Statistical Analysis Plan

Protocol Title:	A Phase 1 First in Human Study Evaluating the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of AMG 176 in Subjects With Relapsed or Refractory Multiple Myeloma and Subjects With Relapsed or Refractory Acute Myeloid Leukemia
Short Protocol Title:	A Phase 1 First in Human Study Evaluating the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of AMG 176
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Version Number	Date (DDMMMYYYY)	Summary of Changes, including rationale for changes
Original (v1.0)	20NOV2015	
Amendment 1 (v2.0)	16MAY2017	
Amendment 2 (v3.0)	26MAY2021	• Updates made as per protocol amendment 11 superseding o Study design: Closed enrollment for Parts 1A , 1B, 3A and added Parts 3B, 3C, 3D and 4. o Sample size section. • Removed the definitions not related to analysis; updated the definitions (DOR, EFS, PFS, OS, TTR, etc.) per Data Element Standards. • Updated the Treatment Emergent Adverse Event definition as per the DES version 8.0 and DLT Evaluable Analysis Set definition. • Added analyses related to the adverse events of COVID-19 • Updated the imputation rules for non-pharmacokinetic measurements above or below the upper quantification limits. • Added the approach on how to handle subjects proceeding to a higher dose or crossover from monotherapy to a combination therapy cohort. Added dose proportionality analysis.
Amendment 3 (v4.0)	12NOV2024	• Updates made based on protocol amendment 16 o QD2 updated to BIW. o Added part 5 (BIW) objective and endpoint; also added exploratory objective and endpoints. o Updated text in the study design. o Updated sample size • Updated definition of overall response rate for MM and AML. • Added dose intensity and relative dose intensity in definition and exposure to investigational product and non-investigational product. • Censoring rule for PFS has been updated in definition. • Interim efficacy analysis set added in section 6.7.1. • Included the text “Interim safety analyses will be performed to support the evaluation of safety by the DLRT” in section 7.1. • Added additional interim analyses information in section 7.1.

		• Added Exploratory endpoint in the section 9.5.3 • Updated the layout in section 9.6.1 • Updated MedDRA version from 24.0 to 26.1 • Added details in section 9.6.9 • Added details in section 9.6.10 • Added Appendix B • Updated section 10 Changes From Protocol-specified Analyses

Table of Contents

List of Abbreviations

Abbreviation or Term	Definition/Explanation
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AML	acute myeloid leukemia
AST	aspartate aminotransferase (SGOT)
AUC	area under the concentration-time curve
$AUC_{0\text{-}168\ hr}$	area under the concentration-time curve from 0 to 168 hours
BAK	B-cell receptor associated kinases
BAX	B-cell lymphoma/leukemia 2 associated X protein
BCL2	B-cell lymphoma/leukemia 2
BCL2-L1	BCL2 like 1
BCL-XL	B-cell lymphoma extra large
BIW	twice weekly
CL	Clearance
C_{max}	maximum observed concentration
C_{min}	minimum observed concentration
COVID-19	coronavirus disease 2019
CPMS	**clinical pharmacology modeling and simulation**
CR	complete response
CrCl	creatinine clearance
CRi	incomplete hematologic recovery; complete response/remission with incomplete recovery of peripheral blood counts
CRF	case report form
CRO	contract research organization
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP3A4	Cytochrome P450 3A4
DDI	drug-drug interaction
DLRM	dose-level review meeting
DLRT	dose-level review team
DLT	dose-limiting toxicity
DOR	duration of response
DBP	diastolic blood pressure
ECG	electrocardiogram
ECHO	echocardiogram

Abbreviation or Term	Definition/Explanation
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EFS	event free survival
ELN	European LeukemiaNet
FAS	Full Analysis Set
FIH	first in human
FISH	fluorescent in situ hybridization
FSH	follicle stimulation hormone
heart rate/HR	number of cardiac cycles per unit of time
IMWG	International Myeloma Working Group
IMWG-URC	International Myeloma Working Group - Uniform Response Criteria
IQR	**interquartile range**
IV	intravenous or roman numeral 4
MCL1	myeloid cell leukemia sequence 1
MedDRA	Medical Dictionary for Regulatory Activities
MFI	medium fluorescent intensity
MLFS	morphologic leukemia free state
MM	multiple myeloma
MRD	minimal residual disease
MRD[-]	minimal residual disease negativity
MTCD	maximum tolerated combination dose
MTD	maximum tolerated dose
mTPI	modified Toxicity Probability Interval
MUGA	multigated acquisition scan
OBD	optimal biological dose
OR	overall response
OS	overall survival
PD	pharmacodynamics
PFS	progression free survival
PK	Pharmacokinetics
PR	partial response
PR interval	PR interval is measured from the beginning of the P wave to the beginning of the QRS complex in the heart's electrical cycle as measured by ECG or partial response
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

Abbreviation or Term	Definition/Explanation
QT	QT interval is a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle as measured by ECG
QTc	QT interval corrected for heart rate using accepted methodology
QTcF	QT interval corrected for heart rate using Fridericia's formula
QW	once weekly
R/R	relapsed or refractory
RP2D	recommended phase 2 dose
RUNX1	runt-related transcription factor 1
SBP	systolic blood pressure
SC	subcutaneous(ly)
sCR	stringent complete response
Screen	Screening
SD	standard deviation
SFU	safety follow-up
SOC	**standard of care**
$t_{½}$	half-life
t_{max}	time of maximum observed serum concentration
TLS	tumor lysis syndrome
ULN	upper limit of normal
UPM	unit probability mass
US	United States
VGPR	very good partial response
WHODRUG	World Health Organization Drug

1. Introduction

The purpose of this Statistical Analysis Plan (SAP) is to provide details of the statistical analyses that have been outlined within the protocol for study 20150161, AMG 176 dated **13 July 2023**. The scope of this plan includes the primary analysis and the final analysis that are planned and will be executed by the Amgen Global Biostatistical Science department unless otherwise specified.

2. Objectives, Endpoints and Hypotheses

2.1 Objectives and Endpoints

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

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

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

Estimand(s) for Primary Objective(s)

Not applicable.

Estimand(s) for Key Secondary Objective(s)

Not applicable.

Estimand(s) for Secondary Objective(s)

Not applicable.

Exploratory	
Multiple Myeloma Part 1a (BIW)	
• **To explore PK/pharmacodynamic (PD) relationships for safety and/or efficacy endpoints**	• **AMG 176 exposure/efficacy and exposure/safety relationships**
• **To identify metabolite(s) of AMG 176 in plasma**	• **AMG 176 metabolites in plasma**

• Evaluate the correlation of clinical responses to disease-specific features in tumor cells	• Relationships of clinical responses to biomarkers including but not limited to protein levels of pro-survival family members, fluorescent in situ hybridization (FISH)/cytogenetic analysis, gene expression profiling, flow cytometric phenotyping and DNA sequencing
Multiple Myeloma Part 1b (QW)	
• To explore PK/PD relationships for safety and/or efficacy endpoints	• AMG 176 exposure/efficacy and exposure/safety relationships
• To identify metabolite(s) of AMG 176 in plasma	• AMG 176 metabolites in plasma
• Evaluate the correlation of clinical responses to disease specific features in tumor cells	• Relationships of clinical responses to biomarkers including but not limited to protein levels of pro survival family members, FISH/cytogenetic analysis, gene expression profiling, flow cytometric phenotyping, and DNA sequencing
Acute Myeloid Leukemia Part 3a (BIW) and 3b (QW)	
• To explore PK/PD relationships for safety and/or efficacy endpoints	• AMG 176 exposure/efficacy and exposure/safety relationships
• To identify metabolite(s) of AMG 176 in plasma	• AMG 176 metabolites in plasma
• Evaluate the correlation of clinical responses to disease specific features in tumor cells	• Relationships of clinical responses to biomarkers including but not limited to protein levels of pro survival family members, FISH/cytogenetic analysis, gene expression profiling, flow cytometric phenotyping, and DNA sequencing
• Demonstrate AMG 176 inactivation of MCL1 by the increase of active BAX and caspase 3 in circulating AML blasts and /or the decrease of circulating blasts or immune cell populations	• BAX and caspase 3 expression in circulating AML blasts and/or monocytes, peripheral AML blast counts, immune cell subset frequencies and medium fluorescent intensity (MFI)
• Patient Interview Substudy (Part 3b only) • To elicit patient reported perceptions of disease, associated symptoms, and symptom impact/burden and interference on patient's life	• Patient reported symptom burden including symptom description, frequency and severity • Subjective assessment of symptom burden interference with daily activities and influence on physical, role, emotional, social, and cognitive function

• To elicit patient perceptions of meaningful changes in symptom burden	• Subjective assessment of symptoms and associated change in burden that represents meaningful improvement and worsening
• To elicit patient perceptions on the relationship between symptom burden and clinical status	• Association between symptom burden, interference, and clinical response
• To explore patient experience with treatment administration route/schedule (frequency), and related caregiver needs	• Subjective assessment of treatment administration route and schedule on time for administration, time away from daily activities due to infusion, adherence and persistence, travel time to infusion center, and caregiver needs to receive infusion
Acute Myeloid Leukemia Part 3c (QW)	
• To explore PK/PD relationships for safety and/or efficacy endpoints in Japan subjects	• AMG 176 exposure/efficacy and exposure/safety relationships
• To identify metabolite(s) of AMG 176 in plasma in Japan subjects	• AMG 176 metabolites in plasma
• Evaluate the correlation of clinical responses to disease specific features in tumor cells in Japan subjects	• Relationships of clinical responses to biomarkers including but not limited to protein levels of pro survival family members, FISH/cytogenetic analysis, gene expression profiling, flow cytometric phenotyping, and DNA sequencing
• Demonstrate AMG 176 inactivation of MCL1 by the increase of active BAX and caspase 3 in circulating AML blasts and/or the decrease of circulating blasts or immune cell populations in Japan subjects	• BAX and caspase 3 expression in circulating AML blasts and/or monocytes, peripheral AML blast counts, immune cell subset frequencies and MFI
Acute Myeloid Leukemia Parts 4 and 5 (QW and BIW)	
• To explore PK/PD relationships for safety and/or efficacy endpoints	• AMG 176 exposure/efficacy and exposure/safety relationships including optimization of dose and frequency
• To identify metabolite(s) of AMG 176 in plasma	• AMG 176 metabolites in plasma
• Evaluate the correlation of clinical responses to disease specific features in tumor cells	• Relationships of clinical responses to biomarkers including but not limited to protein levels of pro survival family members, FISH/cytogenetic analysis, gene expression profiling, flow cytometric phenotyping, and DNA sequencing

• **Demonstrate AMG 176 inactivation of MCL1 by the increase of active BAX and caspase 3 in circulating AML blasts and /or the decrease of circulating blasts**	• **BAX and caspase 3 expression in circulating AML blasts and/or monocytes, peripheral AML blast counts, immune cell subset frequencies and medium fluorescent intensity (MFI)**
• **To evaluate additional measures of efficacy of AMG 176 and azacitidine via minimal residual disease negative (MRD[ ]) assessment**	• **MRD[ ] status at the time of complete response (CR)**
• ***Patient Interview Substudy*** • **To elicit patient reported perceptions of disease, associated symptoms, and symptom impact/burden and interference on patient's life**	• **Patient reported symptom burden including symptom description, frequency and severity** • **Subjective assessment of symptom burden interference with daily activities and influence on physical, role, emotional, social, and cognitive function**
• **To elicit patient perceptions of meaningful changes in symptom burden**	• **Subjective assessment of symptoms and associated change in burden that represents meaningful improvement and worsening**
• **To elicit patient perceptions on the relationship between symptom burden and clinical status**	• **Association between symptom burden, interference, and clinical response**
• **To explore patient experience with treatment administration route/schedule (frequency), and related caregiver needs**	• **Subjective assessment of treatment administration route and schedule on time for administration, time away from daily activities due to infusion, adherence and persistence, travel time to infusion center, and caregiver needs to receive infusion**

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

2.2 Hypotheses and/or Estimations

No formal statistical hypothesis will be tested. The clinical hypothesis is that at least 1 dose level of AMG 176 administered as monotherapy or in combination with azacitidine will achieve acceptable safety and tolerability in subjects with relapsed or refractory MM and AML.

3. Study Overview

3.1 Study Design

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

The study will be conducted in multiple parts as shown in the table below.

A dose-level review team (DLRT) will be responsible for dosing recommendations, which may include escalation to the next nominal or intermediate dose, de-escalation to a lower nominal or intermediate dose; modifications of the ramp-up dosing, alternative dose frequencies, continuation, delay or termination of dosing; or repetition or expansion of a cohort; or determination of recommended dose. For definition of the DLT evaluation period and of a DLT-evaluable subject refer to section 6.7.2.

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

Ramp-up dosing in cycle 1 will be utilized whenever the AMG 176 target dose level is at 180 mg/m^2 or higher to mitigate the risk of tumor lysis syndrome (TLS).

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

Overview of Study Design

Part	Indication/ Number of Subjects	Cohort/ Treatment Group[a]	Design
CLOSED TO ENROLLMENT			
1a	*Multiple Myeloma (36 subjects enrolled)*	*AMG 176 **BIW** IV monotherapy* ***(30, 40, 50, 60, 120, 240 mg/m^2*** ***Ramp-up Dosing implemented: 180, 240, 360, and 480 mg/m^2)***	*A standard 3+3 design was used to identify the MTD (or recommended dose), safety, tolerability, PK, and PD of AMG 176 administered BIW.*

1b	*Multiple Myeloma (12 subjects enrolled)*	*AMG 176 QW IV monotherapy* ***(180, 240, 360, and 480 mg/m^2)***	*A standard 3+3 design was used to identify the MTD (or recommended dose), safety, tolerability, PK, and PD of AMG 176 administered QW. The starting dose level was 180 mg/m^2.*
3a	*AML (**17** subjects enrolled)*	*AMG 176 **BIW** IV monotherapy* ***(60, 120, and 180 mg/m^2)***	*A standard 3+3 design was used to identify the MTD, as well as the safety, tolerability, PK, and PD of AMG 176 administered BIW. The starting dose level was 60 mg/m^2.*
3b	AML (**11 subjects**)	AMG 176 QW IV monotherapy **(120, 180, and 240 mg/m^2)**	A modified toxicity probability interval (mTPI) model design was used to evaluate the safety, tolerability, PK, and PD of AMG 176 administered QW.
3c	***AML (4 subjects enrolled in Japan)***	***AMG 176 QW IV monotherapy (120 mg/m^2)***	***A standard 3+3 design without dose escalation was used to evaluate the safety, tolerability, PK, and PD of AMG 176 administered QW in subjects with AML in Japan.***
Part	Indication/ Number of Subjects	Cohort/ Treatment Group[a]	Design
OPEN TO ENROLLMENT			
3d	AML (**approximately 11** subjects in US)	AMG 176 QW IV 60 mg/m^2 in combination with itraconazole (200 mg) once daily (QD) starting on day -3 through day 4 (total of 7 days) only in cycle 1	A fixed sequence design (itraconazole plus AMG 176 in week 1, followed by AMG 176 in subsequent weeks) will be used to evaluate the effect of itraconazole (strong cytochrome P450 3A4 [CYP3A4] inhibitor) on the PK of AMG 176.
4	AML (**approximately 60** subjects)	**Cohorts 1-4: AMG 176 QW IV (60, 120, 180, and 240 mg/m^2) in combination with azacitidine, with ramp-up dosing of AMG 176 as described for target doses ≥ 180 mg/m^2.** **Cohort 5a: AMG 176 BIW IV (120 mg/m2) in combination with azacitidine** **Cohort 5b: AMG 176 BIW IV (240 mg/m2) in combination with azacitidine**	**An mTPI design will be used to define the combination RP2D. All subjects will receive azacitidine at a dose of 75 mg/m^2 either IV or SC, as recommended in the prescribing information, daily for the first 7 days of a 28-day cycle. Safety, tolerability, PK, and PD of AMG 176 in combination with azacitidine will also be established. Part 4 enrollment will begin after the DLRT established the 120 mg/m^2 dose of AMG 176 as safe and tolerable in combination with azacitidine.**

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

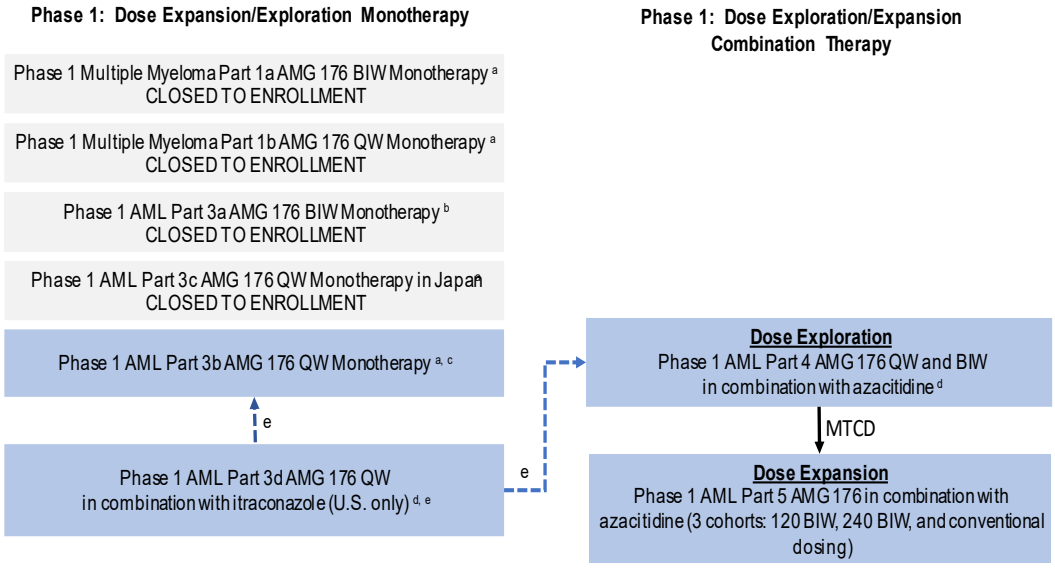
AML = acute myeloid leukemia; BIW = twice weekly; DLRT = dose-level review team; IV = intravenous; MM = multiple myeloma; MTD = maximum tolerated dose; mTPI = modified toxicity probability interval; PD = pharmacodynamics; PK = pharmacokinetics; QD = once daily; QW = once weekly; RP2D = recommended phase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

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

In this study, Part 1 and Part 2 were initially designed to investigate AMG 176 as monotherapy and combinational therapy in subjects with multiple myeloma (MM). As of December 2019, 48 subjects were enrolled in Part 1 where clinical responses were

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

Figure 1-1. Overall Study Design and Treatment Schema



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

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

[b] The AMG 176 starting dose level will be 60 mg/m² BIW.
[c] The AMG 176 starting dose level will be 120 mg/m² QW.
[d] The AMG 176 starting dose level was 60 mg/m² QW.
[e] After week 3, subjects may crossover to Part 3b or Part 4 for continued treatment if approved by the investigator and Amgen medical monitor. Subjects from Part 3d who crossover to Part 3b, will not crossover (for the second time) to Part 4.

3.2 Sample Size

It is anticipated that **approximately** 21**9** subjects will be enrolled in the different parts of this study. Multiple myeloma Part 1a enrolled 36 subjects for dose escalation. Multiple myeloma Part 1b enrolled 12 subjects for dose escalation. Acute myeloid leukemia Part 3a enrolled **17** subjects for dose escalation. **Part 3b enrolled 11 subjects. Acute myeloid leukemia Part 3c enrolled 4 subjects in Japan.** Part 3d will enroll **about 11** subjects in the US. Part 4 will enroll **approximately 60** subjects. Part 5 will enroll approximately **68** subjects.

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

3.3 Adaptive Design

MM Part 1a, Part 1b, and AML Part 3a, **3b**, Part 3c are closed to enrollment.

For AML Part 3b and Part 4, each dose level will initially enroll 3-4 subjects and up to 10 subjects per cohort may be enrolled. A mTPI design will be used to guide dose exploration. The MTD is defined as the highest dose with a probability of DLT lower than or close to a targeted toxicity probability of 0.2. The doses are considered close to the MTD if the toxicity probabilities belong to the proper dosing interval [0.15, 0.25] which corresponds to staying at the current dose (S). The underdosing interval is defined as (0, 0.15) in which the doses are deemed lower than the MTD and corresponds to a dose escalation (E). The overdosing interval is (0.25, 1) in which the doses are deemed higher than the MTD and corresponds to a dose de-escalation (D).

Guidelines for dose level decisions can be found in Table 2. Please note one exception to the guidelines provided in Table 2, a single grade 3 treatment related troponin elevation will result in dose de-escalation regardless of number of subjects treated at current dose.

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

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

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

4. Covariates and Subgroups

4.1 Planned Covariates

There are no planned covariates in this study. The relationship of biomarker and efficacy endpoints may be explored by biomarker team if appropriate.

4.2 Subgroups

Not applicable for this study.

5. Definitions

Age at Enrollment

Subject age at enrollment will be **collected** in years in the clinical database.

Enrollment Date

Enrollment Date is defined as the date collected on the Subject Enrollment eCRF.

Baseline

Unless otherwise specified, baseline will be defined as the last assessment before the first dose of investigational product (AMG 176).

Change From Baseline

Change from baseline is the arithmetic difference between post-baseline and baseline.
Change from Baseline= (Post-baseline Value – Baseline Value)

Percent Change from Baseline

Percent change from baseline is the arithmetic difference between post-baseline value and baseline value divided by baseline value and multiplied by 100.

Percent change from baseline = [(Post-baseline Value – Baseline Value) / Baseline Value] x 100

Study Day

Post study day 1: study day = (date – date of Study Day 1) + 1

Pre study day 1: study day = (date – date of Study Day 1)

Study Day 1

Study day 1 is defined as the first day of administration of the investigational product after enrollment. The day prior to Study Day 1 is considered Day -1.

Duration of Treatment

Date of last administration of investigational product – Study Day 1 + 1

Investigational Product (IP)

IP is used in reference to AMG 176.

Baseline and Post-Baseline ECG Values in Triplicate

The baseline ECG is defined as the mean of all pre-dose assessments; the mean of values in a triplicate should be calculated before taking the mean of the triplicate averages.

For all post-baseline ECG, the mean value for measurements taken at the same assessment will be calculated and used in the analysis.

When an ECG is missing within a triplicate, all available data will be averaged for that time point.

Fridericia-corrected QT Interval (QTcF)

The Fridericia correction will be calculated from the investigator reported QT (msec) and RR interval (msec): $QTcF=QT/(RR/1000)^{1/3}$

Bazett-corrected QT Interval (QTcB)

The Bazett correction will be calculated from the investigator reported QT (msec) and RR interval (msec): $QTcB=QT/(RR/1000)^{1/2}$

DLT Observation Period

The DLT observation period is defined as day 1 through day 28 after the administration of the first dose of AMG 176.

Treatment-Emergent Adverse Event (TEAE)

A treatment-emergent adverse event is any adverse event starting on or after the first dose of investigational product, as determined by "Did event start before first dose of investigational product" equal to "No" or missing on the Events eCRF, and up to and including 30 days after the last dose of investigational product excluding events reported after end of study date. **Events that are directly related to disease progression (including, but not limited to, preferred terms "Disease progression" etc.) will be excluded from TEAE analysis.**

Best Overall Response (BOR):

BOR for a subject is the best observed post-baseline disease response based on investigator assessment.

- AML: BOR is defined as the first response category achieved in the following order: CR_{MRD-}, CR, CRi, MLFS, PR, SD, PD. Response criteria for AML are ELN Response Criteria.
- MM: BOR is defined as the overall response at end of study (data collected on the Best Overall Response CRF). If the overall response is missing, BOR will be derived from the post-baseline disease assessments in the order of: sCR, CR, VGPR, PR, MR, SD, PD. Response criteria for MM are IMWG Uniform Response Criteria.

Duration of Response (DOR)

Duration of response is calculated for subjects who have achieved a response (PR or better). It is defined as time from the first observation indicating a response to the subsequent date of relapse, disease progression or death (due to any cause), whichever is earlier.
DOR time in months: (**earliest** date of relapse, disease progression or death - date of the first observation of response +1)/30.4

Subjects without relapse, disease progression or death until the analysis data cut-off date will be censored at the last adequate disease assessment date after first response; otherwise, at first response.

Event-free Survival (EFS) for AML

Event-free survival is defined as the interval from the first dose of IP to the earlier date of induction treatment failure, relapse for those who have induction treatment success (e.g., complete remission), or death due to any cause. Censoring is at the last evaluable

post-baseline response assessment; otherwise, at the first dose of IP. The event date for induction treatment failure is assigned as the date of the first dose of IP.

EFS time in months: (event date - first dose of IP date +1)/30.4

Overall Response Rate (ORR)

ORR is the incidence of either PR or better based on investigator assessment. All subjects that do not meet the criteria for response (PR or better) by the analysis cutoff date will be considered as non-responders.

For MM subjects: The earliest record where PR or better response has to be confirmed by two consecutive same/better response assessments at any time and should be on/before new anticancer therapy start date. sCR, CR, VGPR and PR are considered as PR or better responses.

For AML subjects: The earliest record where PR or better response collected does not need to be confirmed by subsequent assessment and should be on/before new anticancer therapy start date. CR_{MRD-}, CR, CRi(CR with incomplete hematologic recovery), MLFS and PR are considered as PR or better responses.

Overall survival (OS)

OS is defined as the time from first dose of IP date until death due to any cause.

OS time in months: (date of death - first dose of IP date +1)/30.4

Subjects without event will be censored at their last date known to be alive.

Progression-free survival (PFS) for MM

PFS time is calculated as time from first dose of IP date to disease progression date or death due to any cause, whichever is earlier.

PFS time in months: (event date - first dose of IP date +1)/30.4

Subjects without disease progression or death until the analysis data cut-off date will be censored at the last **non-missing evaluable** disease assessment date. **Subject will be censored at last non-NE post-baseline disease assessment before any anti-cancer therapy**. **If there are no post-baseline disease assessment, then subjects are censored at treatment start date.**

Time to Response (TTR)

Time to response is defined as the time from the first dose of IP until the first documentation of response (PR or better). Only subjects who have achieved a response will be evaluated for TTR.

TTR time in months: (date of the first observation of response - first dose of IP date +1)/30.

Dose intensity

Dose intensity indicates actual dose (mg) given per cycle, which is the cumulative dose divided by the number of cycles started.

Relative Dose intensity

Relative dose intensity is calculated as actual cumulative dose / planned cumulative dose, where

- **Actual cumulative dose [mg] is defined as the total dose given during the study treatment exposure till the course of study. For subjects who did not take any drug the actual cumulative dose is 0 mg.**
- **Planned cumulative dose [mg] is defined as the per-protocol planned dose accumulated over the actual duration on study treatment, whether the actual visit is missing or not.**

6. Analysis Sets

6.1 Full Analysis Set

The FAS is defined as all subjects that are enrolled and receive at least 1 dose of AMG 176.

6.2 Safety Analysis Set

The Safety Analysis Set is same as the Full Analysis Set as described in Section 6.1.

6.3 Per Protocol Analysis Set(s)

Not applicable.

6.4 Health-related Quality-of-Life or Health Economics Analyses Set(s)

Not applicable.

6.5 Pharmacokinetic Analyses Set(s)

The pharmacokinetic analysis set is defined as all subjects who have received at least 1 dose of AMG 176 and for whom PK parameters can be adequately estimated. These

subjects will be evaluated for PK analysis unless the number of data points required for analysis is not enough, or significant protocol deviations have affected the data, or if key dosing or sampling information is missing.

6.6 Interim Analyses Set(s)

Not applicable.

6.7 Study-specific Analysis Set(s)

6.7.1 Interim Efficacy Analysis Set

Interim Efficacy Analysis Set is a subset of the Full Analysis Set (FAS) and it includes subjects whose data cut-off date is at least 4 weeks after the first dose date.

6.7.2 DLT Evaluable Analysis Set

A subject is deemed DLT evaluable if during the DLT observation period the subject met at least one of the following criteria:

- received at least 75% of the planned dose of AMG 176 (and 100% of the planned doses of azacitidine in Part 4) and completed the DLT observation period
- experienced a DLT

7. Planned Analyses

7.1 Interim Analysis and Early Stopping Guidelines

No formal interim efficacy analysis is planned for this study. **Interim safety analyses will be performed to support the evaluation of safety by the DLRT.** However, safety data will be reviewed on an ongoing basis. The Dose Level Review Team (DLRT) will review all available cumulative data by cohort prior to making dose escalation decisions. Adverse events and DLTs observed in all subjects will be evaluated continually and considered in all enrollment and dosing decisions.

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

7.2 Primary Analysis

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

7.3 Final Analysis

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

If FA is close to PA then FA will be performed.

8. Data Screening and Acceptance

8.1 General Principles

The objective of the data screening is to assess the quantity, quality, and statistical characteristics of the data relative to the requirements of the planned analyses.

8.2 Data Handling and Electronic Transfer of Data

The Amgen Global Study Operations-Data Management (GSO-DM) department will receive and store all data to be used in the planned analyses. This study will use the RAVE database.

8.3 Handling of Missing and Incomplete Data

The following imputation for missing or incomplete data will be performed if required:

Incomplete adverse event and concomitant medication dates missing data will be imputed as described in Appendix A.

Non-pharmacokinetic measurements (eg. biomarker data) that are above or below the quantification limits will be considered equal to the upper or lower limit of quantification for all analyses unless specified otherwise.

8.4 Detection of Bias

Lack of protocol compliance and the potential for biased statistical analyses will be examined by assessing the incidence of important protocol deviations in each cohort. The clinical study team will identify and document the criteria for important protocol deviations.

8.5 Outliers

Outlier data will not be excluded unless scientifically justified.

PK concentration data will be evaluated for outliers by visual inspection and decisions to re-assay individual samples will be made in accordance with standard Pharmacokinetics and Drug Metabolism (PKDM) practices.

8.6 Distributional Characteristics

Where appropriate, the assumptions underlying the proposed statistical methodologies will be assessed. If required data transformations or alternative non-parametric methods of analyses will be utilized.

8.7 Validation of Statistical Analyses

Programs will be developed and maintained, and output will be verified in accordance with current risk-based quality control procedures.

Datasets, tables, figures, and listings will be produced and validated in accordance with SOP-430399. Standard macros will be used when available.

The production environment for statistical analyses consists of Amgen-supported versions of statistical analysis software; for example, the SAS System version 9.2 or later.

9. Statistical Methods of Analysis

9.1 General Considerations

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.

When data are summarized by time, the values recorded against the scheduled time points listed in the protocol will be used. When assessing minimum/maximum increases or decreases over the study, all assessments, including unscheduled assessments will be used.

For each indication, efficacy and safety data will be summarized by dose level.

For the subjects who complete the DLT period and proceed to a higher dose level or crossover to a combinational therapy cohort for the following treatment cycle, efficacy and safety will be analyzed by the initial assigned dose level.

Exploratory analysis will be performed separately if needed.

9.2 Subject Accountability

The number and percent of subjects who are enrolled, receive investigational product, completed investigational product, discontinue from investigational product (including reasons for discontinuation), complete study, discontinue the study (including reasons for discontinuation) will be summarized by cohort. Enrollment by country and study site will be summarized.

9.3 Important Protocol Deviations

Important Protocol Deviations (IPDs) categories are defined by the study team before the first subject visit and updated during the IPD reviews throughout the study prior to database lock. These definitions of IPD categories, sub-category codes and descriptions

will be used during the course of the study. Eligibility deviations are defined in the protocol. IPDs and eligibility deviation will be summarized. A listing will be provided for IPD.

9.4 Demographic and Baseline Characteristics

The following descriptive summaries of the demographic and baseline characteristics will be produced: Demographic (i.e., age, age groups [18 **to** < 65, 65 to < 75, 75 to < 85, ≥ 85 years], sex, race, and ethnicity) and baseline characteristics (height, weight, disease type/sub-type, prior lines of therapy, and ECOG Performance Status, Multigated Acquisition (MUGA) Scan or Echocardiogram, Neurological Status) will be summarized using descriptive statistics. If multiple races have been reported for a subject, the subject will be categorized as multiple.

9.5 Efficacy Analyses

9.5.1 Analyses of Primary Efficacy Endpoint(s)/Estimand(s)

Not Applicable.

9.5.2 Analyses of Secondary Efficacy Endpoint(s)/Estimand(s)

Table 3. Efficacy Endpoint Summary

Endpoint	Statistical Analysis Methods
ORR	The proportion of subjects with response (PR or better) with corresponding 2-sided exact 95% CI will be calculated using the Clopper-Pearson method (Clopper and Pearson, 1934) for the Full Analysis Set. Refer Appendix C for code fragment.
DOR, PFS (for MM) **and** EFS (for AML)	Kaplan-Meier estimates and Kaplan-Meier curve will be provided for the Full Analysis Set.
TTR	Descriptive statistics will be provided for subjects with response.

For time to event endpoints (including DOR, TTR, EFS and PFS), summary table or figure may not be generated if the number of events is less than 10. The individual subject-level data will be provided.

9.6 Safety Analyses

9.6.1 Analyses of Primary Safety Endpoint(s)

All the safety analysis will be performed based on full analysis set unless otherwise specified.

Table 4. Safety Endpoint Summary Table

Endpoint	Statistical Analysis Methods
Incidence of Dose-Limiting Toxicities (DLTs), treatment-related and treatment-emergent adverse events, and clinically significant changes in vital signs, electrocardiograms (ECGs), and clinical laboratory tests	• **Treatment-emergent, treatment-related adverse events, vital signs, electrocardiograms, clinical laboratory tests will be performed based on full analysis set.** • **Incidence of dose-limiting toxicitites will be based on DLT evaluable analysis set.**

9.6.2 Adverse Events

The Medical Dictionary for Regulatory Activities (MedDRA) version **26.1** or later will be used to code all events categorized as adverse events or disease related events to a

system organ class and a preferred term. The severity of each adverse event will be graded using CTCAE version 4.0.

Subject incidence of all treatment-emergent adverse events, serious adverse events (SAEs), grade 3 or higher, treatment-related, serious treatment-related, adverse events leading to withdrawal of investigational product, and fatal adverse events will be tabulated by system organ class and preferred term by dose level. The event categories of adverse event and disease related event both will be included.

For subjects who experienced COVID-19, SAEs on or after COVID-19 onset will be summarized.

Subject incidence of DLTs will be summarized by preferred term and dose level using the DLT Evaluable Analysis Set. **Summary table may not be generated if the number of events is less than 5 in each cohort. The individual subject-level data will be provided.** Similar summaries will also be provided to events of interest. A listing of death will be provided.

9.6.3 Laboratory Test Results

Shifts in CTCAE grades of safety laboratory parameters between baseline and the worst post-baseline value for select blood chemistry analytes (creatinine, total bilirubin, aspartate aminotransferase [AST], alanine aminotransferase [ALT], and alkaline phosphatase [ALP]) and hematology analytes (hemoglobin, platelet count, absolute neutrophil count) will be tabulated by dose level.

A summary of potential hepatoxicity by Hy's Law will be tabulated. The criteria are defined as AST or ALT **≥** 3 times upper limit of normal (ULN), total bilirubin **≥** 2 times ULN, and ALP < 2 times ULN assessed within **30** days.

Summary statistics of troponin over time by dose level will be provided based on data availability.

9.6.4 Vital Signs

Vital signs (systolic / diastolic blood pressure, heart rate) over time and change from baseline will be summarized. The analyses of vital signs will include summary statistics over time **for AML parts only**.

9.6.5 Physical Measurements

Not applicable.

9.6.6 Electrocardiogram

All on-study ECG data including PR, QRS, QT, RR, QTcB, and QTcF interval will be summarized **for AML parts only**. **Mean ± SE by visit graph may be plotted for** QTcF and QTcB.

Summaries over time and/or changes from baseline over time will be provided for all ECG parameters.

Subjects will be categorized into the following groups per their maximum change from baseline in QTcF. Unscheduled assessments will be included in the determination of the maximum change.

- ≤30 msec
- >30 – 60 msec
- >60 msec

The number and percentage of subjects in each group will be summarized.

Subjects will also be categorized into the following groups per their maximum post baseline QTcF. Unscheduled assessments will be included in the determination of the maximum post baseline value.

- ≤450 msec
- >450 – 480 msec
- >480 – 500 msec
- >500 msec

The number of subjects in each group will be summarized for each dosing group.

In addition, the relationship between PK concentration of AMG 176 and change from baseline in QTcF may be explored graphically **and performed by clinical pharmacology modeling and simulation (CPMS) team.**

9.6.7 Antibody Formation

The incidence and percentage of subjects who develop anti-AMG 176 antibodies at any time will be tabulated.

9.6.8 Exposure to Investigational Product

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

delivered per day, average dose delivered per treated week, **dose intensity and relative dose intensity** will be summarized. Summaries of the number and percentage of subjects with dose modifications and reason for modification will be provided.

A listing of the unique manufacturing lot numbers and a listing of the subjects administered each manufacturing lot number will be provided.

9.6.9 Exposure to Non-investigational Product(s)

Descriptive statistics will be produced to describe the exposure to azacitidine, itraconazole. **Number of cycles initiated, number of doses, cumulative dose, average dose delivered per day, average dose delivered per treated week, dose intensity and relative dose intensity** will be summarized.

9.6.10 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. **In addition, the number and proportion of subjects receiving anti-cancer therapies during long-term follow-up will be summarized. These analyses will be provided for AML parts only.**

9.7 Other Analyses

9.7.1 Pharmacokinetic Analyses

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

The PK parameters for AMG 176 including, but not limited to C_{max}, minimum observed concentration (C_{min}), AUC, CL, and, if feasible, $t_{½}$ will be estimated using standard non-compartmental PK methods and summarized by dose groups using means, standard deviations, medians, minimums**,** and maximums for intensive and peak/trough determinations. AMG 176 concentrations at each time point along with PK parameter values may be reviewed for each subject. Individual AMG 176 concentration/time profiles will be plotted by dose groups. Summary statistics will be computed for each sampling time and parameter as appropriate. For subjects in Part 3d (DDI assessment with itraconazole), AMG 176 PK parameters (C_{max}, AUC) will be compared from day 1 (with itraconazole) to day 15 (without itraconazole) to evaluate the effect of itraconazole on the PK of AMG 176, **if feasible**. Additional analyses to explore relationship between

exposure and safety and exposure and efficacy may also be performed.

Pharmacokinetic parameters such as C_{max}, AUC, and $t_{½}$, if feasible, will be estimated and summarized for azacitidine.

9.7.2 Analyses of Pharmacokinetic or Pharmacokinetic/Pharmacodynamic Endpoints

Not applicable.

9.7.3 Analyses of Clinical Outcome Assessments

Not appliable.

9.7.4 Analyses of Health Economic Endpoints

Not applicable.

9.7.5 Analyses of Biomarker Endpoints

Not applicable.

10. Changes From Protocol-specified Analyses

The study was terminated early. Synopsis CSR will be provided, and thus selected planned analyses will be performed. The following analyses will not be performed.

1. **PFS (MM), EFS (AML)**
2. **TTR**
3. **BAX and caspase 3**
4. **Events of interest summaries**
5. **Antibody formation**
6. **Prior anti cancer therapies**

11. Literature Citations / References

Clopper CJ, Pearson ES. The use of confidence or fiducial limits illustrated in the case of the binomial. Biometricka. 1934;26:404-413.

American Cancer Society. 2018. https://www.cancer.org/cancer/acute-myeloidleukemia/about/key-statistics.html. Accessed on 9 September 2018.

12. Prioritization of Analyses

There is no prioritization of analyses.

13. Data Not Covered by This Plan

The analyses of PK (including the DDI assessment for Part 3d) and exploratory endpoints are not covered by this plan.

14. Appendices

Appendix A. Handling of Dates, Incomplete Dates and Missing Dates

Imputation Rules for Partial or Missing Dates for Adverse Events and Concomitnt Medications

The reference date for the following rules is the date of first dose of study drug.

Start Date		Stop Date						
		Complete: *yyyymmdd*		Partial: *yyyymm*		Partial: *yyyy*		
		< 1st dose	≥ 1st dose	< 1st dose *yyyymm*	≥ 1st dose *yyyymm*	< 1st dose *yyyy*	≥ 1st dose *yyyy*	missing
Partial: *yyyymm*	= 1st dose *yyyymm*	2	1	2	1	n/a	1	1
	≠ 1st dose *yyyymm*		2		2	2	2	2
Partial: *yyyy*	= 1st dose *yyyy*	3	1	3	1	n/a	1	1
	≠ 1st dose *yyyy*		3		3	3	3	3
Missing		4	1	4	1	4	1	1

1 = Impute the date of first dose
2 = Impute the first of the month
3 = Impute January 1 of the year
4 = Impute January 1 of the stop year
Note: If the start date imputation leads to a start date that is after the stop date, then do not impute the start date. **For subjects who were never treated (first dose date is missing), partial start dates will be set to the first day of the partial month or first day of year if month is also missing.**

1. Imputation rules for partial or missing stop dates:

- Initial imputation
  a. For partial stop date mmyyyy, impute the last of the month.
  b. For partial stop date yyyy, impute December 31 of the year.
  c. For completely missing stop date, do not impute.

- If the stop date imputation leads to a stop date that is after the death date, then impute the stop date as the death date.
- If the stop date imputation leads to a stop date that is before the start date, then set the stop date as missing.

2. Imputation rules for partial or missing death dates:

- If death year and month are available but day is missing:
  a. If YYYYMM for the date last known to be alive equals YYYYMM for death date, set death date to the day after the date last known to be alive.

b. If YYYYMM for the date last known to be alive is less than the YYYYMM for death date, set death date to the first day of the death month.

c. If YYYYMM for the date last known to be alive is greater than YYYYMM for death date, data error, do not impute and censor subject survival time.

- If month and day are missing and year of death is known:

a. If YYYY for the date last known to be alive equals the YYYY for death date, set death date to the day after last known to be alive date.

b. If YYYY for the date last known to be alive is less than the YYYY for death date, set death date to the first day of the death year.

c. If YYYY for the date last known to be alive is greater than YYYY for death date, data error, do not impute and censor the subject survival time.

- If a death date is totally missing, do not impute and censor the subject survival time.

3. General Imputation rules for time to event efficacy endpoints

Unless otherwise specified, the partial/missing event dates will be imputed as follows:

- If event year and month are available but the day is missing:

a. If mmyyyy for the date last known to be event-free equals mmyyyy for event date, set event date to the day after the date last known to be event-free.

b. If mmyyyy for the date last known to be event-free is less than the mmyyyy for event date, set event date to the first day of the event month.

c. If mmyyyy for the date last known to be event-free is greater than mmyyyy for event date, data error and do not impute.

- If month and day are missing and year of event is known:

a. If yyyy for the date last known to be event-free equals the yyyy for event date, set event censor date to the date last known to be event-free.

b. If yyyy for the date last known to be event-free is less than the yyyy for event date, set OS censor date to last day of the prior year.

c. If yyyy for the date last known to be event-free is greater than yyyy for event date, data error and do not impute.

If an event date is totally missing, do not impute.

Appendix B. European LeukemiaNet (ELN) Response Criteria in Acute Myeloid Leukemia (2017)

Category	Definition	Comment
Response		
• CR without minimal residual disease (CR_{MRD}-)	If studied pretreatment, CR with negativity for a genetic marker by RT-qPCR, or CR with negativity by MFC	Sensitivities vary by marker tested, and by method used; therefore, test used and sensitivity of the assay should be reported; analyses should be done in experienced laboratories (centralized diagnostics)
• Complete remission (CR)	Bone marrow blasts < 5%; absence of circulating blasts and blasts with Auer rods; absence of extramedullary disease; ANC ≥1.0 x 10^9/L (1000/μL); platelet count ≥100 x 10^9/L (100 000/μL)	MRD^+ or unknown
• CR with incomplete hematologic recovery (CRi)	All CR criteria except for residual neutropenia (<1.0 x 10^9/L [1 000/μL]) or thrombocytopenia (<100 x 10^9/L [100 000/μL])	
• Morphologic leukemia-free state (MLFS)	Bone marrow blasts <5%; absence of blasts with Auer rods; absence of extramedullary disease; no hematologic recovery required	Marrow should not merely be "aplastic"; at least 200 cells should be enumerated or cellularity should be at least 10%
• Partial remission (PR)	All hematologic criteria of CR; decrease of bone marrow blast percentage to 5% to 25%; and decrease of pretreatment bone marrow blast percentage by at least 50%	Especially important in the context of phase 1-2 clinical trials
Treatment failure		
• Primary refractory disease	No CR or CRi after 2 courses of intensive induction treatment; excluding subjects with death in aplasia or death due to indeterminate cause	Regimens containing higher doses of cytarabine are generally considered as the best option for subjects not responding to a first cycle of 7+3; the likelihood of responding to such regimens is lower after failure of a first
• Death in aplasia	Deaths occurring ≥ 7 d following completion of initial treatment while cytopenic; with an aplastic or hypoplastic bone marrow obtained within 7 d of death, without evidence of persistent leukemia	
• Death from indeterminate cause	Deaths occurring before completion of therapy, or < 7 d following its completion; or deaths occurring ≥ 7 d following completion of initial therapy with no blasts in the blood, but no bone marrow examination available	

Page 1 of 2

Footnotes defined on next page

Category	Definition	Comment
Response criteria for clinical trials only		
• Stable disease	Absence of CR_{MRD-}, CR, CRi, PR, MLFS; and criteria for PD not met	Period of stable disease should last at least 3 mo
• Progressive disease (PD)[a,b]	Evidence for an increase in bone marrow blast percentage and/or increase of absolute blast counts in the blood: • > 50% increase in marrow blasts over baseline (a minimum 15% point increase is required in cases with < 30% blasts at baseline; or persistent marrow blast percentage of > 70% over at least 3 mo; without at least a 100% improvement in ANC to an absolute level (> 0.5 x 10^9/L [500/μL], and/or platelet count to > 50 x 10^9/L [50 000/μL] nontransfused); or • > 50% increase in peripheral blasts (WBC x % blasts) to > 25 x 10^9/L (> 25 000/μL) (in the absence of differentiation syndrome)[b]; or • New extramedullary disease	Category mainly applies for older subject given low intensity or single-agent "targeted therapies" in clinical trials. In general, at least 2 cycles of a novel agent should be administered. Some protocols may require blast increase in 2 consecutive marrow assessments at least 4 wk apart; the date of progression should then be defined as of the first observation date. Some protocols may allow transient addition of hydroxyurea to lower blast counts. Hydroxyurea is unapproved for AML in Japan. "Progressive disease" is usually accompanied by a decline in ANC and platelets and increased transfusion requirement and decline in performance status or increase in symptoms.
Relapse		
• Hematologic relapse (after CR_{MRD-}, CR, CRi)	Bone marrow blasts ≥ 5%; or reappearance of blasts in the blood; or development of extramedullary disease	
• Molecular relapse (after CR_{MRD-})	If studied pretreatment, reoccurrence of MRD as assessed by RT-qPCR or by MFC	Test applied, sensitivity of the assay, and cutoff values used must be reported; analyses should be done in experienced laboratories (centralized diagnostics)

Page 2 of 2

ANC = absolute neutrophil count; d = day(s); IDH = isocitrate dehydrogenase; MLFS = morphologic leukemia-free state; mo = month(s); WBC = white blood cell; wk = week(s)

[a] The authors acknowledge that this new provisional category is arbitrarily defined; the category aims at harmonizing the various definitions used in different clinical trials.

[b] Certain targeted therapies, for example, those inhibiting mutant IDH proteins, may cause a differentiation syndrome, that is, a transient increase in the percentage of bone marrow blasts and an absolute increase in blood blasts; in the setting of therapy with such compounds, an increase in blasts may not necessarily indicate PD.

Appendix C. Code Fragments

The ORR and its 95% CI can be calculated in SAS using PROC FREQ. The sample code is provided below, where RESP is the status of response (eg., 1=responder, 2=non-responder). The CI using the exact method can be found in the OUT data labeled as 'Exact Conf Limits'.

```
proc freq data=TEST;
tables RESP / binomial alpha=0.05;
ods output Binomial=OUT;
run;
```