Statistical Analysis Plan

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
NCT Number:	Not available at the time of amendment
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Version Number	Date (DDMMMYYYY)	Summary of Changes, including rationale for changes
Original (v1.0)	20OCT2021	Original Version
Amendment 1 (v2.0)	10MAY2024	• CMML is added along with R/R MDS in the secondary objectives. • Secondary endpoint 'Evaluate the pharmacokinetics (PK) of the AMG 176 when administered as monotherapy' is added. • Overall response according to Uniform Response Criteria is now changed to overall response according to International Working Group (2006) -MDS/MPN Response criteria throughout the SAP except for objectives and endpoints.

		• The description for Part 1 changed from 'Dose Escalation/ Determination of Maximum Tolerated Combination Dose (MTCD) and Recommended Phase 2 Dose (RP2D)' to 'Dose Escalation/Determination of **Optimal Biological Dose (OBD) and Minimum Safe and Biologically Effective Dose (MSBED)**' • Two dose levels in part 1 changed to three dose levels. • The text of MTDC/RP2D definition is now replaced with '**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**' • In Part 2 the enrollment in newly diagnosed subjects is changed as '**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).**' • Prior distribution parameters are changed to beta (1,1) whereas initially it was beta (0.50, 1.50). • The posterior probability that the incidence is greater than 30% is > 90% is changed to '20% is greater than 80%. • The sample size changed from 110 subjects to 120 subjects and number of subjects in part 1 changed from 50 to 60 • BOR definition is updated as **BOR is defined as the first response category achieved as responders and non-responders. Responders will include CR or PR, whereas**

		non-responders will include SD, PD, NE or NA. • Section 10- changes from protocol specified analysis is updated. • Section 9.1- Updated the general considerations. • **Section 9.5.2- Updated to include listings for responder/non-responder.**

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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
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]
NE	Not evaluable
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
PD	progressive disease
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
SD	stable disease
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

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 superseding amendment 3** for study 20200392, AMG 176 dated **28 April 2022**. The scope of this plan includes the final analysis that is planned and will be executed by the Amgen Global Biostatistical Science department unless otherwise specified.

2. Objectives, Endpoints/Estimands and Hypotheses

2.1 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 $t_{1/2}$

2.2 Hypotheses and/or Estimations

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.

3. Study Overview

3.1 Study 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.**

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 3-1. Details regarding the mTPI model are described in Appendix B.

Table 3-1. 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

	Number of DLTs		
No. of DLT-evaluable[a] subjects treated at current dose	Escalate	Stay at current dose	De-escalate[b]
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.

Part 2 – Dose Expansion (Not Applicable, did not enroll)

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 Protocol Table 3-2 and Table 3-3.

Table 3-2. 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 3-3. 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%

3.2 Sample Size

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.

3.3 Adaptive Design

NA

4. Covariates and Subgroups

4.1 Planned Covariates

There are no planned covariates in this study.

4.2 Subgroups

There are no planned subgroups in this study.

5. Definitions

Age at Enrollment:

Age at Enrollment: Subject age at enrollment will be collected in [years] in the clinical database

Baseline:

Unless otherwise specified, baseline will be defined as the last assessment with nonmissing value before the first dose of investigational product (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.

Bazett-corrected QT Interval (QTcB):

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

Best Overall Response (BOR):

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

BOR is defined as the first response category achieved as responders and non-responders. Responders will include CR or PR, whereas non-responders will include SD, PD, NE or NA.

Response criteria to be used for MDS**/MPN** are International Working Group **(IWG)-MDS** Response Criteria (2006).

Change From Baseline:

Change from baseline is the arithmetic difference between post-baseline and baseline.

Duration of Treatment:

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

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.

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.

Investigational Product (IP):

IP is used in reference to AMG 176.

Last known alive date:

Last known alive date is described in Appendix C.

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.

Transfusion independence:

Transfusion independence is defined as no transfusion for at least 8 consecutive weeks (56 days).

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.

Treatment-related Treatment-emergent Adverse Event (TRAE):

A TRAE is any TEAE whose causal relationship is marked as "Related" on the eCRF.

Event with missing relationship will be assumed to be treatment-related.

6. Analysis Sets

6.1 Full Analysis Set

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

6.2 DLT Evaluable Analysis 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.

6.3 Pharmacokinetic/Pharmacodynamic Analyses Set(s)

The PK Analysis Set defined as all subjects who have received at least 1 dose of the investigational product and have at least 1 PK sample collected. These subjects will be evaluated for PK analysis unless the number of data points required for analysis is not enough, or significant protocol deviations have affected the data, or if key dosing or sampling information is missing.

7. Planned Analyses

7.1 Interim Analysis and Early Stopping Guidelines

As the decision was made to terminate the study early, no formal interim analysis will be performed for this study.

7.2 Primary Analysis

No formal primary analysis will be performed due to early close out of the study.

7.3 Final Analysis

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

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 D.

Non-pharmacokinetic measurements ([redacted]) 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

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 required continuous data like Troponin I and Troponin T will include means, medians, standard deviations, first and third quartiles and ranges.

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.

No formal statistical analysis will be performed for the study and listings will be provided.

9.2 Subject Accountability

No summary of subject accountability will be required to provided.

9.3 Important Protocol Deviations

Important Protocol Deviations (IPDs) categories are defined by the study team before the first subject's initial visit and updated during the IPD reviews throughout the study prior to database lock. These definitions of IPD categories, subcategory codes, and descriptions will be used during the course of the study. Eligibility deviations are defined in the protocol.

No listing of IPDs and eligibility deviations will be provided

9.4 Demographic and Baseline Characteristics

Demographic and baseline characteristic will be listed.

9.5 Efficacy Analyses

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

No formal statistical analyses will be performed for primary efficacy endpoints due to early termination of the study which resulted in insufficient number of subjects.

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

The listing of responder/non-responder will be provided for Part 1A- QW Monotherapy (Dose Exploration) subjects.

9.5.3 Analyses of Exploratory Efficacy Endpoint(s)

NA

9.6 Safety Analyses

9.6.1 Analyses of Primary Safety Endpoint(s)

No summary analysis tables will be provided for the safety endpoints. More details are mentioned in sections from 9.6.2 to 9.6.10

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 to a system organ class and a preferred term.

Subject listing of all treatment-emergent adverse events, serious adverse events, adverse events leading to discontinuation of investigational product, treatment related adverse events, DLTs and fatal adverse events will be provided.

Subject listing of Troponin increased adverse events serious adverse events, adverse events leading to discontinuation of investigational product, treatment related adverse events, and fatal adverse events will be provided.

The grading of adverse events will be based on the guidelines provided in the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

9.6.3 Laboratory Test Results

The subject listing of clinical laboratory will be provided for the full analysis set. The analyses of safety laboratory data for Troponin will be included as summary statistics over time by dose level

9.6.4 Vital Signs

The listing of vital signs including systolic/diastolic blood pressure, heart rate, respiratory rate and temperature will be provided.

9.6.5 Physical Measurements

The subject listing will be provided which will include parameters of physical measurements.

9.6.6 Electrocardiogram

The listing of all on-study ECG data will be provided.

9.6.7 Antibody Formation

No summary tables or listing will be provided.

9.6.8 Exposure to Investigational Product

The subject listings will be provided with IP start and end date. The listing will also include planned dose, actual dose and reason for change or withheld of the planned dose.

9.6.9 Exposure to Non-investigational Product(s)/Auxiliary Medicinal Product(s)

NA

9.6.10 Exposure to Concomitant Medication

No summary tables and listings will be provided.

9.7 Other Analyses

9.7.1.1.1 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.

PK parameters for AMG 176 including, but not limited to, maximum observed concentration (Cmax), area under the concentration-time curve (AUC) and half-life (t1/2) will be estimated, if feasible.

9.7.2 Analyses of Pharmacokinetic or Pharmacokinetic/Pharmacodynamic Endpoints

NA

9.7.3 Analyses of Clinical Outcome Assessments

NA

9.7.4 Analyses of Health Economic Endpoints

NA

9.7.5 [redacted]

NA

10. Changes From Protocol-specified Analyses

During the initial development of this document, it was realized that there are protocol-specified analyses that cannot be implemented/performed and the protocol is not required to be amended. Following changes are required-

- **Though protocol states that the Uniform Response criteria were used for deriving the responses; however, International Working Group MDS Response Criteria (2006) (Appendix E) were used to classify responses for patients with MDS (based on NCCN guidelines Jan 2024). No patients with CMML were enrolled.**
- Tables based on the primary analysis endpoints and secondary endpoints will not be generated due to the limited number of subjects and early close out of the study. These changes will also be documented in the Clinical Study Report.

Primary endpoints will not be analyzed using tables; however, listings will be provided only for clinical laboratory tests, vital signs, ECG, and adverse events including DLTs, treatment-related and treatment-emergent adverse events.

1. Part 1A – QW Monotherapy (Dose Exploration)- 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.

No analysis will be performed for below secondary endpoints:

1. Part 1B – QW Combination Therapy (Dose Exploration) – Overall response according to the **IWG-MDS Response criteria** for MDS/MPN (2006), EFS, time to response, and DOR
2. Part 2 – QW Combination Therapy (Dose Expansion) –
    a. Time to transformation to Acute Myeloid Leukemia (AML)
    b. Duration of Response (DOR)
    c. Overall Survival (OS)
    d. Time to Next MDS Treatment (TTNT)
    e. EFS

11. Literature Citations / References

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12. Prioritization of Analyses

There is no prioritization of analyses.

13. Data Not Covered by This Plan

The analyses of PK are not covered by this plan.

14. Appendices

Appendix A. 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;
```

Appendix B. 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.

Appendix C. Last Known Alive Date

For subjects who do not have death date available i.e., subject was alive throughout, derive last known alive date as the latest of all the date variables below:

1. Events form: Date Started, Date Ended or Resulted in Death, hospitalization admission date, hospitalization date discharged.

2. Date collected on Chemistry (Local lab), Chemistry (Local lab) (Unsched), Coagulation (Local Lab), Coagulation (Local Lab) (Unsched), Hematology (Local Lab), Hematology (Local Lab) (Unsched), Urinalysis (Local Lab), Urinalysis (Local Lab) (Unsched), Immunology (Local Lab), Reproductive Status and Pregnancy Test (Local Lab), Male Reproductive Status, Liver Biopsy Results, Liver Biopsy - Abnormal Findings, Liver Biopsy - Abnormal Architecture Findings, Liver Biopsy - Abnormal Liver Cell or Hepatocyte Findings, Liver Biopsy - Liver Cell or Hepatocyte Inclusion or Vacuole Types, Liver Biopsy - Hepatocyte or Liver Cell Nuclear Abnormality Types, Liver Biopsy - Liver or Lobular Infiltrate Types, Liver Biopsy - Portal Tract Inflammation Types, Liver Biopsy - Abnormal Bile Duct Findings, Liver Biopsy - Abnormal Portal Vein Findings, Liver Biopsy - Liver Infection Findings, Liver Biopsy - Parasite or Ova Findings, Liver Biopsy - Histological Staining or Additional Study Details, Liver Imaging Results, Hepatic Event Labs, Chemistry (Local Lab) (DILI), Coagulation (Local Lab) (DILI), Hematology (Local Lab) (DILI), Immunology (Local Lab) (DILI), Toxicology (Local Lab) (DILI), Chemistry (Local Lab) (Non-TP), Hematology (Local Lab) (Non-TP), Urinalysis (Local Lab) (Non-TP), Coagulation (Local Lab) (Non-TP), [redacted], [redacted] (Non-TP) (Cardiac monitoring tests), Chemistry (Local Lab) (TLS monitoring tests), Chemistry (Local Lab) (Cardiac monitoring tests), Bone Marrow Aspirate for MDS, Chemistry (Local Lab) (Unsched) (TLS monitoring tests), Chemistry (Local Lab) (Unsched) (Cardiac monitoring tests), Hematology (Local Lab) (Peripheral Blood Counts), Hematology (Local Lab) (Unsched) (Peripheral Blood Counts), Hematology (Local Lab) (Peripheral Blood Counts) (Non-TP) forms.

3. Date first taken, Date last taken on the Concomitant medications, Other Protocol Required Therapy (Allopurinol or equivalent), Anti-Cancer Therapies (On Study) forms.

4. Date performed on CT or MRI, ECOG performance status, Electrocardiogram - Triplicate (On-study), Electrocardiogram (on-study), Procedure, Transfusions,

NYHA Classification, Vital signs, Vital Signs (DILI), MUGA Scan or Echocardiogram, MUGA Scan or Echocardiogram (DILI), Electrocardiogram (On-study) (Non-TP),

Electrocardiogram - Triplicate (On-study) (Non-TP), Vital Signs Log (VS200), Vital Signs Log (VS200) (Non-TP) forms.

5. Date subject has ended IP, End of Investigational Product Administration, End of Non-Investigational Product Administration (Azacitidine), End of Safety Follow-up, EOS forms only if the status is not dead or lost to follow-up.

6. Hospitalization admission and dfischarge dates on hospitalization form

7. Date first taken, Date last taken, Progression Date, Best Response Date on the Anti-cancer therapies form.

8. Start and stop dates on Investigational Product administration, Non- Investigational Product Administration (Azacitidine) forms.

9. Date of examination on physical measurement, Physical Measurement (Weight), Physical Measurement (Height/Weight/BMI_C) forms.

10. Date consent signed, Date consent withdrawn on additional consents/withdrawals of consent form

11. Date of contact/search, subject status date on the Survival Status form if the subject status is not unknown.

12. Date of assessment on Disease Response (MDS) form.

13. All the date fields on Best Overall Response/Progression form.

14. All dates from NDB data.

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

Imputation Rules for Partial or Missing Start Dates

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*		Missing
		< 1st dose	≥ 1st dose	< 1st dose *yyyymm*	≥ 1st dose *yyyymm*	< 1st dose *yyyy*	≥ 1st dose *yyyy*	
Partial: *yyyymm*	= 1st dose *yyyymm*	2	1	n/a	1	n/a	1	1
	≠ 1st dose *yyyymm*		2	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: 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.

Imputation Rules for Partial or Missing Stop Dates

Initial imputation

- If the month and year are present, impute the last day of that month.
- If only the year is present, impute December 31 of that year.
- If the stop date is entirely missing, assume the event or medication is ongoing.

If the imputed stop date is before the start date, set stop date to missing.

If the imputed stop date is after the death date, impute as death date.

Imputation Rules for Partial or Missing Death Dates

If death year and month are available but day is missing:

- 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.
- 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.

- If yyyymm for the date last known to be alive is greater than yyyymm for death date, assume date last known to be alive is in error, set death date to the first day of the death month.

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

- If yyyy for the date last known to be alive equals yyyy for death date, set death date to the day after last known to be alive date.
- If yyyy for the date last known to be alive is less than yyyy for death date, set death date to the first day of the death year.
- If yyyy for the date last known to be alive is greater than yyyy for death date, assume date last known to be alive is in error, set death date to the first day of the death year.

If a death occurred and a death date is totally missing:

- Do not impute and censor the subject survival time.

Appendix E. MDS Diagnostic and Response Criteria

Proposed modified International Working Group response criteria for altering natural history of MDS

Category	Response criteria (responses must last at least 4 wk)
Complete remission	Bone marrow: ≤ 5% myeloblasts with normal maturation of all cell lines*
	Persistent dysplasia will be noted*†
	Peripheral blood‡
	Hgb ≥ 11 g/dL
	Platelets ≥ 100×10^9/L
	Neutrophils ≥ 1.0×10^9/L†
	Blasts 0%
Partial remission	All CR criteria if abnormal before treatment except:
	Bone marrow blasts decreased by ≥ 50% over pretreatment but still > 5%
	Cellularity and morphology not relevant
Marrow CR†	Bone marrow: ≤ 5% myeloblasts and decrease by ≥ 50% over pretreatment†
	Peripheral blood: if HI responses, they will be noted in addition to marrow CR†
Stable disease	Failure to achieve at least PR, but no evidence of progression for > 8 wks
Failure	Death during treatment or disease progression characterized by worsening of cytopenias, increase in percentage of bone marrow blasts, or progression to a more advanced MDS FAB subtype than pretreatment
Relapse after CR or PR	At least 1 of the following:
	Return to pretreatment bone marrow blast percentage
	Decrement of ≥ 50% from maximum remission/response levels in granulocytes or platelets
	Reduction in Hgb concentration by ≥ 1.5 g/dL or transfusion dependence
Cytogenetic response	Complete
	Disappearance of the chromosomal abnormality without appearance of new ones
	Partial
	At least 50% reduction of the chromosomal abnormality
Disease progression	For patients with:
	Less than 5% blasts: ≥ 50% increase in blasts to > 5% blasts
	5%-10% blasts: ≥ 50% increase to > 10% blasts
	10%-20% blasts: ≥ 50% increase to > 20% blasts
	20%-30% blasts: ≥ 50% increase to > 30% blasts
	Any of the following:
	At least 50% decrement from maximum remission/response in granulocytes or platelets
	Reduction in Hgb by ≥ 2 g/dL
	Transfusion dependence