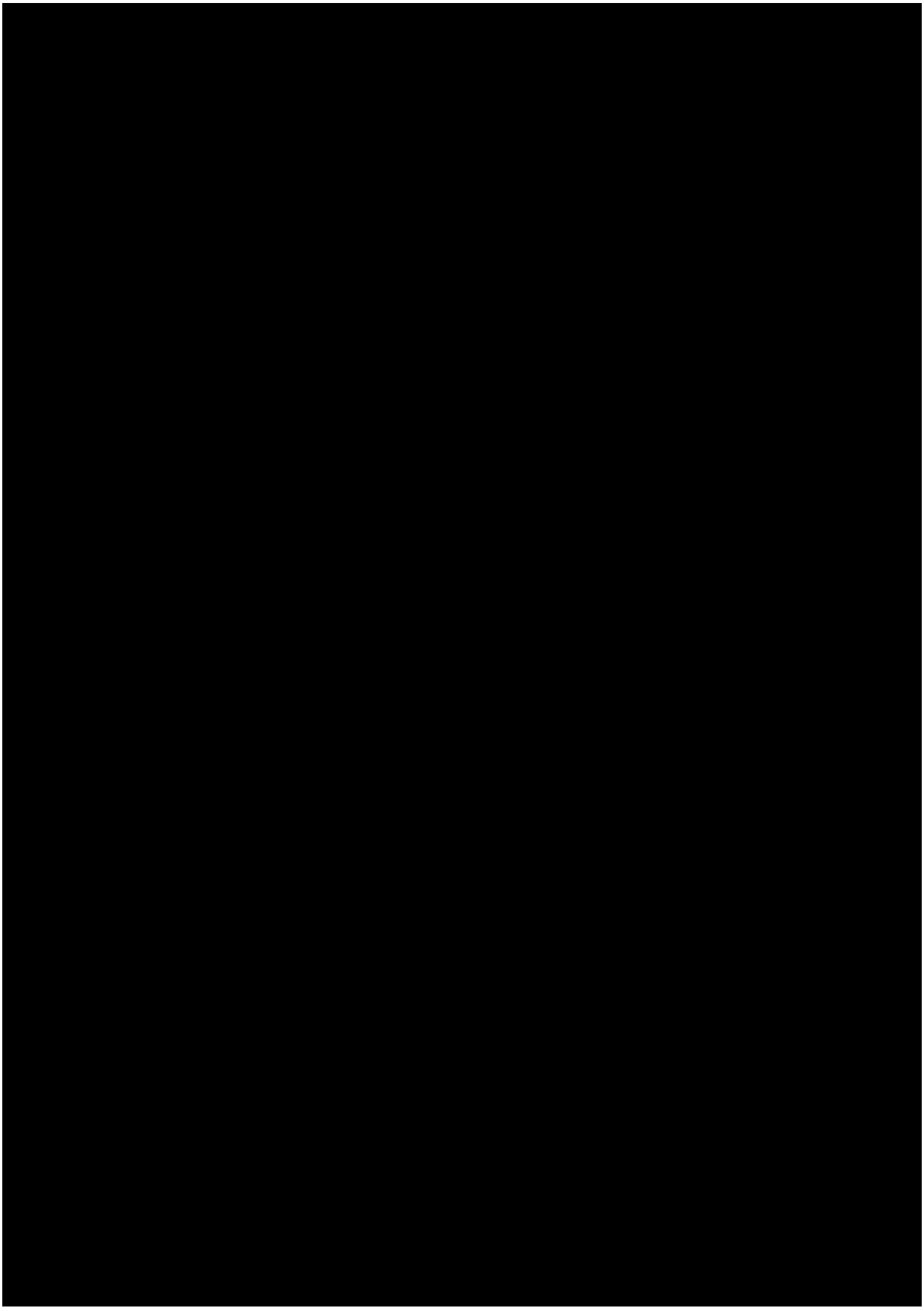
Additional on-treatment pregnancy testing may be performed at the investigator's discretion or as required per local laws and regulations.

8.5 Pharmacokinetic Assessments

All subjects enrolled will have pharmacokinetic samples assessed.

Blood samples of approximately 328 mL or 22.2 tablespoon will be collected for measurement of blood concentrations of AMG 176 as specified in the Schedule of Activities (Section 1.3). Instructions for the collection and handling of biological samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded. Sample collection, processing, storage, and shipping instructions are provided in a separate laboratory manual.

[redacted]



9. Statistical Considerations

9.1 Statistical Hypotheses

The clinical hypothesis is that at least 1 dose level of AMG 176 administered in combination with azacitidine will achieve acceptable safety and tolerability in subjects with HR-MDS. No formal statistical hypothesis will be tested.

9.2 Sample Size Determination

It is anticipated that up to 120 subjects will be enrolled in the study, with up to 60 subjects in Part 1 and 60 subjects in Part 2.

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 OBD/MSBED.

9.3 Populations for Analysis

The following populations are defined:

Population	Description
Full Analysis Set (FAS)	All subjects who are enrolled and receive at least one dose of the investigational product (AMG 176).
DLT Evaluable Set	Subjects are considered DLT-evaluable if they experience a DLT during the DLT evaluation period, or if they complete the DLT evaluation period and receive at least 75% of the planned doses of AMG 176 and 100% of the planned dose of azacitidine.

9.3.1 Covariates

There are no planned covariates in this study.

9.3.2 Subgroups

There are no planned subgroups in this study.

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 4.4.

9.4.1 Planned Analyses

9.4.1.1 Interim Analysis and Early Stopping Guidelines

No formal interim efficacy analysis is planned. Safety data will be reviewed on an ongoing basis. The DLRM will review all available data by cohort before making dose escalation recommendations. Details of dose escalation and stopping rules are described in Section 4.1.1.

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 AMG176.

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, and biomarker 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. 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

Endpoint	Statistical Analysis Methods
Primary	The ORR with corresponding 2-sided exact 95% CI will be calculated.
Secondary	Kaplan-Meier (KM) curve will be presented for OS, TTNT, EFS, DOR, **time to response** and time to transformation to AML.
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 incidence of DLT will be summarized for the DLT Evaluable Subjects. The primary analysis for each part will only include DLTs that occur within the protocol defined DLT evaluation period.

9.4.2.3.2 Adverse 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 discontinuation from investigational product or other protocol-required therapies, and ≥ grade 3 TEAEs will also be provided.

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 by cohort.

9.4.2.3.5 Physical Measurements

The analyses of physical measurements will include summary statistics over time by cohort.

9.4.2.3.6 Electrocardiogram

Summaries over time and/or changes from baseline over time will be provided for all ECG parameters. Subjects' maximum change from baseline in QTcF 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 listed and select parameters of interest plotted.

9.4.2.3.7 Antibody Formation

The incidence and percentage of subjects who develop anti-AMG176 antibodies at any time will be tabulated.

A listing of antibody results for all timepoints tested for each subject will be reported.

9.4.2.3.8 Exposure to Investigational Product

Descriptive statistics will be produced to describe the exposure to AMG 176. The number of cycles initiated, the treatment duration, cumulative dose, and average dose of AMG 176 will be summarized.

9.4.2.3.9 Exposure to Non-investigational Product

Descriptive statistics will be produced to describe the exposure to azacitidine. The number of cycles initiated, the duration of therapy and cumulative dose will be summarized.

9.4.2.3.10 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.

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.

Pharmacokinetic parameters for AMG 176 and azacitidine including, but not limited to, maximum observed concentration (C_{max}), minimum observed concentration (C_{min}), Area Under the plasma Concentration time curve (AUC), CL, and, if feasible, $t_{1/2}$ will be estimated using standard noncompartmental PK methods and summarized by dose groups using means, standard deviations, medians, minimums, and maximums for intensive and peak/trough determinations. Concentrations at each time point along with PK parameter values may be reviewed for each subject. Individual concentration-time profiles will be plotted by dose groups. Summary statistics will be computed for each sampling time and parameter as appropriate. 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, if feasible. Additional analyses to explore relationship between exposure and safety and exposure and efficacy may also be performed.

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11. Appendices

11.1 Appendix 1. List of Abbreviations

Abbreviation	Explanation
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ALT	alanine aminotransferase
AML	acute myeloid leukemia
ANC	absolute neutrophil count
AST	aspartate aminotransferase
ASTX727	cedazuridine
AUC	area under the curve
BAK	pro-apoptotic effector proteins BCL2 homologous antagonist/killer
BAX	pro-apoptotic effector proteins BCL2-associated X
BCL2	B-cell lymphoma/leukemia 2
BCRP	breast cancer resistance protein
BH3	pro-apoptotic BCL2 homology 3
BIM	BCL2-interacting mediator of cell death
BUN	blood urea nitrogen
CC-486	azacitidine
CFR	U.S. Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
CK-MB	creatine kinase-muscle/brain
CL	clearance
C_{max}	maximum concentration
CMML/CMMoL	chronic myelomonocytic leukemia
COVID-19	Coronavirus Disease 2019
CR	complete remission
CrCl	creatinine clearance
CRF	case report form
CRi	incomplete count recovery
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DDI	drug-drug interaction
DILI	drug induced liver injury
DLRM	dose level review meeting
DLRT	dose level review team
DLT	dose limiting toxicity

DOR	duration of response
DR	durable response
ECG	electrocardiogram
Echo	echocardiogram
ECOG PS	Eastern Cooperative Oncology Group Performance Status
eCRF	electronic case report form
EDC	electronic data capture
EFS	event-free survival
EOS	end of study
EOT	end of treatment
FAB	French – American – British subtypes
FAS	full analysis set
FDA	Food and Drug Administration
FIH	first in human
[redacted]	[redacted]
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
G-CSF	granulocyte-colony stimulating factor
GLP	good laboratory practices
GSO	Global Safety Officer
HALs	Houston Area Locations
HbcAb	hepatitis B core antibody
HbsAb	hepatitis B surface antibody
HbsAg	hepatitis B surface antigen
HCVAb	hepatitis C virus antibody
hERG	human ether-à-go-go-related gene
Hgb	hemoglobin
HI	hematologic improvement
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HMA	hypomethylating agent
HNSTD	highest-non-severely-toxic dose
HR	higher-risk
HSCT	hematopoietic stem cell transplant
IB	Investigator's Brochure
IC50	half-maximal inhibitory concentration
ICF	informed consent form
ICH	International Council for Harmonisation

ICJME	International Committee of Medical Journal Editors
IEC	Independent Ethics Committee
IND	Investigational New Drug
INR	international normalized ratio
IPSS	International Prognostic Scoring System
IPSS-R	Revised IPSS
IRB	Institutional Review Board
IRT	interactive response technology
ISS	International Staging System
ITT	intent-to-treat
IUD	intrauterine device
IUS	intrauterine hormonal-releasing system
IV	intravenous
IWG-MDS	International Working Group for the Prognosis of MDS
Ki	mean inhibitory constant
KM	Kaplan-Meier
LDH	lactate dehydrogenase
LVEF	left ventricular ejection fraction
MAD	maximum administered dose
MCL1	Myeloid Leukemia Cell 1
mCR	marrow/morphologic complete remission
MDS	myelodysplastic syndrome
MDSCs	Myeloid Derived Suppressor Cells
MM	Multiple Myeloma
MOA	mechanism of action
MOLM	acute monocytic leukemia (AML-M5a) cell lines
MOMP	mitochondrial outer membrane permeabilization
MPN	myeloproliferative neoplasm
MPN-SAF	MPN Symptoms Assessment Form
MRD	minimum residual disease
MRI	magnetic resonance imaging
MSBED	minimum safe and biologically effective dose
mTPI	modified Toxicity Probability Interval
MUGA scan	Multigated Acquisition scan
NCI	National Cancer Institute
NCT	National Clinical Trials
[redacted]	[redacted]
NK cells	natural killer cells

NT-pro BNP	N-terminal prohormone of brain natriuretic peptide
NYHA	New York Heart Association
OATP	organic anion polypeptide transporters
OBD	optimal biological dose
ORR	overall response rate
OS	overall survival
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
PFS	progression free survival
PI	principal investigator
PK	pharmacokinetics
PLT	platelets
PR	partial remission
PUMA	p53-upregulated modulator of apoptosis
Q2W	every 2 weeks
QD2	once daily for 2 consecutive days
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
QTc	corrected QT interval
QTcF	QT interval with Fridericia's correction
QW	once weekly
R/R	relapsed or refractory
RA	refractory anemia
RAEB	refractory anemia with excess blasts
RAEB-T	refractory anemia with excess blasts in transformation
RARS	refractory anemia with ringed sideroblasts
RBC	red blood cell
SAP	statistical analysis plan
SC	subcutaneous
siRNA	small interfering RNA
SOC	standard of care
STD	severely-toxic dose
$t_{1/2}$	half-life
TBL	total bilirubin
TI	transfusion independence
TLS	tumor lysis syndrome
TSS	Total Symptom Score

TTNT	time to next treatment
ULN	upper limit of normal
UPM	Unit Probability Mass
URL	Upper Reference Limit
USPI	United States Prescribing Information
Ven	venetoclax
WBC	white blood cells
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. 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). All locally obtained test results are to be recorded in the eCRF. Pharmacokinetic, [redacted].

Protocol-specific requirements for inclusion or exclusion of subjects are detailed in Sections 5.1 to 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

Central Laboratory		
PK [redacted] Bone marrow aspirate Bone marrow biopsy Cardiac enzymes including troponin-I, CK-MB, and NT-pro-BNP		
Local Laboratory		
Chemistry	**Hematology**	**Urinalysis**
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 Troponin (I or T) Uric acid Haptoglobin	ANC[a] Hematocrit Hemoglobin[a] MCH MCHC MCV Platelets[a] 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
	Coagulation	**Other Labs**
	PT or INR aPTT	Pregnancy HBsAg HBsAb HBcAb Hepatitis C antibody HCV PCR (if applicable) HBV PCR (if applicable)

ALP = alkaline phosphatase; ALT = alanine aminotransferase; 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; DILI = drug induced liver injury; 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; WBC = white blood cell.

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

If the subject is being followed for possible DILI, the following analytes may be tested at the local laboratory depending on the clinical situation (see Section 11.7):

Table 11-2. DILI Potential Analyte Listing

Chemistry	Total bilirubin, direct bilirubin, ALP, LDH, AST (SGOT), ALT (SGPT), creatine kinase, ferritin, gamma-glutamyl transferase, haptoglobin
Hematology	Hemoglobin, Platelets, RBC Morphology, WBC Count, WBC Differential
Coagulation	PT, INR
Immunology	5 Prime Nucleotidase, Alpha-1 Antitrypsin, Antinuclear Antibodies, Anti-Smooth Muscle Antibody, Anti-Soluble Liver Ag/Liver-Pancreas Ag, Cytomegalovirus IgG Antibody, Cytomegalovirus IgM Antibody, Endomysial IgA Antibody, Epstein-Barr Virus EDA IgG Antibody, Epstein-Barr Virus NA IgG Antibody, Epstein-Barr Virus VCA IgG Antibody, Epstein-Barr Virus VCA IgM Antibody, Hepatitis A Virus IgG Antibody, Hepatitis A Virus IgM Antibody, Hepatitis B Core Antibodies, Hepatitis B Core IgM Antibody, Hepatitis B Surface Antigen, Hepatitis B Virus DNA Genotyping, Hepatitis B Virus Surface Antibody, Hepatitis C Antibodies, Hepatitis C Virus RNA Genotyping, Hepatitis D Virus Antibody, Hepatitis E IgG Antibody, Hepatitis E IgM Antibody, Herpes Simplex Virus Type 1_2 IgG AB, Herpes Simplex Virus Type 1_2 IgM AB, Human Herpes Virus 6 DNA, Human Herpes Virus 7 DNA, Human Herpes Virus 8 DNA, Immunoglobulin G, Liver Kidney AB 1, Parvovirus IgM/IgG Antibody, Serum Caeruloplasmin, Tissue Transglutaminase IgA Antibody, Toxoplasma IgM/IgG, Varicella Zoster Virus Antibody
Toxicology	Acetaminophen

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; DILI = drug induced liver injury; EDA = ectodysplasin; Ig = immunoglobulin; INR = international normalized ratio; LDH = lactate dehydrogenase; NA = nuclear antigen; PT = prothrombin time; PTT = partial thromboplastin time; RBC = red blood cell; SGOT = serum glutamic-oxaloacetic transaminase; SGPT = serum glutamic-pyruvic transaminase; WBC = white blood cell

11.3 Appendix 3. Study Governance Considerations

Dose Level Review Team

Dose Level Review Meetings (DLRM)

A DLRM is conducted to review and interpret safety data for the purposes of making recommendations about dose-level escalation (either to the next planned dose or to an intermediate dose), dose level de-escalation, cohort continuation, or cohort expansion; making recommendations about non-dose escalation cohorts (eg, expanded, highest dose and/or final cohort); and evaluating safety signals for purposes of applying Dose Cohort Stopping Rules. The required DLRT members are the Medical Monitor, Global Safety Officer (GSO), and Site Investigators. The DLRT will include all Site Investigators. The Medical Monitor, GSO, and Site Investigators are the only voting DLRT members. The following non-voting Amgen representatives may also be part of the DLRT: clinical study manager, biostatistician; additional members may be added as needed (eg, clinical pharmacologist).

The Medical Monitor must be in attendance and cannot be represented by a voting designee or delegate. Voting designees can be identified as appropriate by the GSO or Site Investigator(s). A Site Investigator may identify a delegate (eg, sub-Investigator) who is listed in the Delegation of Authority. If a Site Investigator does this, the Site Investigator must provide written agreement with the designee or delegate's vote.

For a DLRM to occur, the Medical Monitor must attend, and the GSO or delegate must attend. In addition, a quorum of Site Investigators must be present. A quorum is defined as greater than or equal to 50% of the participating investigators or their qualified designee (ie, sub-investigator, research nurse or study coordinator possessing a hard copy document [eg, email] of the Investigator's vote regarding the dose level review; this email is required to be submitted to Amgen). The DLRM will be rescheduled if these requirements are not met.

All available study data, including demographics, IP administration, medical history, concomitant medications, adverse events, ECG, vital signs, laboratory results, and PK information will be reviewed. Data to be reviewed will be cleaned.

DLRM voting will occur as follows: there will be a total of 3 votes, 1 for the Medical Monitor, 1 for the GSO or delegate, and 1 for all of the Site Investigators or delegates combined. Regardless of how many Site Investigators there are, all of the Site

Investigators combined will have a total of 1 vote decided by a majority of the investigators (defined as greater than or equal to 50%).

DLRM recommendations to escalate to the next planned cohort, or to an intermediate cohort, must be by unanimous vote. If the voting members of the DLRT are not able to reach a unanimous recommendation on whether to escalate to the next planned cohort or to an intermediate cohort, then this should be reflected in the DLRM Memo. Other recommendations, such as expanding a cohort or lowering a dose will be made by a majority vote.

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 (CIOMS) 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.

During the course of the study, if new information becomes available that alters the benefit-risk of the study or the study drug, Amgen will follow applicable regulations to notify investigators, the IRB/IEC, and regulatory authorities, as appropriate.

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 U.S. 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 or 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 or their legally authorized representative defined as an individual or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical study 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 (HIPAA) 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 or a legally acceptable representative 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 rescreening 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.

The 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.

Subject data should be kept in a secure location. Access to subject data will be limited to authorized individuals, 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.

Amgen complies with all relevant and applicable laws and regulations that protect personal information in order to ensure subject confidentiality and privacy. Subjects are designated by a unique subject identification number in the Sponsor's systems. The Sponsor uses access-controlled systems to house, review and analyze subject data. These systems are backed-up regularly to minimize the risk of loss of subject data; procedures are also defined for data recovery in the event of data loss. The Sponsor

has standard operating procedures in place that restrict access to subject data to those who require access to this data based on their role and have also completed the required training. These procedures also outline the process for revoking access to such data when it is no longer needed. In the event of a security breach, the Sponsor has procedures in place for notification of privacy incidents and to address these incidents, via its Business Conduct Hotline.

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 Uniform Requirement for Manuscripts Submitted to Biomedical Journals International Committee of Medical Journal Editors (ICJME) 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 Investigator who provided significant contributions to either the design or interpretation of the study
- An Investigator 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 or certain demographic information, such as gender, race, and ethnicity).

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 pre-study 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.
- Non-investigational product documentation, 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 Investigator'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 a separate 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 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. • 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 MDS 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 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:
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 mandatory 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(s), other protocol-required therapies, and/or study-mandated activity and/or procedures;
  - 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 electronic case report form (eCRF).
- It is not acceptable for the investigator to send photocopies of the subject's medical records to the sponsor 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**, version 5.0 which is available at the following location:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

Assessment of Causality

- The investigator is obligated to assess the relationship between investigational product(s), protocol-required therapies, and/or study-mandated activity and/or procedure(s) 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

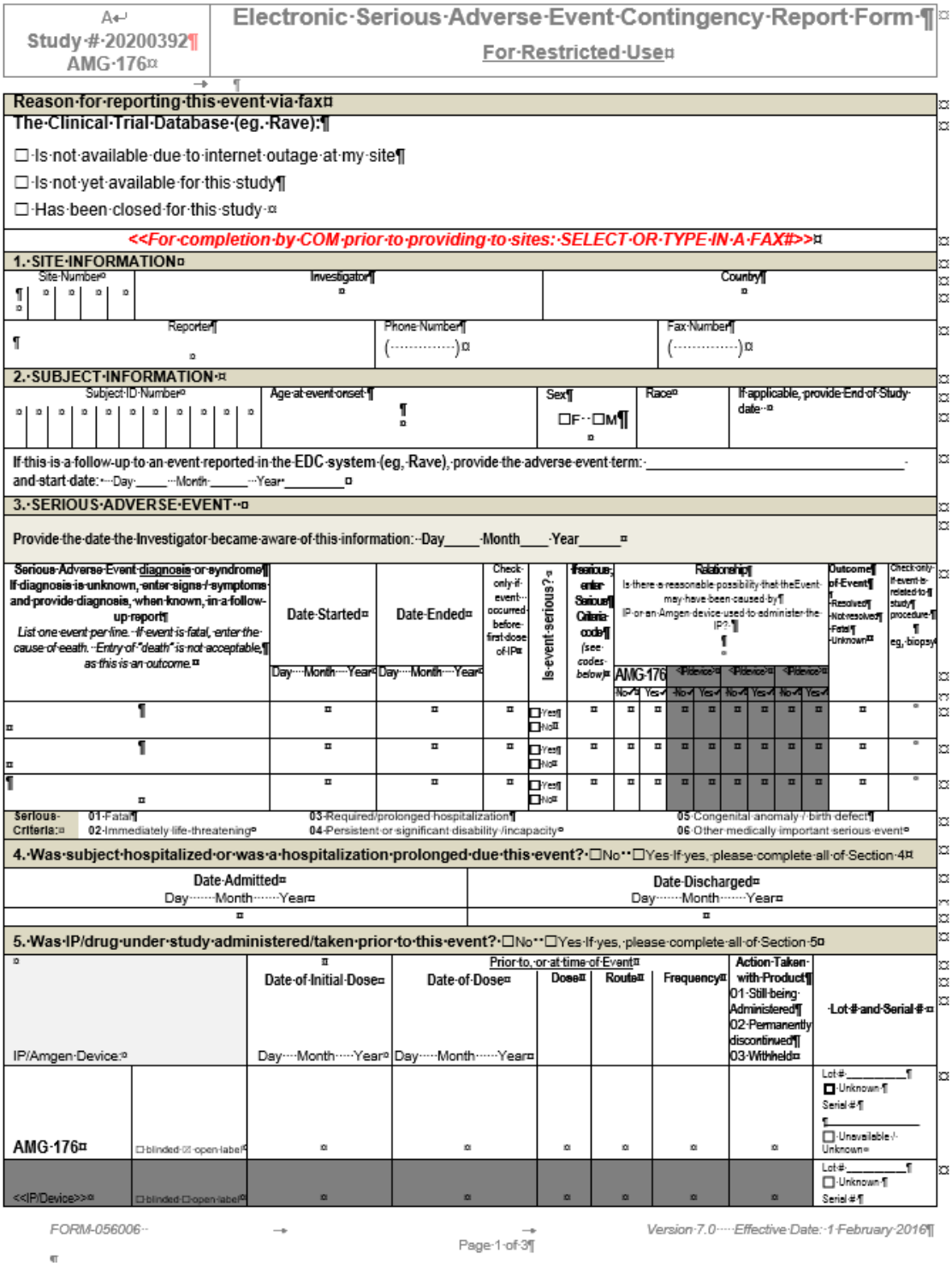
- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Amgen to elucidate the nature and/or causality of the adverse event or serious adverse event as fully as possible. This may include additional 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.
- [If a subject dies during participation in the study or during a recognized follow-up period, the investigator will provide Amgen with a copy of any post-mortem findings including histopathology.
- 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 within 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 a paper-based Serious Adverse Event Contingency Report Form (also referred to as the electronic Serious Adverse Event (eSAE) Contingency Report Form) (see Figure 11-1) within 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 system has been taken off-line, then the site can report this information on the paper-based Serious Adverse Event Contingency Report Form (see Figure 11-1).
- Once the study has ended, serious adverse event(s) suspected to be related to investigational product should 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 Report Form (paper-based form)



A
Study #: 20200392
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 ☐F ☐M | Race | If applicable, provide End of Study date

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?	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? AMG 176 No / Yes; <Placebo> No / Yes; <Placebo> No / Yes; <Placebo> No / Yes	Outcome of Event Resolved / Not resolved / Fatal / Unknown	Check only if event is related to study procedure, eg, biopsy
				☐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	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
<<IP/Device>>	☐ blinded ☐ open label							Lot #: _____ ☐ Unknown Serial #:

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☐ 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 Years	Stop Date Day Month Years	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:

Test / Unit / Date Day Month Year											

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

Page Break

A Study #:20200392 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

11.5 Appendix 5. Contraceptive Guidance and Collection of Pregnancy and Lactation Information

Study-specific contraception requirements for male and females of childbearing potential are outlined in Section 5.2. Contraceptive use and methods should be consistent with local regulations for subjects participating in clinical studies.

Female subjects of childbearing potential should be advised of the pregnancy prevention requirements and the potential risk to the fetus if they become pregnant during treatment and for **3** months after the last dose of protocol-required therapies.

Male subjects should be advised of the pregnancy prevention requirements and the potential risk to the fetus if they father a child during treatment and for 4 months after the last dose of protocol-required therapies.

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 documented hysterectomy, bilateral salpingectomy, and bilateral oophorectomy. Females with documented permanent infertility due to an alternate medical cause (eg, Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), can be considered not of childbearing potential.

Note: Bilateral tubal ligation/occlusion is not considered a permanent sterilization method.

Note: Documentation from the following sources is acceptable to provide confirmation of each sterilization method: 1) review of subject's medical records; 2) subject's medical examination; or 3) subject's medical history interview.

A postmenopausal female is defined as:

- A woman of ≥ 55 years with no menses for 12 months without an alternative medical cause OR
- A woman age < 55 years with no menses for at least 12 months and with a follicle-stimulating hormone (FSH) level within the definition of "postmenopausal range" for the laboratory involved. In the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.

Contraception Methods for Female Subjects

Highly Effective Contraceptive Methods

- 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, implantable).
- Intrauterine device (IUD).
- Intrauterine hormonal-releasing system (IUS).
- 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).

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 during treatment and for an additional 4 months after the last dose of protocol-required therapies.

The female partner should consider using a method of contraception for female subjects stated above (a female condom should not be used 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.

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 within 24 hours of the site's awareness 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 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 elective termination of a pregnancy for medical reasons will be reported as an adverse event or serious adverse event. Abnormal pregnancy outcomes (eg, spontaneous abortions, stillbirth, fetal death, congenital anomalies) 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.
- 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).

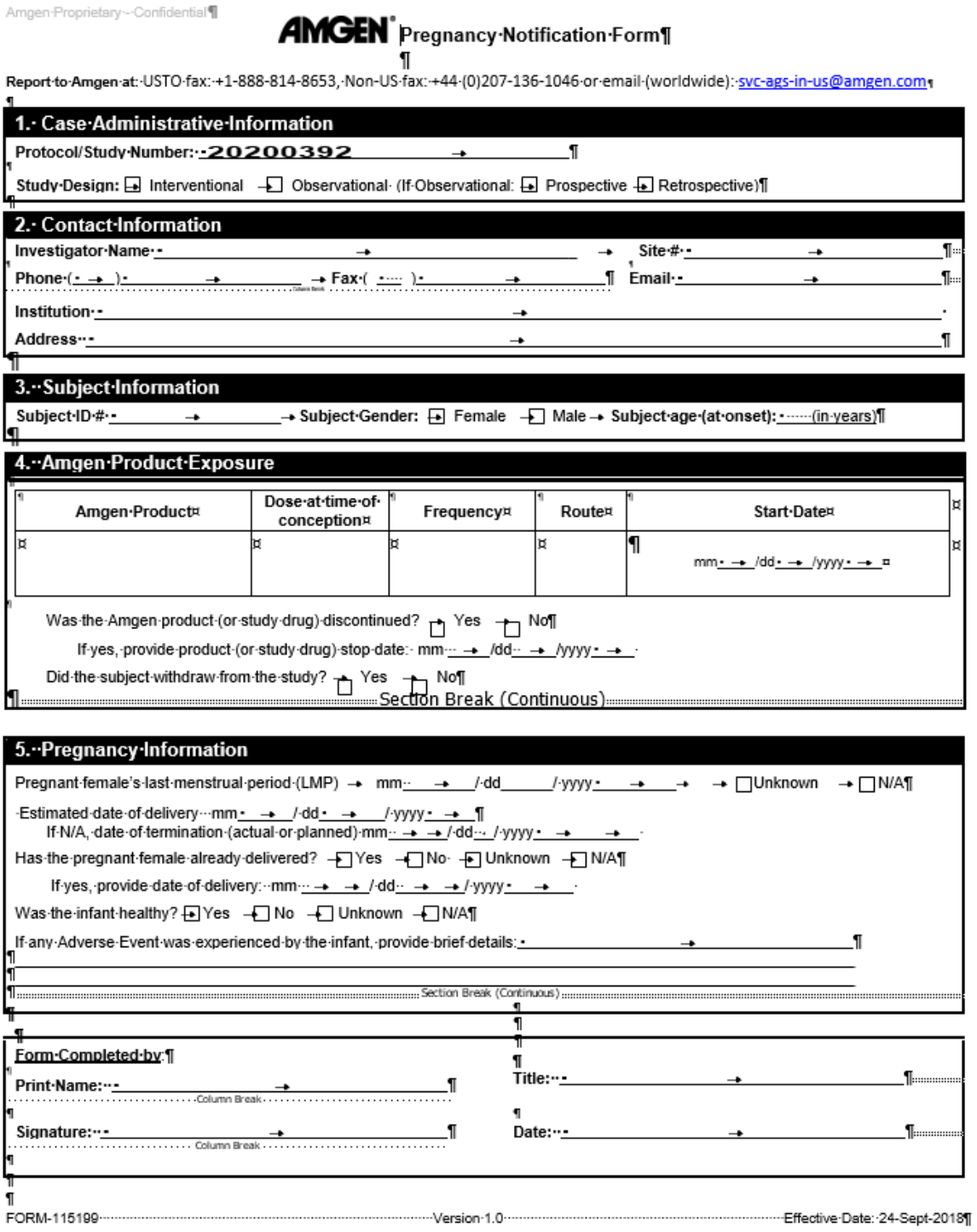
Male Subjects with Partners Who Become Pregnant

- In the event a male subject fathers a child during treatment, and for an additional 4 months after 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 within 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).
- Males with pregnant partners or whose partners become pregnant during treatment and for an additional 4 months after discontinuing protocol-required therapies must practice sexual abstinence or use a condom through 4 months after discontinuing protocol-required therapies.
- 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 within 24 hours of the investigator's awareness of the event.
- Study treatment will be discontinued if female subject breastfeeds during the study as described in exclusion criterion 225.
- 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 discontinuing protocol-required therapies.

Figure 11-2. Pregnancy and Lactation Notification Forms



Amgen Proprietary – Confidential

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: 20200392

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

Section Break (Continuous)

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: _____

Section Break (Continuous)

Form Completed by:

Print Name: _____ Title: _____

Column Break

Signature: _____ Date: _____

Column Break

FORM-115199 Version 1.0 Effective Date: 24-Sept-2018

AMGEN Lactation Notification Form

Report to Amgen at: US TO 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: 20200392

Study Design: ☐ Interventional ☐ Observational (If Observational: ☐ Prospective ☐ Retrospective)

Section Break (Continuous)

2. Contact Information

Investigator Name: _____ Site #: _____

Phone ( ) _____ Fax ( ) _____ Email: _____

Institution: _____

Address: _____

3. Subject Information

Subject ID #: _____ Subject age (at onset): _____ (in years)

Section Break (Continuous)

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: _____

Section Break (Continuous)

Form Completed by

Print Name: _____ Title: _____

Signature: _____ Date: _____

FORM-115201 Version 1.0 Effective Date: 24-Sept-2018

11.6 Appendix 6. Sample Storage and Destruction

Any blood and tumor sample 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) [redacted] 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.

[redacted]

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 biomarkers (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 11-3. 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	> 3x ULN at any time	> 2x ULN
		OR
INR	--	> 1.5x (for subjects not on anticoagulation therapy)
	OR	AND
AST/ALT	> 8x ULN at any time > 5x ULN but < 8x ULN for ≥ 2 weeks > 5x ULN but < 8x ULN and unable to adhere to enhanced monitoring schedule > 3x 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 > 3x ULN (when baseline was < ULN)
	OR	
ALP	> 8x 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.

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 11-2) 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 Case Report Form (CRF) (eg, Events 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 11-2 or who experience AST or ALT elevations > 3 x 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 > 2x 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. Protocol-specific Anticipated Serious Adverse Events

Anticipated serious adverse events are events that are anticipated to occur in the study population at some frequency independent of investigational product exposure and do not need to be reported individually as an FDA IND safety report by the sponsor. Identification and reporting of anticipated serious adverse events is the responsibility of the sponsor; the investigator is responsible for reporting adverse events and serious adverse events as described in Appendix 11.4.

Anticipated Serious Adverse Events for Study 20200392.02

Preferred Term[1]
Acute myeloid leukaemia
Acute myeloid leukaemia recurrent
Acute myeloid leukaemia refractory
Neutropenia
Anaemia
Thrombocytopenia
Leukocytosis
Leukopenia
White blood cell decreased
Hemoglobin decreased
Platelet count decreased
White blood cell increased

[1] MedDRA Version 24.0

11.9 Appendix 9. Tumor Lysis Syndrome

11.9.1 Cairo-Bishop Tumor Lysis Syndrome Definition and Grading

Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 classifies tumor lysis syndrome (TLS) in grade 3 (present), grade 4 (life threatening consequences; urgent intervention indicated) and grade 5 (death). Presence of TLS is not clearly defined by CTCAE version 5.0. Cairo and Bishop developed a system for defining and grading TLS based on Hande-Garrow classification of laboratory or clinical TLS (Coiffier et al, 2008). For this trial the Cairo-Bishop classification will be used to define presence of TLS, ie, presence of laboratory TLS (see Table 1-1) and clinical TLS (see Table 11-5) including grading as detailed below.

Based on the Cairo and Bishop system, laboratory TLS is present when levels of 2 or more serum values of uric acid, potassium, phosphorus, or calcium are more than or less than normal at presentation or if they change by 25% within 3 days before or 7 days after initiation of treatment (Section 1.3).

Table 11-4. Cairo-Bishop Definition of Laboratory Tumor Lysis Syndrome

Element	Value	Change from Baseline
Uric acid	≥ 476 µmol/L or 8 mg/dL	25% increase
Potassium	≥ 6.0 mmol/L or 6 mg/L	25% increase
Phosphorus	≥ 2.1 mmol/L for children or ≥ 1.45 mmol/L for adults	25% increase
Calcium	≤ 1.75 mmol/L	25% decrease

Note: Two or more laboratory changes within 3 days before or 7 days after cytotoxic therapy will constitute laboratory tumor lysis syndrome.

Clinical TLS requires the presence of laboratory TLS in addition to 1 or more of the following significant complications: renal insufficiency, cardiac arrhythmias/sudden death, and seizures (Table 11-5). The grade of clinical TLS is defined by the maximal grade of the clinical manifestations as detailed in Table 11-5.

Table 11-5. Cairo-Bishop Clinical Tumor Lysis Syndrome Definition and Grading

Grade	Creatinine[a, b]	Cardiac Arrhythmia[a]	Seizure[a]
0	≤ 1.5 x ULN	none	none
1	1.5 x ULN	intervention not indicated	--
2	> 1.5 – 3.0 x ULN	non urgent medical intervention indicated	one brief, generalized seizure; seizure(s) well controlled by anticonvulsants or infrequent focal motor seizures not interfering with ADL
3	> 3.0 – 6.0 x ULN	symptomatic and incompletely controlled medically or controlled with device (eg, defibrillator)	seizure in which consciousness is altered; poorly controlled seizure disorder; with breakthrough generalized seizures despite medical intervention
4	> 6.0 x ULN	life-threatening (eg, arrhythmia associated with CHF, hypotension, syncope, shock)	seizure of any kind which are prolonged, repetitive or difficult to control (eg, status epilepticus, intractable epilepsy)
5	Death	death	death

Note: Laboratory TLS and at least 1 clinical complication will constitute clinical TLS.
ADL = activities of daily living; CHF = congestive heart failure; TLS = tumor lysis syndrome, ULN = upper limit of normal
[a] not directly or probably attributable to therapeutic agent
[b] if no institutional ULN is specified, age/sex ULN creatinine may be defined as follows: > 1 to < 12 years of age, both male and female, 61.6 µmol/L; ≥ 12 to < 16 years, both male and female, 88 µmol/L; ≥ 16 years, female 105.6 µmol/L, male 114.4 µmol/L.

11.9.2 Tumor Lysis Syndrome Laboratory Monitoring

Tumor lysis syndrome prophylaxis must be initiated prior to all lead-in 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. Chemistry labs must include serum potassium, phosphorous, calcium, uric acid, and creatinine, and be performed for the following timepoints:

- AMG 176: pre-dose (within 4 hours before AMG 176 administration), 2, 4, 8, 12, and 24 hours after the start of AMG 176 infusion. Note: For AMG 176 180 mg/m^2 with lead-in dose: Subjects will also be hospitalized in week 2.
- Azacitidine: pre-dose, 6 to 8 hours after each new dose during ramp-up and 24 hours after reaching final dose

Since subjects on this trial may be at risk for developing TLS, measures will be implemented to help reduce and manage this risk, including staggered initiation of the two BH3 mimetics, ramp up dosing, and hospital admission during cycle 1 during the first doses of AMG 176 and azacitidine.

To further mitigate any possible risk of TLS, several measures will be implemented:

- Electrolyte levels, including serum potassium, calcium, phosphorous, and uric acid will be checked prior to treatment to make sure they are within the normal range. Hyperkalemia (Potassium > 5.0) should be corrected prior to starting therapy. Phosphate binders should be started (unless contraindicated) in subjects with elevated phosphorous.
- Subjects with medium (white blood cell [WBC] 10 to 20) risk for tumor lysis should be initiated on allopurinol (or other uric acid lowering treatment) prior to therapy. Subjects with n > 20 should have cytoreduction (with hydrea) or delay therapy to make sure the WBC to less than 20 prior to starting therapy in protocol. If the uric acid is elevated above 9, the patient should be given a dose of rasburicase per institutional protocol.
- Oral and when needed, IV hydration, will also be implemented per institutional standards to help mitigate the risk for TLS.

11.9.3 Prophylaxis and Management of Tumor Lysis Prophylaxis

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 per SOC. 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.
- All patients should have WBC count less than 25 x 10^9/L prior to initiation of azacit**i**dine. Cytoreduction prior to treatment may be required.
- Hospitalization and monitoring: beginning the night before AMG 176 administration until at least 24 hours post-first AMG 176 dose.
- Intravenous hydration must be started the night before AMG 176 administration and to be continued until at least 24 hours post–dose during hospitalization as clinically tolerated (see below 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 for:

  AMG 176:

  - Prior to the week 1, day 1 dose
  - Prior to each dose during the lead-in period
  - Prior to the initial dosing at the target dose level

  Azacitidine:

  - Pre-dose, 6 to 8 hours after each new dose during ramp-up, and 24 hours after reaching final dose
- Prior to administering these doses, all electrolyte values (including lactate dehydrogenase [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.
  - All 24-hour laboratory assessments may be taken ± 2 hours, if necessary.
  - Perform hematology labs at pre-dose (within 4 hours before AMG 176 administration) and 24 hours after the start of AMG 176 infusion.
  - 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.
- 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.

All subjects will receive TLS prophylaxis as described above. 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.

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 or azacitidine 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 ECG.

Vital signs should be taken at time of all blood draws or any intervention.

For subjects with risk factors for TLS (eg, circulating blasts, high burden of leukemia involvement in bone marrow, elevated pre-treatment LDH levels, or reduced renal function), consider additional measures, including increased laboratory monitoring and reducing azacitidine starting dose.

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.

Table 11-6. Tumor Lysis Syndrome Management Recommendations

Abnormality	Management Recommendations
Hyperkalemia (including rapidly rising potassium)	
• Potassium ≥ 0.5 mmol/L increase from prior value (even if potassium within normal limits [WNL])	• Recheck potassium, phosphorus, uric acid, calcium and creatinine in 1-hour 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 WNL, 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 x 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 x 1. • Administer insulin 0.1 U/kg IV + D25 2 mL/kg IV. • Administer sodium bicarbonate 1 to 2 mEq/kg IV push. If sodium bicarbonate is used, rasburicase should not be used as this may exacerbate calcium phosphate precipitation. • Administer calcium gluconate 100 to 200 mg/kg IV slowly if there is ECG/telemetry evidence of life-threatening arrhythmias. Do not administer in same IV line as sodium bicarbonate. • Recheck potassium, phosphorus, uric acid, calcium and creatinine every hour STAT.

Table 11-6. Tumor Lysis Syndrome Management Recommendations

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.

Table 11-6. Tumor Lysis Syndrome Management Recommendations

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.

Page 3 of 3

ECG = electrocardiogram; IV = intravenous; ULN = upper limit of normal
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. DOI: 10.1056/NEJMoa1513257

11.10 Appendix 10: Cardiac Monitoring

11.10.1 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. Local assessment should include troponin (I or T), CK-MB, and NT-pro-BNP. Serum samples are collected for centralized assessment. Central testing of troponin-I with ADVIA Centaur XP TnI assay will be performed for all screening, grading, and withholding decisions.

Grading of Troponin-I Elevation:

Central testing of cardiac troponin-I will be performed for eligibility determination, grading, and withholding decisions. The following criteria is developed based on CTCAE version 5.0 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 or 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

11.10.2 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 Activities (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 arrhythmia related to AMG 176 administration, AMG 176 should be permanently discontinued.

11.11 Appendix 11: ECOG Performance Status and NYHA Classification

11.11.1 Eastern Cooperative Oncology Group (ECOG) Performance Status

0	Fully active, able to carry on all predisease performance without restriction
1	Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (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

ECOG = Eastern Cooperative Oncology Group; NYHA = New York Heart Association.

11.11.2 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.

11.12 Appendix 12. Uniform Response Criteria for Myelodysplastic/ Myeloproliferative Neoplasms (MDS/MPN)

CR (presence of all of the following improvements)[a]

Bone marrow: ≤ 5% myeloblasts (including monocytic blast equivalent in case of CMML) with normal maturation of all cell lines and return to normal cellularity[a]

- Osteomyelofibrosis absent or equal to "mild reticulin fibrosis" (≤ grade 1 fibrosis)[b]
  - Peripheral blood[c]
    - WBC ≤ 10 x 10^9 cells/L
    - Hgb ≥ 11 g/dL
    - Platelets ≥ 100 x 10^9/L; ≤ 450 x 10^9/L
    - Neutrophils ≥ 1.0 x 10^9/L
    - Blasts 0%
    - Neutrophil precursors reduced to ≤ 2%
    - Monocytes ≤ 1 x 10^9/L

Extramedullary disease: Complete resolution of extramedullary disease present before therapy (eg, cutaneous disease, disease-related serous effusions), including palpable hepatosplenomegaly

Provisional category of CR with resolution of symptoms[c]: CR as described above, and complete resolution of disease-related symptoms as noted by the MPN Symptoms Assessment Form (MPN-SAF) Total Symptom Score (TSS)

Persistent low-level dysplasia is permitted given subjectivity of assignment of dysplasia[a]

Complete Cytogenetic Remission

Resolution of previously present chromosomal abnormality (known to be associated with myelodysplastic syndrome, myeloproliferative neoplasms, or MDS/MPN), as seen on classic karyotyping with minimal of 20 metaphases or FISH[d]

Partial Remission

Normalization of peripheral counts and hepatosplenomegaly with bone marrow blasts (and blast equivalents) reduced by 50%, but remaining > 5% of cellularity *except* in cases of MDS/MPN with ≤ 5% bone marrow blasts at baseline

Marrow Response

Optimal marrow response: Presence of all marrow criteria necessary for CR without normalization of peripheral blood indices as presented above

Partial marrow response: Bone marrow blasts (and blast equivalents) reduced by 50%, but remaining > 5% of cellularity, *or* reduction in grading of reticulin fibrosis from baseline on at least 2 bone marrow evaluations spaced at least 2 months apart

Clinical Benefit

Requires 1 of the following in the absence of progression or CR/partial response and independent of marrow response (cord blood response must be verified at ≥ 8 weeks) to be considered a clinical benefit

- Erythroid Response
  - Hemoglobin (Hgb) increase by ≥ 2.0 g/dL
  - Transfusion independence (TI) for ≥ 8 weeks for patients requiring at least 4 packed red blood cell transfusions in the previous 8 weeks
  - Only red blood cell transfusions given based on physician's judgment for a pretreatment Hgb of ≤ 8.5 g/dL will count in the red blood cell TI response evaluation[e]
- Platelet Response
  - Transfusion independence when previously requiring platelet transfusions of at least a rate of 4 platelet transfusions in the previous 8 weeks
  - Pretreatment ≤ 20 x 10^9/L: increase from < 20 x 10^9/L to > 20 x 10^9/L and by at least 100%
  - Pretreatment > 20 x 10^9/L but ≤ 100 x 10^9/L: absolute increase of ≥ 30 x 10^9/L[e]
- Neutrophil Response
  - Pretreatment ≤ 0.5 x 10^9/L at least 100% increase and an absolute increase ≥ 0.5 x 10^9/L
  - Pretreatment > 0.5 x 10^9/L and ≤ 1.0 x 10^9/L at least 50% increase and an absolute increase ≥ 0.5 x 10^9/L[e]
- Spleen Response

- Either a minimum 50% reduction in palpable splenomegaly of a spleen that is at least 10 cm at baseline or a spleen that is palpable at more than 5 cm at baseline becomes not palpable

- Symptom Response
  - Improvement in symptoms as noted by decrease of ≥ 50% as per the MPN-SAF TSS scoring < 20 were not considered eligible for measuring clinical benefit[f]

Progression

Requires at least one of the following in the absence of another explanation (eg, infection, bleeding, ongoing chemotherapy, etc.):

- **≥ 50% reduction from maximum response levels in granulocytes or platelets**
- **Reduction in hemoglobin by ≥ 1.5 g/dL**

Transfusion dependence

Relapse

Requires at least one of the following:

- **Return to pre-treatment bone marrow blast percentage**
- **Decrease of ≥ 50% from maximum response levels in granulocytes or platelets**
- **Transfusion dependence or hemoglobin level ≥ 1.5 g/dL lower than prior to therapy**

CMML = chronic myelomonocytic leukemia; CR = complete response; FISH = fluorescence in situ hybridization; Hgb = hemoglobin; IWG = International Working Group; MDS = myelodysplastic syndrome; MPN = myeloproliferative neoplasm; MPN-SAF = MPN Symptoms Assessment Form; TI = transfusion independence; TSS = Total Symptom Score; WBC = white blood cells

[a]Presence of dysplastic changes, which may be interpreted within the scope of normal range of dysplastic changes, may still exist in the presence of CR as allowed in MDS IWG. Marrow should exhibit age-adjusted normocellularity in CR.

[b]If there is no significant fibrosis present on the initial bone marrow biopsy, a second biopsy is not required to prove resolution of fibrosis. Grading of fibrosis in measurement of treatment response should be according to the European Consensus System.

[c]Given the current lack of a validated tool to assess complete resolution of symptoms in MDS/MPN, "CR with resolution of symptoms" (a complete resolution of disease-related symptoms as noted by the MPN-SAF TSS in presence of CR) will be a provisional category of disease response.

[d]Loss of cytogenetic burden of disease by (via FISH or classic karyotyping) known to adversely affect prognosis is required to reach complete cytogenetic remission. Decrease in the cytogenetic burden of disease must be by ≥ 50% (via FISH or classic karyotyping) to be indicative of a partial cytogenetic response. Given variability of fluorescent probes used in FISH, cytogenetic normalization via FISH will depend on the performance characteristics of the specific probes used.

[e]Resolution of abnormal peripheral blood counts must persist for at least 2 separate analyses over at least 8 weeks. In the case of proliferative MDS/MPN, CR will include resolution of thrombocytosis to a normal platelet count (150 to 450 x 10^9/L) and resolution of leukocytosis to WBC ≤ 10 x 10^9 cells/L but ≥ 1.5 x 10^9/L. Hemoglobin should be maintained > 11 g/dL and platelets ≥ 100 x 10^9/L without the support of transfusions. Clinical benefit may occur when these changes occur in absence of other changes required for CR or marrow response. Platelet and packed red blood cell TI would be considered for clinical benefit, and duration of TI should be monitored. Reduction in myeloid precursors (promyelocytes, myelocytes, metamyelocytes, nucleated red blood cells) to less than appreciable levels (≤ 2 to 3%) and/or 1 x 10^9/L monocytosis in the absence of infection, cytokine treatment, or other reactive causes.
[f]MPN-SAF TSS validation among patients with MDS/MPN is currently under way (Mesa, 2014).

11.13 Appendix 13. Medications That may Cause QTc Prolongation

List of medications known to cause corrected QT interval (QTc) interval prolongation is available at the following link: http://www.azcert.org/medical-pros/drug-lists/drug-lists.cfm

If participant 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 participant 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. 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[a]	> 24 hours, wide interpatient variability		
Arsenic trioxide	Not characterized		
Azithromycin	40 hours		
Bepridil	42 hours (26 to 64)		10
Chloral hydrate	Readily converted to Trichloroethanol (active metabolite $t_{1/2}$ = 7 to 10 hours)	48	
Chloroquine	Prolonged (days to weeks)		
Chlorpromazine	30 ± 7 hours		
Clarithromycin	Non-linear PK3 to 4 hr (250 mg Q12) 5 to 7 hr (500 mg Q12)	36	
Chloroquine	6 to 60 days; mean 20 days		
Desipramine[a]	> 24 hours, wide interpatient variability		
Disopyramide	6.7 hr (4 to 10)	36	
Dofetilide	10 hours	48	
Dolasetron	8.1 hours		
Domperidone	7 to 8 hours	48	
Doxepin[a]	> 24 hours, wide interpatient variability		
Droperidol	2.2 hours	10	

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Footnotes defined on the 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[a]		
Felbamate	20 to 23 hours		5
Flecainide	20 hours (12 to 27)		5
Foscarnet	87.5 ± 41.8 hours distribution and release from bone[a]		20
Fosphenytoin	12 to 29 hours		6
Gatifloxacin	7 to 14 hours	48	
Gemifloxacin	7 hours	48	
Grepafloxacin	16 hours		3
Halofantrine	6 to 10 days (variable among individual)		45
Haloperidol	18 ± 5 hours		5
Ibutilide	6 hours (2 to 12) variable among subject[a]	36	
Imipramine*	> 24 hours, wide interpatient variability		
Indapamide	14 hours (biphasic elimination)		3
Isradipine	8 hours (multiple metabolites)	48	
Levofloxacin	6 to 8 hours	48	
Levomethadyl	Multiple compartment PK with active metabolite 2.6 days for LAAM, 2 day for nor-LAAM, 4 day for dinor-LAAM		20
Lithium	24 hours (10 to 50)		7
Mesoridazine	24 to 48 hours (animal study)		10
Methadone	15 to 30 hours		7
Moexipril/HCTZ	2 to 9 hours (include active metabolite) for moexipril; 5.6 to 14.8 hours for HCTZ	48	
Moxifloxacin	12 ± 1.3 hours	72	
Naratriptan	6 hours	36	
Nicardipine	~ 2 hour post IV infusion	12	
Nortriptyline[a]	> 24 hours, wide interpatient variability		
Octreotide	1.7 hours	12	
Ofloxacin	5 to 7.5 hours		2
Ondansetron	4 hours (IV/IM); 3 hours (PO)		1 to 3
Pentamidine	6.4 ± 1.3 hours	36	
Pimozide	55 hours		10
Procainamide	3 to 4 hours for PA and NAPA (active metabolite)	24	
Protriptyline[a]	> 24 hours, wide interpatient variability		

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Footnotes defined on the last page of the table.

Compounds	Compound Half-life	Possible Washout Period – Hours	Possible Washout Period - Days
Quetiapine	6 hours	36	
Quinidine	6 to 8 hours in adult; 3 to 4 hours in children	36	
Quinine	4 to 5 hours		
Risperidone	3 to 20 hours (extensive to poor metabolizer) 9-hydroxyrisperidone (active metabolite) $t_{1/2}$ = 21 to 30 hours (extensive to poor metabolizer)		4
Salmeterol	5.5 hours (only one datum)	36	
Sotalol	12 hours	72	
Sparfloxacin	20 hours (16 to 30)		4
Sumatriptan	2.5 hours	12	
Tacrolimus	~ 34 hours in healthy; ~19 hours in Kidney transplant		7
Tamoxifen	5 to 7 days (biphasic)		30
Telithromycin	2 to 3 hours	24	
Thioridazine	20 to 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 to 3.7 hours (higher in female)	18	

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HCTZ = hydrochlorothiazide; IV = intravenous; IM = intramuscular; LAAM = levo-alpha-acetylmethadol; NAPA = N-acetylprocainamide; OVD = O-desmethylvenlafaxine; PA = procainamide; PK = pharmacokinetics; PO = once daily; Q12 = every 12 hours; QT = QT interval; $t_{1/2}$ = elimination half-life.

[a] 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 subjects 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

11.14 Appendix 14. Modified Toxicity Probability Interval Design

A modified Toxicity Probability Interval (mTPI) design will be used to guide dose exploration. The OBD/MSBED is defined as the minimum safe and biologically effective combination 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 OBD if the toxicity probabilities belong to the proper dosing interval (0.25, 0.35) which corresponds to staying at the current dose (S). The underdosing interval is defined as (0, 0.25) in which the doses are deemed lower than the OBD and corresponds to a dose escalation (E). The overdosing interval is (0.35, 1) in which the doses are deemed higher than the OBD 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 (1,1) 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 (up to 30 subjects in monotherapy part and up to 30 subjects in combination therapy part) are treated or all doses are determined to be intolerable.

Amendment 3

Protocol Title: A Phase 1 Study of AMG 176 as Monotherapy and in Combination with Azacitidine in Higher-Risk Myelodysplastic Syndrome and Chronic Myelomonocytic Leukemia

Amgen Protocol Number AMG 176 20200392

Amendment Date: 11 April 2022

Rationale:

The 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 URL to 0.059 ng/mL and maintaining the URL of 0.04 ng/mL for

females in relevant sections of the protocol. Minor changes were also made to clarify/correct other items in the protocol.

Changes include:

- Update to inclusion criterion #103 to separate the note for clarity.
- Update to inclusion criterion #104 to remove prior cohort completion and data review by FDA since the statement does not define eligibility, and to separate the note.
- Update exclusion criterion #214 to reduce COVID-19 vaccination time point prior to dosing from 28 days to 14 days.
- A clarification to remove biomarker from central lab testing was made to the schedule of activities (section 1.3) as the standard of care would be performed by the local laboratory.
- 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 6.2.2.2.5) and (section 11.10.1).
- Update to grading of troponin-I elevation (section 6.2.2.2.5) and (section 11.10.1) to align female and male requirements with assay manufacturer guidelines.
- Update to Uniform Response Criteria for Myelodysplastic/Myeloproliferative Neoplasm (section 11.12) to clarify the definition of progression and relapse
- Administration, typographical, and formatting changes were made throughout the protocol.

Amendment 2

Protocol Title: A Phase 1 Study of AMG 176 as Monotherapy and in Combination with Azacitidine in Higher-Risk Myelodysplastic Syndrome and Chronic Myelomonocytic Leukemia

Amgen Protocol Number AMG 176 20200392

EudraCT number: TBD

NCT Number: TBD

Amendment Date: 14 February 2022

Rationale:

This protocol is being amended to include changes as described in Amgen's response to the Food and Drug Administration (FDA) potential hold comments and deficiencies received on 19 November 2021. Changes include the following:

- Addition of a 240 mg/m^2 dose level to Part 1A and Part 1B.
- Minor formatting, administrative, and typographical edits.

Amendment 1

Protocol Title: A Phase 1 Study of AMG 176 as Monotherapy and in Combination with Azacitidine in Higher-Risk Myelodysplastic Syndrome and Chronic Myelomonocytic Leukemia

Amgen Protocol Number AMG 176 20200392

EudraCT number: TBD

NCT Number: TBD

Amendment Date: 25 October 2021

Rationale:

This protocol is being amended to include changes as described in Amgen's response to the Food and Drug Administration (FDA) potential hold comments and deficiencies received on 06 October 2021. Additionally, required safety template language was added in Section 8.4.6. Changes include the following:

- Revision of dose-limiting toxicity (DLT) criteria as per FDA's recommendations, specifically cardiac DLTs, hematologic DLTs, and DLTs related to tumor lysis syndrome (TLS).
- Revision of the targeted toxicity probability to 0.2 as well as revision of the modified Toxicity Probability Interval (mTPI) based guidelines for dose level decisions.
- Revision of dose expansion stopping rules.
- Revision of the protocol to indicate the primary objective is to find the Optimal Biological Dose (OBD), rather than the maximum tolerated dose (MTD), escalating to the Minimum Safe and Biologically Effective Dose (MSBED).
- Clarified the number of dose reductions a subject is eligible for.

- Revision of protocol Section 2.2.2.4, AMG 176 Clinical Experience, to summarize the available data from the ongoing Study 20150161, Part 4, for AMG 176 (60 and 120 mg/m^2 dose) in combination with azacitidine.
- Revision throughout the protocol to clarify that subjects will not be enrolled into the "Newly Diagnosed" cohort in Part 2 until all previous cohorts have been completed and the data reviewed by the FDA.
- Revision of the response criteria to utilize the Uniform Response Criteria for Myelodysplastic/Myeloproliferative Neoplasms (MDS/MPN) as included in Appendix 12 of the protocol.
- Revision to Section 4.1.2 to clarify that subjects may remain on treatment with either or both AMG 176 and azacytidine as long as, in the opinion of the investigator, the subject continues to derive clinical benefit and has otherwise not had an event requiring permanent discontinuation.
- Revision to remove the enrollment requirement of blast count of ≥ 5% in patients who are otherwise eligible.
- Revision to include required template safety reporting language in Section 8.4.6.
- Administrative, typographical, and formatting changes throughout the protocol.