A PHASE 1, OPEN-LABEL, DOSE FINDING STUDY OF CC-95251 ALONE AND IN COMBINATION WITH ANTINEOPLASTIC AGENTS IN SUBJECTS WITH ACUTE MYELOID LEUKEMIA AND MYELODYSPLASTIC SYNDROMES

PROTOCOL NUMBER:	**CA059-001**
COMPOUND CODE:	**CC-95251 (also known as BMS-986351)**
DATE FINAL:	**16 Jun 2021**
AMENDMENT 1.0 FINAL:	**17 Aug 2021**
AMENDMENT 2.0 FINAL:	**19 Dec 2022**
AMENDMENT 3.0 FINAL:	**19 May 2023**
EudraCT NUMBER:	**2021-002799-38**
IND NUMBER:	**154328**
SPONSOR NAME/ ADDRESS:	Celgene Corporation 86 Morris Avenue Summit, NJ 07901

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CELGENE THERAPEUTIC AREA HEAD SIGNATURE PAGE

[redacted]

Signature of Celgene Therapeutic Area Head

[redacted]

Printed Name of Celgene Therapeutic Area Head and Title

By my signature, I indicate I have reviewed this protocol and find its content to be acceptable.

SITE PRINCIPAL INVESTIGATOR SIGNATURE PAGE

Signature of Site Principal Investigator	**dd mmm yyyy**
Printed Name of Site Principal Investigator **Institution Name:**_____ By my signature, I agree to personally supervise the conduct of this study at my study site and to ensure its conduct is in compliance with the protocol, informed consent, Institutional Review Board (IRB)/Ethics Committee (EC) procedures, instructions from Celgene representatives, the Declaration of Helsinki, International Council for Harmonisation (ICH) Good Clinical Practices Guidelines, and local regulations governing the conduct of clinical studies.	

COORDINATING PRINCIPAL INVESTIGATOR SIGNATURE PAGE

Signature of Coordinating Principal Investigator	**dd mmm yyyy**
Printed Name of Coordinating Principal Investigator **Institution Name:**_____ By my signature, I agree the protocol has been written to comply with ICH Good Clinical Practices guidelines and agree to offer guidance throughout the study as needed.	

OVERALL RATIONALE FOR PROTOCOL AMENDMENT 3.0:

The purpose of global amendment 3.0 is to add cohorts to evaluate the safety and preliminary efficacy of the investigational product CC-95251 (also known as BMS-986351) administered in combination with injectable azacitidine and venetoclax in eligible subjects with relapsed/refractory (R/R) (Part A) and treatment-naïve (TN) acute myeloid leukemia (AML) (Part D).

CC-95251 is a first-in-class, high-affinity, fully human antibody, designed to bind to signal regulatory protein alpha (SIRPα) and block its interaction with cluster of differentiation 47 (CD47), interrupting a macrophage inhibitory signaling pathway providing a mechanism for immune escape in AML. Preclinical studies including those conducted using SIRPα-positive tumor cells such as AML cell lines and patient-derived xenograft cultures have demonstrated anti-tumor activity of CC-95251 as monotherapy or in combination with azacitidine. Clinical experience in subjects with R/R AML and R/R myelodysplastic syndromes (MDS) has demonstrated preliminary safety and efficacy with CC-95251 as monotherapy and in combination with azacitidine.

The B-cell lymphoma-2 inhibitor venetoclax (Venclexta) is approved by the US Food and Drug Administration and European Commission in combination with injectable azacitidine for adults with newly diagnosed (ND) AML ineligible for standard induction, and this regimen has improved response rates and overall survival in this population compared to azacitidine monotherapy. Despite this improvement, prognosis in patients treated with this regimen remains poor, and the addition of agents with different mechanisms of action may confer added benefit. Currently, other agents targeting the CD47-SIRPα axis such as magrolimab (Hu5F9G4, an anti-CD47 monoclonal antibody) and ALX148 (SIRPα fusion protein CD47 blocker) are under clinical study in subjects with AML and MDS including in combinations with azacitidine or azacitidine and venetoclax. Preliminary results from these studies have primarily demonstrated signs of improved clinical efficacy in the front-line TN setting. However, in contrast to the clinical experience with CC-95251, CD47-targeting agents have been noted to have associated hematologic toxicities including significant anemia due to off-tumor, on-target activity on CD47-expressing red blood cells and may compound cytopenias seen with venetoclax. Therefore, the addition of CC-95251 to azacitidine and venetoclax may provide additional clinical benefit with a more favorable safety profile. The updated protocol design enables evaluation of this triplet in the front-line setting, where clinical benefit is most likely to be derived.

In addition to the cohorts described above, additional revisions and clarifications based on the clinical trial experience to date have been incorporated into this amendment. Other clarifications, corrections of minor typographical errors, and incidental formatting changes were made throughout the document, including removal of the [redacted] deficiency test from the Table of Events in [redacted]

SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 3.0		
Section Number & Title	**Description of Change**	**Brief Rationale**
Medical Monitor / Emergency Contact Information	Updated personnel and contact information.	Changes in study personnel.
Protocol Summary	The Protocol Summary was updated to reflect changes made throughout the protocol.	Updated to include rationale for Protocol Amendment 3.0. Introduced triplet combinations of CC-95251 with injectable azacitidine and venetoclax in relapsed/refractory (R/R) and newly diagnosed (ND) acute myeloid leukemia (AML) subjects.
Section 1.1.1: Acute Myeloid Leukemia Section 1.2.3: Venetoclax Section: 1.3.1: Study Rationale and Purpose Section 1.3.4.2: Rationale for Combination of CC-95251 with Azacitidine Venetoclax Section 1.3.5: Rationale for Pharmacodynamics and Potential Predictive Biomarkers	Added background, mechanism of action for venetoclax, and clinical and safety data in AML subjects treated with venetoclax plus azacitidine.	To permit addition of triplet combinations of CC-95251 with azacitidine and venetoclax, which is supported by data from recent study.
Section 1.3.2: Rationale for the Study Design Section 3.1: Study Design Section 3.1.1: Part A Section: 3.1.4 Part D Section: 3.1.5 Study Treatments [redacted]	Added a new cohort of CC-95251 in combination with azacitidine plus venetoclax (triple combination) in study design, Part A dose escalation, and Part D dose expansion, foot note e, f, and g. Clarified roles of the Safety Review Committee.	
Section 4.1: Number of Subjects Section 4.2: Inclusion Criteria, 6a-6d. Section 4.3: Exclusion criteria Section: 4.4 Lifestyle Restrictions Section 4.4.1: Meals and Dietary Restrictions	Updated study population to include a new cohort of CC-95251 in combination with azacitidine plus venetoclax (triple combination). Added definition for treatment-naïve (TN) AML; added language regarding venetoclax use in subjects of childbearing potential; added venetoclax-specific exclusion criteria including recent use of strong cytochrome P450 (CYP)3A inhibitors, lifestyle and dietary restrictions, and conditions limiting absorption of orally administered drugs.	

SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 3.0

Section Number & Title	Description of Change	Brief Rationale
Section 1.3.3: Rationale for Dose Schedule, and Regimen Selection Section 3.1.5: Study Treatments [redacted] Section 7.1.3: Venetoclax Section: 7.2.1.3: Venetoclax	Added new sections for drug description, preparation and administration, dosing, schedules, and supply information for venetoclax. Added dose modification guidelines including adjustments due to hematologic toxicity in triple combination cohorts	
Section: 7.2.7.8.3 Monitoring and Management of [redacted]	Addition of background and guidance for monitoring and management of [redacted] to this section	
[redacted] Section 6.4: Efficacy Assessment [redacted]	[redacted] Added venetoclax-related data collection: venetoclax administration; medication diary; whole blood for T-cell. B-cell, and natural killer cell; disease assessment, [redacted] bone marrow (BM) assessment specific to subjects receiving venetoclax; adjusted timing of [redacted]	
[redacted]	Added dose modification guidelines for CC-95251 in combination with azacitidine plus venetoclax (triple combination).and footnotes a and b	

SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 3.0		
Section Number & Title	**Description of Change**	**Brief Rationale**
[redacted]		
7.2.7.10: Definition of Overdose	Clarification of criteria for overdose of IV (CC-95251 and azacitidine) and SC (azacitidine) administration of study drugs and addition of PO overdose criteria (venetoclax)	
7.6: Investigational Product Compliance	Added description of venetoclax compliance monitoring to this section.	
Section 6.2: Treatment Period Section: 7.2.7.8.2: Prophylaxis and Management of Tumor Lysis Syndrome Section 7.2.7.8.4: Hematological Toxicity	Added venetoclax-related toxicity management including tumor lysis syndrome and hematological toxicity.	
Section 8.2: Prohibited Concomitant Medications and Procedures	Added premedication guidelines for azacitidine and venetoclax.	
Section 8.3: Required Concomittent Medications and Procedures Section 9.10: Safety Review Committee Table 12: Management of Potential Venetoclax Interaction with CYP3A and P-gp Inhibitors	Provided updated language regarding BMS safety process. Added venetoclax related prohibited concomitant medication. Added table to describe venetoclax dose modifications in subjects receiving CYP3A or P-gp inhibitors.	
Table 1: Risk Assessment Table 2: Study Objectives Table 3: Study Endpoints [redacted]	Adapted the language to align with addition of a new cohort of CC-95251 in combination with azacitidine plus venetoclax (triple combination) in Part A dose escalation and Part D Dose expansion. [redacted]	To align language throughout protocol.

SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 3.0		
Section Number & Title	**Description of Change**	**Brief Rationale**
[redacted] Section 7.5 Investigational Product Accountability and Disposal Section 7.2.7.3: Permitted Study Drug Adjustments Section 7.2.3: Definition of a Subject Evaluable for DLT Section 7.3: Method of Treatment Assignment Section 9.1 Overview Section 9.7 Safety Analysis Section 9.9.6 Figure 4: Overall Study Design	Clarified that PK of CC-95251 will be characterized as a single agent and in combination with antineoplastic agents.	
Section: 1.4 Risk/Benefit Assessment Section 1.4.1: Benefit Assessment Section 1.4.2: Risk Assessment Table 1: Risk Assessment Section 1.4.3: Overall Risk/Benefit Conclusion	Added language regarding the risk/benefit assessment, including risk of venetoclax. Section 1.4 Risk/Benefit Assessment and Table 1 replaces prior section 1.4 Safety Monitoring Plan	To permit addition of triple combination arm. With the integration of Celgene and Bristol-Myers Squibb Company's protocol development and risk-benefit assessment process, the information on relevant/potential risks and mitigation strategy has been summarized in Table 1: Risk Assessment, and benefit assessment and overall assessments have been added.
Sections 3.1.5.2: Treatment Period Sections 7.2.1.1: CC-95251 Section 7.2.1.3: Venetoclax [redacted]	Clarification that subjects are going observed for [redacted] between administrations when receiving azacitidine and CC-95251 [redacted]	To comply with [redacted] mg per vial presentation as detailed in the CC-95251 Pharmacy Manual.

SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 3.0		
Section Number & Title	**Description of Change**	**Brief Rationale**
[redacted]		
Section 7.2.7.1: Criteria for Stopping a Dose Cohort Section 9.3: Sample Size and Power Considerations Table 13: Definition of study population [redacted]	Added statistical consideration including sample size and power considerations and safety stopping rules for triple combination for Part A Dose escalation and Part D Dose expansion.	To permit addition of triple combination arm.
[redacted]	Removal of erroneous [redacted] deficiency test.	In Protocol amendment 2.0 mandatory requirement for [redacted] testing was removed as an exclusion criterion, and the screening assessment was deleted from [redacted] Screening for all potential schedules in the Table of Events were correctly removed.
Section 1.2.1.5: Clinical Experience with CC-95251	Updated clinical experience for CC-95251.	To align with the most current version of CC-95251 Investigator's Brochure

SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 3.0		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 6.2.6: Clinical Laboratory Tests [redacted]	Updated [redacted] as an optional test.	C-reactive protein was determined to be a more globally utilized and specific test and therefore, due to limitations of [redacted] availability, this test was deemed optional.
All	Minor typographical and formatting errors were corrected, and minor edits and clarifications were made.	Minor; therefore, have not been summarized.

PROTOCOL SUMMARY

Study Title

A Phase 1, Open-label, Dose Finding Study of CC-95251 Alone and in Combination with Antineoplastic Agents in Subjects with Acute Myeloid Leukemia and Myelodysplastic Syndromes

Indication

Relapsed or refractory (R/R) and treatment-naïve (TN) intensive chemotherapy ineligible acute myeloid leukemia (AML)

R/R and TN myelodysplastic syndromes (MDS)

Primary Objectives

- To determine the safety and tolerability of CC-95251 (also known as BMS-986351) alone and in combination with antineoplastic agents
- To define the recommended Phase 2 dose (RP2D) of CC-95251 alone and in combination with antineoplastic agents in subjects with AML and MDS

Secondary Objectives

- To assess the preliminary efficacy of CC-95251 as a single agent and in combination with antineoplastic agents in AML and MDS
- To characterize the pharmacokinetics (PK) of CC-95251
- To evaluate the presence, frequency, and functional impact of anti CC-95251 antibodies (anti-drug antibodies [ADA])

Exploratory objectives and endpoints for the study are outlined in Section 2.

Study Design

Study CA059-001 is an open-label, multicenter, Phase 1 study testing the safety and efficacy of CC-95251, a monoclonal antibody directed against signal regulatory protein alpha (SIRPα), alone and in combination with antineoplastic agents in subjects with R/R or TN AML and R/R or TN MDS. This protocol is intended to evaluate various drug combinations with CC-95251, as separate arms, over the life of the protocol, using the same objectives. CC-95251 as a single agent and as part of each of the combinations will be evaluated separately (ie, the intention is not to compare between monotherapy or combinations) for the purposes of the objectives, trial design, and statistical analysis.

The study will consist of 4 parts with a dose escalation (Part A) and dose expansions (Parts B, C, and D) as detailed below [redacted]

- Part A: Dose escalation with CC-95251 alone and in combination with injectable azacitidine in subjects with R/R AML and R/R intermediate, high or very high risk (ie, Revised International Prognostic Scoring System score [IPSS-R] [redacted] MDS. Dose escalation with CC-95251 in combination with injectable azacitidine and venetoclax (triple combination) in subjects with R/R AML.

- Part B: Dose expansion testing CC-95251 alone and in combination with injectable azacitidine in R/R AML and R/R intermediate, high, or very high risk (ie, IPSS-R[redacted]) MDS.
- Part C: CC-95251 dose expansion in combination with injectable azacitidine in TN subjects with intermediate, high or very high risk (ie, IPSS-R[redacted] MDS.
- Part D: CC-95251 dose expansion in combination with injectable azacitidine and venetoclax (triple combination) in subjects with TN AML ineligible for intensive chemotherapy.
- Other combinations of CC-95251 and antineoplastic agents in subjects with R/R or TN AML and/or R/R or TN MDS may be explored at the recommendation of the Safety Review Committee (SRC) and will be added by subsequent protocol amendment.

Part A

Part A will evaluate the safety and tolerability of escalating doses of CC-95251 administered intravenously (IV) as a single agent (monotherapy) to determine the preliminary recommended Phase 2 dose (RP2D) of single agent CC-95251 in subjects with R/R AML or R/R MDS. An additional dose escalation evaluating the safety and tolerability of CC-95251 administered IV in combination with azacitidine administered IV or subcutaneously (SC) (double combination) will also take place in Part A with the aim of determining the preliminary RP2D of CC-95251 plus injectable azacitidine in subjects with R/R AML or R/R MDS. Further dose escalation evaluating the safety and tolerability of CC-95251 administered IV in combination with azacitidine administered IV or SC and venetoclax administered orally (triple combination) will also take place in Part A with the aim of determining the preliminary RP2D of CC-95251 plus injectable azacitidine and venetoclax in subjects with R/R AML.

[redacted] will be utilized to guide CC-95251 dose escalation/de-escalation decisions for monotherapy, double combination, and triple combination, with the final decisions being made by the SRC. The SRC membership will be comprised of Investigators (and/or designated representatives), the Sponsor's Medical Monitor, safety physician, clinical scientist, and the study manager. Ad hoc attendees may include the study PK scientist, biostatistician, and translational research scientist. Other internal and external experts may be consulted by the SRC, as necessary.

The proposed dose levels for testing the CC-95251 monotherapy include a starting dose [redacted] 20 mg/kg weekly (QW) and [redacted] 30 mg/kg to be administered by IV infusion. A 20 mg/kg QW dose of CC-95251 has been demonstrated to be tolerated in subjects with advanced solid cancers in the CC-95251-ST-001 study (NCT03783403). In the event that [redacted] is not tolerated in the CC-95251 monotherapy cohort, a lower dose [redacted] of 10 mg/kg CC-95251 may be recommended by the SRC.

The proposed starting dose (DL1a) for CC-95251 in combination with azacitidine (double combination) is 10 mg/kg QW, [redacted]. The Part A dose escalation may enroll subjects in the CC-95251 plus azacitidine cohorts in parallel with the CC-95251 monotherapy cohorts. [redacted]

[redacted]

The proposed starting dose (DL1b) for CC-95251 in combination with azacitidine and venetoclax (triple combination) is 20 mg/kg QW, [redacted]. Dose de-escalation to dose level [redacted] (10 mg/kg QW of CC-95251 in combination with azacitidine and venetoclax) may be recommended by the SRC if the starting dose is not tolerated or to explore a lower dose level based on the available safety, PK, and pharmacodynamic (PD) data. The Part A dose escalation may enroll subjects in the CC-95251 plus azacitidine and venetoclax cohorts in parallel with the CC-95251 monotherapy and double combination cohorts. [redacted]

All subjects within each dose level will be observed [redacted] before initiation of the next dose level. Subject treatment on Cycle 1 Day 1 (C1D1) will be staggered with [redacted] between subjects in a given cohort during Part A.

A decision table ([redacted] based on [redacted] are provided to guide CC-95251 dose escalation/de-escalation decisions for monotherapy, double combination cohorts, and triple combination cohorts. The SRC will make dose escalation/de-escalation recommendations based on real-time integrated assessment of available safety, efficacy, PK and pharmacodynamics (PD) in each dose cohort.
After enrollment has been completed in the corresponding Part A cohorts, the SRC will undertake an evaluation of the available safety, PK, PD, and preliminary efficacy data to make a determination of the preliminary RP2D of CC-95251 to test in the expansion cohorts (Parts B, C, and D). [redacted]. The preliminary [redacted], and may differ based on indication (ie, MDS versus AML). For a dose level to be selected by the SRC for dose expansions (Part B, C, and D), at least [redacted] subjects should be evaluable for DLT in Part A to declare a tolerable dose level. Subjects non-evaluable for DLT may be replaced.

During dose escalation, the decision to evaluate additional subjects within a dose cohort, a higher dose level, intermediate dose levels, an alternate dosing interval, or declare the RP2D will be determined by the SRC, based on their review of available safety, PK, PD, and preliminary efficacy data for a given dose level. The investigation of any other alternate dosing schedule beyond those stipulated in the current protocol version will be submitted in a protocol amendment.

Part B

Part B will further evaluate the safety and efficacy of CC-95251 alone and in combination with injectable azacitidine in R/R AML and R/R MDS (IPSS-R [redacted] The expansion cohorts of each

individual treatment may start after a dose and schedule is shown to be tolerated in the corresponding Part A cohort and the SRC has selected the Part B dose and schedule.

Approximately [redacted] subjects per cohort will be enrolled to further evaluate the safety and assess the efficacy of:

1. CC-95251 alone in R/R AML
2. CC-95251 in combination with injectable azacitidine in R/R AML
3. CC-95251 alone in R/R MDS (IPSS-R [redacted]
4. CC-95251 in combination with injectable azacitidine in R/R MDS (IPSS-R [redacted]

at the preliminary RP2D of CC-95251 monotherapy or RP2D of CC-95251 in combination with injectable azacitidine established in Part A. The SRC may choose [redacted] based on review of the available safety, PK, PD and preliminary efficacy data from Part A and will regularly review safety and emerging response data during expansion to make recommendations about continuation and dose modification, as appropriate (Section 7.2.7).

Additional cohorts of subjects testing CC-95251 in combination with additional antineoplastic agents in subjects with R/R AML or R/R MDS may be considered at the recommendation of the SRC and will be included by protocol amendment.

Part C

Part C will evaluate subjects with treatment-naïve (ie, previously untreated), intermediate, high or very high risk (ie, IPSS-R [redacted]) MDS with CC-95251 in combination with standard of care azacitidine.

[redacted] The SRC will review the safety data from this group of subjects utilizing [redacted] prior to the opening of the Part C expansion. The dose of CC-95251 selected for Part C may occur at the preliminary RP2D established in dose escalation, or at an alternative tolerable dose based on review of available safety, PK, PD, and preliminary efficacy data.

The Part C expansion will initially evaluate at least [redacted] with TN MDS [redacted] The SRC will review the available safety utilizing [redacted], PK, PD and preliminary efficacy data in the initial [redacted] to determine if the dose and schedule is tolerated prior to escalating the CC-95251 dose to the proposed Part C expansion dose and schedule. [redacted] may be selected for continued enrollment in the expansion based on SRC review of the available data from the initial [redacted] Thereafter, a total of approximately [redacted] additional subjects with TN MDS may be enrolled in Part [redacted]. During enrollment in Part C the SRC will review available safety data from Cycle 1

of every [redacted] subjects treated in the cohort to evaluate for excessive toxicity. Enrollment in Part C may proceed concurrently with enrollment in the Part B expansion cohorts.

The SRC will continue to review safety data regularly throughout the study and make recommendations about study continuation, dose modification and establishment of a RP2D as appropriate.

Part D

The Part D expansion will evaluate CC-95251 in combination with azacitidine and venetoclax in subjects with TN AML and who are not candidates to receive IC due to comorbidities or age (ie, ≥ 75 years)

Enrollment in Part D [redacted] The SRC will review the safety data from this group of subjects utilizing [redacted] prior to the opening of the Part D expansion. The dose of CC-95251 selected for Part D may occur at the preliminary RP2D established in dose escalation, or at an alternative tolerable dose based on review of available safety, PK, PD, and preliminary efficacy data.

The Part D expansion will initially evaluate at least [redacted] subjects with TN AML treated [redacted] Subject treatment on C1D1 will be staggered with at least one day between subjects for the initial [redacted] subjects. [redacted] An additional [redacted] subjects may be enrolled based on the response seen in the initial [redacted] subjects ([redacted] and Section 9.3: Sample Size and Power Considerations). During enrollment in Part D, the SRC will review available safety data from Cycle 1 of every [redacted] subjects treated in the cohort to evaluate for excessive toxicity.

The SRC will continue to review safety data regularly throughout the study and make recommendations about study continuation, dose modification and establishment of a RP2D as appropriate.

Study Population

Up to approximately [redacted] subjects ([redacted] in Part A dose escalation, [redacted] in Part B expansion, [redacted] in Part C expansion, and [redacted] in Part D expansion) may be enrolled.

The Study Population will be subjects ≥ 18 years of age and defined as follows:

- R/R AML (Parts A and B): AML as defined by the 2016 World Health Organization (WHO) Classification (Appendix B) who have failed or who are ineligible for all available therapies for AML which may provide clinical benefit

- R/R MDS (Parts A and B): MDS as defined by the 2016 WHO Classification (Appendix D) with intermediate, high or very high risk by IPSS-R (IPSS-R [redacted] and who have failed or who are ineligible for all available therapies for MDS which may provide clinical benefit.
- TN MDS (Part C): Treatment-naïve MDS as defined by the 2016 WHO Classification (Appendix D) with intermediate, high or very high risk by IPSS-R (IPSS-R [redacted]).
- TN AML (Part D): Treatment-naïve AML as defined by the 2016 WHO Classification (Appendix B), including secondary AML and therapy-related AML in subjects who are IE for IC and allogeneic [redacted] due to having one of the following:
  - ♦ Severe cardiac comorbidities (including congestive heart failure, left ventricular ejection fraction <45%, and chronic stable angina)
  - ♦ Pulmonary comorbidity (diffusing capacity of the lung for carbon monoxide ≤ 65% or forced expiratory volume in 1 second ≤ 65%)
  - ♦ Any other comorbidity incompatible with intensive chemotherapy upon approval of the Sponsor Medical Monitor
  - ♦ Aged ≥ 75 years, regardless of the presence of any of the above comorbidities
  - – Subjects must have a projected life expectancy of ≥ 12 weeks.
  - – Additionally, TN AML subjects who have not received hypomethylating agents, venetoclax, or chemotherapy in the setting of antecedent MDS are eligible. Prior treatment for antecedent MDS including, but not limited to, growth factors (eg, erythropoiesis-stimulating agents), hydroxyurea, and lenalidomide is allowed.

Length of Study

The full length of the study is expected to be approximately 36 to 48 months including recruitment, screening, treatment, and follow up. Approximately 16 to 19 months will be required to enroll subjects in the dose escalation portion of the study (Part A). Approximately 12 to 18 months will be required to enroll and evaluate subjects in the dose expansion portion of the study (Parts B, C, and D).

The End of Trial is defined as either the date of the last visit of the last subject to complete the post-treatment follow-up, or the date of receipt of the last data point from the last subject that is required for primary, secondary and/or exploratory analysis, as prespecified in the protocol, whichever is the later date.

Study Treatments

CC-95251 will be administered intravenously in two phases starting with a more frequently dosed induction phase followed by a maintenance phase.

- During induction phase, subjects will be dosed weekly for Cycles 1 through 4 (QW, eg, on Day 1, Day 8, Day 15, and Day 22 of each cycle). After Cycle 4, subjects will enter the maintenance phase.
- During the maintenance phase, CC-95251 will be administered every two weeks (Q2W, eg, on Day 1 and Day 15 of each cycle).

The SRC may change the frequency of dosing [redacted] based on review of the available safety, PK, PD, and preliminary efficacy data [redacted] The investigation of any other alternate dosing schedule beyond those stipulated in the current protocol version will be submitted in a protocol amendment.

In combination cohorts, azacitidine will be administered at 75 mg/m^2 on Days 1-7 (or Days 1-5 and 8-9) of each 28-day cycle as an IV or SC injection throughout the course of the study treatment per local prescribing information and institutional standard of care.

In triple combination cohorts, venetoclax will be administered orally once daily on Days 1 through 28 of each 28-day cycle. A brief dose ramp-up occurs during Cycle 1, with the dosing of 100 mg on Day 1, 200 mg on Day 2, and 400 mg on Day 3. Venetoclax will be administered at 400 mg on subsequent days. Doses may be adjusted for subjects receiving concurrent P-glycoprotein or cytochrome P450 3A inhibitors.

Parts A, B, C, and D will consist of 3 periods: Screening, Treatment, and Follow-up (refer to Figure 4).

Screening Period

The Screening Period starts 28 days prior to first dose of study intervention. The informed consent form (ICF) must be signed and dated by the subject and the administering staff prior to the start of any other study procedures. All screening tests and procedures must be completed within the 28 days prior to the first dose of study treatments.

Treatment Period

Upon confirmation of eligibility, subjects will be enrolled and begin treatment in the assigned dose level cohort.

The Sponsor will supply the investigational product (IP), CC-95251, for IV administration (Section 7.1.1).

Azacitidine will be supplied or obtained according to local clinical study agreement and in accordance with local guidelines. When provided by the Sponsor, azacitidine for injection will be supplied as a lyophilized powder in 100 mg single-dose vials for reconstitution and administration.

Venetoclax will be supplied or obtained according to local clinical study agreement and in accordance with local guidelines. When provided by the Sponsor, venetoclax will be supplied as tablets in 10 mg, 50 mg, and 100 mg blister/bottles for administration.

In Part A, subjects with AML in the monotherapy and double combination cohorts will be hospitalized for at least 24 hours after the first dose of CC-95251 (C1D1) for IV hydration and [redacted] and to monitor for adverse events. Subjects with AML in triple combination cohorts in Part A or Part D will be hospitalized during venetoclax ramp-up (3-5 days) for IV hydration, [redacted], and to monitor for adverse events based on the ongoing risk of TLS (see Section 7.2.7.8.2). [redacted]

[redacted] Subjects with [redacted] Full emergency resuscitation facilities should be immediately available, and subjects should be under close supervision of the Investigator or designated staff during and for [redacted] following CC-95251 administration with serial vital signs obtained and pulse oximetry performed.

[redacted]

CC-95251 infusion will be started at [redacted] mg/hr [redacted] mg/hr [redacted] mg/hr. Further changes to the rate of infusion may be considered during the course of the trial based on review of clinical data and approval from the SRC.

For subjects receiving azacitidine in combination with CC-95251, subjects will receive azacitidine prior to starting CC-95251 infusion on days receiving both treatments. Subjects should be observed for [redacted]

For subjects receiving triple combination, on Day 1 of each cycle, CC-95251, azacitidine, and venetoclax will be administered on the same day. Azacitidine should be administered prior to starting CC-95251 infusion. Subjects should be observed [redacted] between administrations. Venetoclax should be taken orally at least [redacted] after CC-95251 infusion. Subjects should be instructed to take their daily dose at approximately the same time each day [redacted] hours.

[redacted]

Thus, in Part A dose escalation, the window for evaluation of DLT during Cycle 1 will be up to [redacted] days ([redacted] days); Cycles 2 and higher will be 28 days in length. In dose expansion, all cycles will be 28 days in length. [redacted] Subjects will only be considered DLT evaluable during the first cycle of their initial enrollment in Part A (dose escalation).

All treatments will be administered in 28-day cycles. To optimally benefit from the treatment, Investigators should aim to treat subjects for at least [redacted] cycles, although subjects can be discontinued from the protocol earlier if they demonstrate documented relapse from CR or partial remission (PR), disease progression, unacceptable adverse event(s), intercurrent illness that prevents further administration of treatment, investigator's decision to withdraw the subject, subject withdraws consent, pregnancy of the subject, noncompliance with trial treatment or procedure requirements, or administrative reasons. Subjects may continue treatment if they are deriving benefit from treatment without unacceptable toxicity (any CR, MLFS, PR, or stable disease [SD] with demonstrated clinical benefit eg, reduction in transfusion burden), as judged by the Investigator, [redacted] or until disease progression, loss of clinical benefit, unacceptable toxicity, or decision to withdraw by subject or Investigator. Subjects who discontinued one study treatment in a combination arm for reasons other than relapse or resistant disease may continue on the non-discontinued drug(s) if the subjects are receiving benefit as per Investigator's discretion until there is evidence of relapse or resistant disease, or until they are no longer able to tolerate treatment due to an adverse event (AE). Retreatment (within [redacted] from last dose of CC-95251 in the prior study treatment period) will be permitted (refer to Section 7.2.7.9 for details). Subjects may be retreated only once during the study and the total duration in the study will be no longer than 4 years from the original C1D1.

Follow-up Period

All subjects will be followed for [redacted] days after the last dose of study drug for AE reporting. In addition, serious adverse events (SAEs) made known to the Investigator at any time thereafter that are suspected of being related to study drug are to be reported until such SAEs have recovered (returned to baseline), recovered with sequelae, or death (due to the SAE). Subjects will also be followed for all AEs (SAEs and non-serious AEs) associated with confirmed or suspected severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection until resolution, the condition stabilizes, the event is otherwise explained, the event is deemed irreversible, the subject is lost to follow-up, or for suspected cases, until SARS-CoV-2 infection is ruled-out (Section 6.3.1).

Subjects who discontinue treatment for reasons other than disease progression (or relapse) or start of a new anticancer therapy will have efficacy evaluations (refer to Section 6.3.2) up to a maximum of [redacted] or until progression of disease (or relapse), initiation of a new anticancer therapy, withdrawal from the study, death, or the End of Trial, whichever comes first.

All subjects will be followed starting from the end of treatment according to the schedule for the efficacy long term follow-up (refer to Section 6.3.2), for survival for up to [redacted] or until death, lost to follow-up, or the End of Trial, whichever occurs first. Survival follow-up may be conducted by record review (including public records) and/or telephone contact with the subject, family, or the subject's treating physician.

During follow-up, information (including dates) on new anticancer therapies will be collected until withdrawal from the study, death, or the End of Trial, whichever comes first.

The study will be conducted in compliance with International Conference on Harmonisation (ICH) Good Clinical Practices (GCPs).

Overview of Key Efficacy Assessments

Efficacy assessments include (Section 6.4):

- Clinical findings (eg, physical examinations, constitutional symptoms)
- Complete blood counts (CBC) and peripheral blood smears (PBS)
- Bone marrow examination (biopsy and/or aspiration)

Bone marrow (BM) aspiration and/or biopsy for disease burden assessments will be collected to be evaluated for [redacted] at Screening, end of [redacted] In addition, bone marrow aspirates (BMA) or biopsies (BMB) are performed to confirm CR or CRi or morphologic CR with partial hematologic recovery (CRh), relapse after CR/CRi/CRh (as assessed by the Investigator based on CBC with white blood cell [WBC] differential results), or disease progression. Additional aspirates and/or biopsies will be collected as clinically indicated, based on Investigator's medical judgement.

Complete blood count and peripheral blood smear (PBS) will be performed at the time of each bone marrow collection. Starting with [redacted] subjects will be monitored for disease status using CBC and PBS [redacted] for the second year or until progression of disease (or relapse).

Response to treatment will be assessed by Investigator using local laboratory results according to modified 2017 European Leukemia Network (ELN) AML Response Criteria (Döhner, 2017) for AML and modified International Working Group (IWG) Response Criteria (Cheson, 2006) for MDS. Hematologic response/transfusion dependence will also be evaluated. In addition, CRh will be reported for both AML and MDS (Bloomfield, 2018).

AML response criteria will be summarized by best overall response categories: complete remission rate (CRR) defined as CR + CRi + CRh, and objective response rate (ORR) defined as all responses of CR (ie, CR_{MRD-}, morphologic CR, CRh, CRi) + MLFS + PR. For MDS, the complete remission rate (CRR) is defined as CR rate, objective response rate (ORR) includes all responses (CR + CRh + marrow CR + PR). The efficacy variable of focus will be complete remission rate (CRR) and ORR. Other measures of clinical activity include duration of remission, duration of response, stable disease rate (MDS only), relapse-free survival, event-free survival, progression-free survival (PFS), time to remission/response, transfusion independence, time to AML transformation for MDS subjects, and overall survival (OS) rates at 6 and 12 months.

Secondary and exploratory endpoints include evaluation of CC-95251 PD and predictive biomarkers in blood and/or bone marrow, and exploration of PK, PD, toxicity and activity relationships.

Overview of Key Safety Assessments

The safety variables for this study include:

- Dose-limiting toxicities
- AE and SAE
- Physical examination
- Vital signs/weight
- Eastern Cooperative Oncology Group Performance Status (ECOG PS)
- Safety clinical laboratory assessments (including hematology, clinical chemistry, coagulation studies, and urinalysis)
- Cardiac monitoring: [redacted]
- Exposure to study treatment
- Assessment of concomitant medications/procedures

Overview of Pharmacokinetic Assessments

All subjects will be required to participate in PK sampling in the study, and serial blood samples will be collected at specified times for measurement of CC-95251. All post-dose assessments should be timed from the end of CC-95251 infusion (EOI). If an infusion is terminated early, EOI sampling should still be performed. PK sampling is performed as indicated in [redacted], [redacted]).

PK parameters (C_{max}, C_{min}, t_{max}, $AUC_{(0-T)}$, $AUC_{(TAU)}$, C_{trough}, CLT) of CC-95251, where feasible, will be calculated from the serum concentration-time data of CC-95251 using non-compartment methods. The sponsor may conduct additional PK and PK/PD analyses to follow up on the safety of the study treatment or to better understand the progression of the disease or the response to study treatment.

Overview of Pharmacodynamic Assessments

Pharmacodynamic biomarkers will be collected in all subjects on study to further explore CC-95251 activity and identify potential predictors of response. Pharmacodynamic biomarker assessments include but are not limited to, [redacted]

Pharmacodynamic sampling is performed as indicated in [redacted]

Reflecting the molecular diversity of AML, different minimal residual disease (MRD) platforms are available for detecting MRD. As per ELN recommendation, MRD assessments will be

performed in BM aspirates using either or both, multiparameter flow cytometry and molecular MRD by next generation sequencing.

The sponsor may conduct additional analyses on the PD samples to further evaluate the safety of the study treatment, to better understand the progression of the disease or to assess response to the study treatment.

Overview of Key Immunogenicity Assessments

The development of ADA may impact drug exposure in subjects on the study. Serum will be collected for analysis of ADA during study treatment prior to study drug infusion (pre-dose) and during the follow-up phase. ADA sampling is performed as indicated in the Table of Events ([redacted]) and Section 6.5.

Statistical Methods

Dose escalation/de-escalation decisions for monotherapy, double combination, and triple combination will be guided per the [redacted]. Preliminary estimation of the [redacted] will be based on the estimation of the [redacted] The final determination of RP2D will be decided by the SRC.

Statistical analyses will be performed by dose level or dose schedule and a combination product as needed or applicable. Study data will be summarized for disposition, demographic and baseline characteristics, exposure, efficacy, safety, PK, and PD per respective analysis population defined in Section 9 and Table 13 as applicable. All analyses will be descriptive in nature.

AEs, including treatment-emergent adverse events, will be summarized by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 5 grades, except for cytokine release syndrome (CRS) and TLS, which will be graded according to the revised CRS grading system ([Lee, 2014] and Cairo-Bishop TLS grading system [Cairo, 2004], respectively). The frequency of AEs will be tabulated by Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term. Grade 3 or higher AEs, AEs leading to discontinuation of study treatment or to death, study intervention-related AEs, and SAEs will be tabulated separately. Changes from baseline in selected laboratory analytes for example transfusion dependence (platelet count or red blood cell [RBC] transfusion units), vital signs, and [redacted] will be summarized.

For dose expansion, efficacy variables to be analyzed include complete remission rate (CRR) and ORR, duration of remission, duration of response, stable disease rate (MDS only), relapse-free survival, event-free survival, PFS, time to remission/response, transfusion independence, time to AML transformation for MDS subjects, and overall survival (OS) rates at 6 and 12 months. Point estimates and 2-sided 90% exact Clopper-Pearson confidence intervals of CRR and ORR will be reported. For time to event endpoints, Kaplan-Meier survival analyses will be performed.

During the dose expansion (Parts B, C, and D), a non-binding Bayesian safety monitoring method will be utilized to continuously monitor for excessive toxicities defined as the occurrence of AEs that would fulfill the DLT criteria defined at any time during study treatment (Section 9.9.2). Weakly informative priors [eg, beta [redacted] will be constructed for estimating the stopping boundaries. After a minimum of [redacted] subjects have enrolled and completed at least one cycle of study treatment, the non-binding Bayesian stopping criterion based on the posterior distribution of excessive toxicity will be calculated (refer to [redacted] The study may pause when there is a greater than [redacted] chance that toxicity rate is over [redacted]. The excessive toxicity rate [redacted] is established to be consistent with the target toxicity rate specified in dose escalation. If the stopping rule is triggered, the SRC will conduct a comprehensive review of available safety, PK, PD, and preliminary efficacy data to make continuation decisions.

In Parts B, C, and D, a [redacted] analysis based on CRR will be performed. In Part B, at least [redacted] efficacy evaluable subjects who complete at least one cycle of study treatment for each cohort will initially be accrued; [redacted] In Part C, at least [redacted] efficacy evaluable subjects who complete at least one cycle of study treatment at RP2D will initially be accrued; [redacted]. In Part D, at least 20 efficacy evaluable subjects who complete at least one cycle of study treatment at RP2D will initially be accrued; [redacted].

The [redacted] decision will be made by the SRC upon reviewing all available safety, PK, PD, and any efficacy results in dose expansion phase, including considerations on adjustment of the RP2D dose. Otherwise, the cohort will be expanded to up to approximately [redacted] evaluable subjects in Part B. approximately [redacted] evaluable subjects in Part C, and approximately [redacted] evaluable subjects in Part D (Section 9.9.2).

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1 INTRODUCTION

1.1 Disease Background

1.1.1 Acute Myeloid Leukemia

Acute Myeloid Leukemia (AML) is a genetically heterogeneous cancer of bone marrow (BM) myeloid progenitors that, when untreated or unresponsive to treatment, leads to death within weeks to months due to BM failure or effects of leukemia cells on circulation or organ function. AML is the most commonly reported type of acute leukemia in adults in the United States (US). Based on Surveillance, Epidemiology, and End Results (SEER, 2023) estimates, approximately 20,380 people will be diagnosed with AML in 2023 in the US and 11,310 will die from the disease. It remains a challenging disease to treat with an estimated relative 5-year survival of 31.7% for AML patients diagnosed in the years 2013 to 2019. AML remains a disease primarily of older adults, with a median age at diagnosis of 69 years (SEER, 2023).

Standard curative treatment for AML consists of intensive induction chemotherapy followed by consolidation chemotherapy, allogeneic stem cell transplantation, or both. Elderly patients with AML have significant comorbidities, an increased frequency of adverse cytogenetic abnormalities, poor performance status, a higher incidence of AML arising from myelodysplastic syndromes (MDS), and resistance to conventional treatments (Dombret, 2008). For these reasons, elderly patients may not be candidates for standard intensive chemotherapy induction regimens (DiNardo, 2019). Furthermore, treatment options are few for patients who choose not to or are considered ineligible by their physician to receive intensive induction chemotherapy. Patients considered ineligible for intensive induction chemotherapy are generally patients older than 75 years of age or those 60 to 75 years old with significant comorbidities, poor performance status, or with complex cytogenetic abnormalities (Milligan, 2006). Though there have been promising developments in the use of lower-intensity therapies in this population such as low-dose cytarabine or recently approved combination regimens with the B-cell lymphoma-2 (BCL-2) inhibitor venetoclax (Venclexta Package Insert, 2020), the durability of response and overall prognosis remains poor. Targeted therapies may also be utilized in distinct subpopulations of AML patients. For individuals with FMS-like tyrosine kinase 3 (FLT3) mutated AML, tyrosine kinase inhibitors including midostaurin, gilteritinib or sorafenib (with HMAs [hypomethylating agents]) have a therapeutic role; ivosidenib or enasidenib can be used for patients with isocitrate dehydrogenase-1/isocitrate dehydrogenase-2 mutations, respectively; gemtuzumab ozogamicin can be used for patients with CD33-positive AML (NCCN, 2021a).

For the majority of patients with relapsed or refractory (R/R) AML with unfavorable prognostic features, intensive chemotherapy or other standard treatment options have poor outcomes with complete remission rate (CRR) no higher than 15% and median overall survival (mOS) less than 6 months (Estey, 1996; Ritchie, 2013; Roboz, 2014; Perl, 2019). Among AML patients who relapsed after having achieved a first complete remission (CR1), about 45% do so within 6 months, 75% within 12 months and 85% within 18 months (Breems, 2005; Estey 1996). While the minority of patients who experience relapse after more than 1 or 2 years in CR1 generally fare better, chances to achieve long term disease control for the majority of patients with R/R AML are dismal, exemplified by 3-year survival of 11% for adults up to 55 years old and 6% for patients above age

55 determined by analysis of eight pooled Eastern Cooperative Oncology Group (ECOG) studies for relapsed AML (Rowe, 2010). More recently, Onureg, an oral formulation of the hypomethylating agent azacitidine, in AML maintenance demonstrated improvement in both progression free survival (PFS) and overall survival (OS) for patients in CR1 that are ineligible for allogeneic stem cell transplantation (SCT) (Wei, 2020). While this is encouraging, the experience needs to be built upon (Reville, 2021). Although the approved combination regimen of venetoclax and azacitidine (DiNardo, 2020) has improved response rates and survival in this patient population compared with prior regimens (see Section 1.2.3), complete remission (CR) rates remain low and rates of eventual relapse are high, and this remains a population with a high unmet need. Continuing research efforts are needed to develop new agents and treatment regimens that are tolerable and effective in R/R AML patient population, and the addition of investigational agents to the combination of venetoclax and azacitidine may increase the remission rate and prolong survival, therefore addressing an important unmet medical need in patients with newly diagnosed (ND) and R/R AML.

1.1.2 Myelodysplastic Syndromes

Myelodysplastic syndromes are an umbrella term for a heterogeneous collection of hematopoietic stem cell disorders primarily affecting older adults. It is estimated that between 2 and 4 cases per 100,000 persons per year are diagnosed with MDS. The elderly are particularly vulnerable with annual incidence rates between 15 and 50 cases per 100,000 persons per year (Steensma, 2003). The prognosis depends on the individual's risk factors, with a median survival ranging from 5.3 years in low-risk patients to 1.6 and 0.8 years in high- and very high-risk patients, respectively (Greenberg, 2012).

Myelodysplastic syndromes are typically characterized by ineffective hematopoiesis in the BM and peripheral blood (PB) leading to cytopenias that manifest clinically as anemia, neutropenia, and/or thrombocytopenia of variable frequency and severity. Other less common presenting clinical features related to the cytopenias are an increased risk of infection or hemorrhage and a propensity to progress to AML (Catenacci, 2005).

For certain subtypes of MDS, excess blast cells are present (Bennett, 1982). Progress in understanding the pathobiology of MDS has evolved rapidly, as have an increasing number of myeloablative and supportive care strategies. The mainstay of therapy has been supportive care, which includes the use of red cell or platelet transfusions, treatment of infections, and the use of epoetin alfa or myeloid growth factors when needed (NCCN, 2021b; Silverman, 2000; Lübbert, 2000). Vidaza (azacitidine) has been shown to increase overall survival (OS) in patients with higher-risk MDS (HR-MDS) relative to conventional care, but it is not curative (Fenaux, 2009). Bone marrow transplantation has been effective both in patients under the age of 50 and in those older than 50 years who are in good health. However, this approach has limited value since most patients with MDS are older than 65 years of age and have significant comorbidities (Silverman, 2000).

The International Prognostic Scoring System (IPSS) is a validated standard for assessing the prognosis of primary untreated adult patients with MDS. The IPSS-R is a revision to the original IPSS which is particularly notable for the incorporation of prognostic cytogenetic features of MDS.

For patients with HR-MDS who have failed hypomethylating therapy, the prognosis is comparable to R/R AML with mOS between 4.5 and 11 months dependent on prognostic factors of age, performance status, cytogenetics, myeloblast percentage, platelet count and red cell transfusion dependency (Nazha, 2017; Bewersdorf, 2020a).

Relapsed or refractory HR-MDS patients are a high-unmet need population for which there is no standard of care and novel therapies are needed.

1.2 Compound Background

1.2.1 CC-95251

The investigational product CC-95251 (also known as BMS-986351) is a first-in-class, high affinity, fully human antibody, designed to bind to and modulate the biology of the macrophage inhibitory receptor signal regulatory protein alpha (SIRPα) by blocking the binding of SIRPα to cluster of differentiation (CD) 47. CD47 binding to SIRPα on macrophages and other phagocytes triggers a signaling pathway that inhibits phagocytosis, thus enabling CD47-expressing cells to avoid phagocytic removal. CC-95251 has an immunoglobulin G1 (IgG1) framework [redacted] CC-95251 did not induce cytokine release from human [redacted] in immobilized or soluble formats, with or without myeloid or T cell pre-activation, nor does it have antibody-dependent cellular phagocytosis (ADCP) activity against autologous T cells or monocytes. In combination with effector-competent, tumor-targeting antibodies (eg, cetuximab, rituximab), CC-95251 enhances macrophage-mediated phagocytosis of tumor cells in in vitro phagocytosis assays. CC-95251 is being developed as an injectable intravenous (IV) treatment for solid tumors and hematological malignancies and to date has been administered in subjects as a single agent or in combination with effector-competent tumor targeting antibodies (eg, cetuximab, an anti-epidermal growth factor receptor [anti-EGFR] monoclonal antibody; rituximab, an anti-cluster of differentiation 20 [anti-CD20] monoclonal antibody).

[redacted]

Please refer to the CC-95251 IB (Investigator Brochure) (for detailed information concerning the available pharmacology, toxicology, drug metabolism, clinical studies, and adverse event (AE) profile of CC-95251 (CC-95251 IB).

1.2.1.1 Nonclinical Pharmacology

1.2.1.1.1 Mechanism of Action

SIRPα is an immunoglobulin (Ig)-like family member and is expressed on monocytic and neuronal lineage cells. Macrophage phagocytic receptors can discriminate altered self-molecules on aged or dying cells from normal self-markers on healthy cells, resulting in either activation or inhibition of the phagocytosis response (Taylor, 2005). CD47 is a transmembrane protein ubiquitously expressed on human cells but may also be overexpressed by many different tumor cells (Chao, 2012; Edris, 2012; Willingham, 2012). The inhibitory CD47-SIRPα ligand-receptor pair has been identified as an important, but not universal, innate immune negative checkpoint regulator in the homeostatic clearance of apoptotic cells by macrophage-mediated phagocytosis (Matlung, 2017). The biology of SIRPα is differentiated from its related family members SIRP beta (β) and SIRP gamma (γ) due to the identified interactions and downstream signaling with its cognate ligand CD47 as a negative regulator of phagocytosis (Matlung, 2017). In the context of cancer, several types of neoplastic cells have been reported to overexpress CD47, providing an immune evasion mechanism by enhancing this "don't-eat-me" signal (Majeti, 2009; Chao, 2010; Willingham, 2012). Extensive preclinical in vitro and in vivo models disrupting the CD47-SIRPα interaction have demonstrated that hematologic and solid tumor clearance can be promoted by targeting either CD47 or SIRPα (Russ, 2018). Examples of CD47-SIRPα checkpoint blockade, either alone or in combination with well-known cancer opsonizing therapeutic antibodies, have been shown to effectively promote anti-tumor activity (Chao, 2010; Zhao, 2011).

The potential mechanisms of action of CC-95251 alone and in combination with azacitidine against AML include the following (numbers correspond to [redacted]

- CC-95251 binds to SIRPα on macrophages and other phagocytes disrupting the CD47-SIRPα "don't eat me" signaling and thus promoting phagocytosis of AML.
- Hypomethylating agents including azacitidine increase the expression of "eat me" signals such as calreticulin on AML, further promoting phagocytosis of the AML by macrophages via "eat me" receptors.
- [redacted]

1.2.1.1.2 In Vitro Pharmacology

1.2.1.1.2.1 Distribution of SIRPα and CD47

The distribution of SIRPα in normal and cancerous human tissues was investigated using immunohistochemistry (IHC). SIRPα expression was limited to the normal resident cells of monocyte origin in many tissues including spleen, lymph nodes, lung, gastrointestinal tract, and liver. Strong immunoreactivity was also observed in neural tissue of brain and spinal cord. Staining of lesser intensity was observed in transitional epithelium, glandular epithelia (mammary and prostate glands), kidney glomeruli, and pancreatic ductal epithelium.

In cancerous tissues, expression of SIRPα was confirmed on infiltrating macrophages in most tumor types including AML. Notably, SIRPα expression was evident in the neoplastic cells of several tumor types including melanoma, renal cell carcinoma, squamous cell carcinoma of the head and neck (SCCHN), AML, and diffuse large B-cell lymphoma. In AML, expression of SIRPα was evident in all cases, but was most prominent in those exhibiting monocytic differentiation as determined by the French-American-British (FAB) classification of acute myelomonocytic leukemia or M4.

In AML, CD47 expression is present across the bulk leukemia population but is increased in the self-renewing leukemia stem cell (LSC) fraction (Majeti, 2009). Increased CD47 expression portends a poor prognosis in AML (Majeti, 2009). Similarly, expression of CD47 in MDS is

increased in high-risk patients (by IPSS) compared with low-risk MDS and normal controls (Jiang, 2013).

1.2.1.1.2.2 CC-95251-mediated phagocytosis of AML

[redacted]

Azacitidine treatment of an AML cell line has been shown to increase the surface expression of the pro-phagocytic ligand calreticulin, which correlated with an increase in phagocytosis by monocyte-derived macrophages. Blockade of CD47 further augmented the phagocytosis of azacitidine-treated AML cells (Chao, 2020). [redacted]

[redacted]

[redacted] CC-95251 did not induce cytokine release from multiple human donor PBMCs in either platebound or soluble formats, with or without myeloid or T cell pre-activation.

[redacted]

1.2.1.3 Nonclinical Toxicology

All in vivo toxicity studies were conducted in the cynomolgus monkey as it is the pharmacologically relevant species identified for evaluation of potential CC-95251-related toxic effects. The highest dose evaluated in the 3 repeat-dose toxicity studies was [redacted] mg/kg CC-95251. Although ADAs were detected in individual monkeys, exposure to circulating free CC-95251 was achieved and maintained throughout the dosing phases in all studies at all dose levels, enabling appropriate evaluation of potential toxicities. All CC-95251-related effects were considered nonadverse due to their low severity.

In the 28-day exploratory toxicity study, the effects of CC-95251 were evaluated following separate administration to female cynomolgus monkeys twice (Days 1 and 15) as bolus IV injections at dose levels of [redacted] mg/kg/dose. No test article-related changes were observed; therefore, the no observed effect level for both molecules was [redacted] mg/kg/dose, the highest dose evaluated in this study.

In the pivotal GLP-compliant toxicity study, CC-95251 was also well-tolerated when administered to male and female cynomolgus monkeys via IV injection at doses of [redacted] mg/kg/dose weekly for a total of 5 doses. Six of 10 animals in the [redacted] mg/kg dose group were positive for anti-drug antibodies (ADA) by Dose 4, but exposure to CC-95251 was maintained in all animals negative for ADA in this low-dose group, and in all animals in the mid- and high-dose groups, throughout the study. CC-95251 was well tolerated with CC-95251--related findings limited to minimal to mild decreases in eosinophils at doses [redacted] mg/kg, with partial to complete recovery at the end of the 4-week treatment-free period. Due to the low severity, these findings were considered nonadverse. Therefore, the no observed adverse effect level and the highest non-severely toxic dose were the highest dose evaluated in this study, [redacted] mg/kg/dose.

In a GLP-compliant human tissue cross-reactivity study, CC-95251 demonstrated a pattern of staining generally consistent with the reported expression of SIRPα. Specifically, cell membrane staining was noted in mononuclear cells across a variety of tissues where these cells may normally be found (eg, lymphoid tissues), as well as in macrophages (alveolar and Kupffer cells), blood neutrophils, and marrow hematopoietic cells. Some epithelial cell types also stained (tonsil, thymus, intestine, prostate, pancreas, salivary glands). In some tissues (eg, pituicytes, spermatogenic cells, cardiomyocytes), only cytoplasmic elements stained; however, antibody binding to cytoplasmic sites in tissue cross-reactivity studies generally is considered of little to no toxicologic significance due to the inability of antibody drugs to access the cytoplasmic compartment in vivo (Hall, 2008; Leach, 2010). Staining of the neuropil of the brain and spinal cord was also observed; however, due to the inability of antibody drugs to cross blood-tissue barriers (eg, brain, spinal cord, eye) in vivo (Garbuzova-Davis, 2014; Ghate, 2006; Palmer, 2013; Pardridge, 2015), binding to these tissues in vitro is also generally considered of little to no toxicologic significance.

1.2.1.4 Nonclinical Pharmacokinetics

The pharmacokinetics (PK) parameters of CC-95251 were characterized after single and multiple IV doses. Systemic exposure to CC-95251 in [redacted]

[redacted]

1.2.1.5 Clinical Experience with CC-95251

A summary of the clinical experience with CC-95251 as of 14 Feb 2022 is provided in the CC-95251 IB (CC-95251 IB). There are 2 clinical trials with CC-95251 currently ongoing: CC-95251-ST-001, with [redacted] subjects enrolled as of the IB data cutoff date of 14-Feb-2022 and CA059-001, [redacted] AML/MDS specific data were available at the time of clinical data cutoff for the CC-95251 IB. Please refer to the IB for additional details and interim summary of pharmacodynamic, PK, and safety data (CC-95251 IB).

First-in-human (FIH) clinical study CC-95251-ST-001 is a Phase 1, open-label, dose escalation (Part A) and dose expansion (Parts B and C) study in subjects with advanced solid and hematologic cancers. As of 14 Feb 2022, [redacted] received at least one intravenous dose of CC-95251 [redacted]

The safety and tolerability of single agent CC-95251 [redacted] was evaluated in subjects with advanced solid cancers who have progressed on standard anticancer therapy or for whom no other approved conventional therapy exists and is summarized below.

The results of preliminary clinical safety assessments of the treated subjects in the CC-95251 monotherapy show the most frequently reported treatment-emergent adverse events (TEAEs) were [redacted]

[redacted] who had TEAEs that were suspected by the Investigator to be related to CC-95251. [redacted]

Investigator to be related to CC-95251 [redacted]

One subject in the [redacted]

In the monotherapy settings of CC-95251, [redacted]

Study CA059-001 is an open-label, Phase 1 dose-finding study of CC-95251 alone and in combination with antineoplastic agents in subjects with AML and MDS. No study-specific data were available at the time of clinical data cutoff for the CC-95251 IB. Please refer to the CC-95251 IB for detailed information concerning the available pharmacology, toxicology, drug metabolism, clinical studies, and adverse event profile of CC-95251.

1.2.2 Azacitidine

Azacitidine, an analog of the pyrimidine nucleoside cytidine, has effects on cell differentiation, gene expression, deoxyribonucleic acid (DNA) synthesis and metabolism, and causes cytotoxicity. Vidaza (azacitidine for injection) is approved by the United States Food and Drug Administration (US FDA) for the following 5 subtypes of the French-American-British (FAB) classification system of MDS: refractory anemia (RA) or refractory anemia with ringed sideroblasts (if accompanied by neutropenia or thrombocytopenia or requiring transfusions), refractory anemia with excess blasts, refractory anemia with excess blasts in transformation , and chronic myelomonocytic leukemia (CMMoL) (Vidaza package insert, 2022). Vidaza is also approved by the European Commission for the treatment of adult patients who are not eligible for hematopoietic stem cell transplantation with intermediate-2 (int-2) and high-risk MDS according to the IPSS, CMMoL with 10% to 29% marrow blasts without myeloproliferative disorder, AML with 20% to 30% blasts and multilineage dysplasia, and AML with > 30% marrow blasts according to the World Health Organization (WHO) classification. As of 18 May 2020, Vidaza has received marketing authorization in 86 countries worldwide, including the US and those in the EU. Current approved routes of administration include subcutaneous (SC) and IV (approvals vary by country).

Azacitidine has been extensively studied in MDS and has been shown in a large, randomized Phase 3 trial of higher-risk MDS patients to provide a survival advantage of 9.4 months over conventional care regimens (CCRs), thus altering the natural course of MDS. The median OS of azacitidine-treated patients was 24.5 months compared with 15.0 months for the combined CCR group, which included best supportive care, low-dose cytarabine, and intensive chemotherapy (Fenaux, 2009). In a subset of 113 patients with WHO-defined AML (mean age 70 years, 24% with unfavorable karyotype, median bone marrow blasts 23%) from the larger MDS study discussed above, the median OS was 24.5 months (N = 55) in the azacitidine arm compared with 16.0 months (N = 58) in the CCR arm (Fenaux, 2008; Fenaux, 2010). Additionally, the outcome was not significantly different in patients with an unfavorable karyotype, although the sample size was small. Silverman et al, using WHO AML criteria for diagnosis, reported a median OS of 19.3 months (N = 27) in azacitidine treated patients compared with 12.9 months (N = 25) in patients who received best supportive care (Silverman, 2006).

Additionally, Goldberg et al, reported on 33 patients who received azacitidine (N = 11, median age 74) or 7 + 3 intensive chemotherapy (N = 22, median age 67 years). Median blast counts at baseline were 42% in the azacitidine group and 65% in the intensive chemotherapy group. The median OS was 13.2 months in azacitidine treated patients compared with 9.2 months in intensive chemotherapy patients (Goldberg, 2006).

The efficacy of SC azacitidine to treat AML was evaluated in a controlled Phase 3 study (azacitidine [N = 241] vs CCR [N = 247]) in 488 patients age ≥ 65 years with newly diagnosed AML with > 30% blasts (Dombret, 2015). Azacitidine increased median OS by 3.8 months vs CCR arm (10.4 vs 6.5 months; P = .1009). One-year survival rates with azacitidine and CCR were 46.5% and 34.2%, respectively. A prespecified analysis that censored patients who received AML treatment after discontinuing study drug showed median OS with azacitidine vs CCR was 12.1

months vs 6.9 months. Azacitidine safety in patients age ≥ 65 years with AML (> 30% blasts) was consistent with its known safety profile in other trials.

The most commonly observed adverse reactions (SC or IV route) treated with azacitidine include nausea, anemia, thrombocytopenia, vomiting, pyrexia, leukopenia, diarrhea, injection site erythema, constipation, neutropenia, ecchymosis. Most common adverse reactions by IV route also included petechiae, rigors, weakness and hypokalemia. Cytopenias were the most common reason for dose reduction or discontinuation (Vidaza package insert, 2022).

Please refer to the current local prescribing information for detailed information concerning the available pharmacology, toxicology, drug metabolism, clinical studies, and adverse event profile of azacitidine.

1.2.3 Venetoclax

Venetoclax is a selective and orally bioavailable small-molecule inhibitor of B-cell lymphoma-2 (BCL-2), an anti-apoptotic protein. Overexpression of BCL-2 has been demonstrated in chronic lymphocytic leukemia and AML cells where it mediates tumor cell survival and has been associated with resistance to chemotherapeutics. Venetoclax helps restore the process of apoptosis by binding directly to the BCL-2 protein, displacing pro-apoptotic proteins like BCL-2-interacting mediator of cell death, triggering mitochondrial outer membrane permeabilization and the activation of caspases. In nonclinical studies, venetoclax has demonstrated cytotoxic activity in tumor cells that overexpress BCL-2.

In a Phase 1b study, the preliminary safety and efficacy of venetoclax in combination with HMA (either decitabine or azacitidine) in elderly patients with newly diagnosed (ND) AML was demonstrated (DiNardo, 2019). In VIALE-A (NCT02993523), a confirmatory Phase 3 study, patients with ND AML not eligible for intensive chemotherapy (IC) were randomized to receive venetoclax plus azacitidine (n = 286) or placebo plus azacitidine (n = 145) (DiNardo, 2020). Efficacy was established based on an improvement in OS with median OS of 14.7 months (95% confidence interval [CI]: 11.9, 18.7) in patients treated with venetoclax plus azacitidine compared to 9.6 months (95% CI: 7.4, 12.7) in those receiving placebo plus azacitidine (hazard ratio [HR] 0.66; 95% CI: 0.52, 0.85; $p < 0.001$). Patients treated with venetoclax plus azacitidine also demonstrated an improvement in CR rate: 37% (95% CI: 31%, 43%) versus 18% (95% CI: 12%, 25%) (FDA, 2020).

The incidence of the composite CR (CR or complete remission with incomplete blood recovery [CRi]) was 66.4% (95% CI, 60.6 to 71.9) in the azacitidine and venetoclax group versus 28.3% (95% CI, 21.1 to 36.3) in the control group ($p < 0.001$). (Dinardo, 2020). Based on this data, in October 2020 the FDA granted regular approval to venetoclax in combination with injectable azacitidine for adults with ND AML aged > 75 years or who have comorbidities precluding IC, followed by approval in May 2021 by the European Commission.

Data on R/R AML are scarce and heterogenous. Outcomes in patients with R/R AML are dismal, with a median OS of 3 to 7 months, and there is no approved standard of care (SOC). A systematic literature review and meta-analysis assessed overall response rate (ORR), and rates of CR/CRi for R/R AML subjects treated with venetoclax or venetoclax plus HMA/low-dose cytarabine (LDAC)

(Bewersdorf, 2020b). This systematic review and meta-analysis of venetoclax treatment in R/R AML included 7 studies with a total of 224 subjects and demonstrated an ORR of 38.7% and a CR rate of 19% for R/R AML subjects treated with venetoclax plus HMA/LDAC. Moreover, the meta-analysis showed that prior treatment with HMA did not preclude a response to subsequent venetoclax-based treatment.

The safety of venetoclax in combination with azacitidine (N = 283) versus placebo in combination with azacitidine (N = 144) was evaluated in the VIALE-A study. Subjects were randomized to receive venetoclax 400 mg orally once daily (QD) after completion of the ramp-up phase in combination with azacitidine (75 mg/m^2 either IV or SC on Days 1 through 7 of each 28-day cycle) or placebo in combination with azacitidine. Serious adverse reactions were reported in 83% of subjects who received venetoclax in combination with azacitidine, with the most frequent (≥ 5%) being febrile neutropenia (30%), pneumonia (22%), sepsis (excluding fungal; 19%), and hemorrhage (6%). Fatal adverse reactions occurred in 23% of subjects who received venetoclax in combination with azacitidine, with the most frequent (≥ 2%) being pneumonia (4%), sepsis (excluding fungal; 3%), and hemorrhage (2%).

In subjects with AML who followed the current 3-day ramp-up dosing schedule and the tumor lysis syndrome (TLS) prophylaxis and monitoring measures, the rate of TLS was 1.1% in subjects who received venetoclax in combination with azacitidine (VIALE-A). In subjects with AML, baseline neutrophil counts worsened in 95% to 100% of subjects treated with venetoclax in combination with azacitidine, decitabine, or low-dose cytarabine. Neutropenia can recur with subsequent cycles.

A detailed description of the chemistry, pharmacology, efficacy, and safety of venetoclax in combination with azacitidine is provided in the Summary of Product Characteristics (SmPC) and/or package insert approved in the local country (venetoclax Package Insert, 2020) (venetoclax SmPC, 2022).

1.3 Rationale

1.3.1 Study Rationale and Purpose

The study will explore the safety, tolerability, and preliminary clinical activity of CC-95251 as a single agent and in combination with antineoplastic agents in subjects with relapsed or refractory and treatment-naïve (TN) AML, relapsed or refractory and TN higher risk MDS (ie, IPSS-R [redacted]

There is strong rationale for evaluating CC-95251 as a single agent, in combination with injectable azacitidine (double combination), and in combination with injectable azacitidine and venetoclax (triple combination) in the previously mentioned indications.

In the context of cancer, several types of neoplastic cells have been reported to overexpress CD47, providing an immune evasion mechanism by enhancing the “don’t-eat-me” signal. In AML, CD47 expression is present across the bulk leukemia population but is increased in the self-renewing leukemic stem cell (LSC) fraction. Additionally, increased CD47 expression portends a poor prognosis in AML (Majeti, 2009). Similarly, expression of CD47 in MDS is increased in high-risk patients compared with low-risk MDS and normal controls (Jiang, 2013).

[redacted]

Azacitidine treatment of an AML cell line has been shown to increase the surface expression of the pro-phagocytic ligand calreticulin which correlated with an increase in phagocytosis by monocyte-derived macrophages. Blockade of CD47 further augmented the phagocytosis of azacitidine-treated AML cells (Chao, 2020). [redacted]

In vitro phagocytosis assays reported in the literature demonstrated that treatment with venetoclax or azacitidine induced phosphatidylserine in MOLM-13 cells, which may function as a pro-phagocytic signal and contribute to the enhanced phagocytosis. The mechanisms of increased phagocytosis and the induction of "eat-me signals" by combination treatment with venetoclax andazacitidine are currently under investigation (Jia, 2021).

Additionally, recent clinical data targeting the CD47-SIRPα pathway has shown anti-cancer activity across a variety of solid cancers and hematologic malignancies. Magrolimab (Hu5F9-G4), an anti-CD47 monoclonal antibody in combination with azacitidine demonstrated preliminary clinical activity in an ongoing Phase 1b trial evaluating previously untreated subjects with chemotherapy ineligible AML and intermediate to very high risk MDS (Sallman, 2020a, Sallman, 2020b).

More recent studies are evaluating the combination of azacitidine and venetoclax with agents targeting the CD47/SIRPα axis including magrolimab (NCT04435691) and ALX148, a high affinity CD47 blocker fusion protein (NCT04755244) in both R/R and TN AML. These studies have demonstrated limited response in the R/R setting, particularly in subjects previously exposed to venetoclax; however, they have demonstrated promising results in the front-line setting, notably in subjects with TP53-mutated AML (Daver, 2022, Garcia-Manero, 2022).

Taken together, this evidence highlights a strong biological rationale for the evaluation of CC-95251 as monotherapy and in combination with either azacitidine or azacitidine and venetoclax in the treatment of subjects with AML and higher risk MDS.

A cumulative benefit and risk assessment for this study is provided below (Section 1.4). Please refer to the CC-95251 IB for additional details regarding the physical and chemical properties, nonclinical studies, and toxicology data for CC-95251.

1.3.2 Rationale for the Study Design

Part A

The dose escalation part (Part A) of the study will be conducted using [redacted] to guide CC-95251 dose escalation / de-escalation decisions, with the final decisions being made by the SRC, whose members include Investigators (and/or designated representatives), the Sponsor's Medical Monitor, safety physician, clinical scientist, and the study manager. Ad hoc attendees may include the study PK scientist, biostatistician, and translational research scientist. Other internal and external experts may be consulted by the SRC, as necessary. [redacted]

After enrollment has been completed in the corresponding Part A cohorts, the SRC will undertake an evaluation of the available safety, PK, PD, and preliminary efficacy data to make a

determination of the preliminary dose and schedule of CC-95251 to test in the expansion cohorts (Parts B, C, and D).

Part B

[redacted]

Additional cohorts of subjects testing CC-95251 in combination with additional antineoplastic agents in subjects with R/R AML or R/R MDS may be considered at the recommendation of the SRC and will be included by protocol amendment.

Part C

The heterogeneous collection of clonal hematopoietic stem cell disorders that broadly make up MDS remain a challenging clinical scenario with very limited therapeutic options in the front-line setting. The elderly are particularly vulnerable to the development of MDS with annual incidence rates between 15 and 50 cases per 100,000 persons per year (Steensma, 2003). The prognosis depends on the individual's risk factors, with a limited median survival of only 0.8 to 1.6 years in patients with high or very high-risk presentations, respectively (Greenberg, 2012).

While hypomethylating agents such as azacitidine have been shown to increase OS in patients with high-risk MDS relative to conventional care, they do not represent a curative option (Fenaux, 2009) and the majority of these patients continue to experience only a limited extent and duration of benefit with this class of drugs. Furthermore, potentially curative bone marrow transplantation has limited applicability to the broader MDS population in light of advanced age and comorbidities (Silverman, 2000). There also remains both a significant risk of transformation of MDS into AML and no approved agents that impact survival in those who have failed to respond or progressed on hypomethylating agents, highlighting the need to attain better disease control in the front-line setting. In conclusion, there remains a significant need to expand on therapeutic options available to the treatment-naïve HR-MDS patient population. The safety profile of CC-95251 to date and the potential to combine this differentiated mechanism of action with that of standard-of-care azacitidine supports evaluating this combination in the treatment -naïve (ie, previously untreated), intermediate, high or very high risk (ie, IPSS-R [redacted]) MDS population in the Part C dose expansion.

[redacted]

Part D

Part D expansion will evaluate CC-95251 in combination with injectable azacitidine and venetoclax in subjects with TN AML and who are not candidates to receive IC due to comorbidities or age (ie, ≥ 75 years). Venetoclax is approved by the FDA and European Commission in this setting; however, while this regimen has improved response rates and OS in this population compared to azacitidine monotherapy, prognosis remains poor, and this remains an area of high unmet need. The addition of agents with different mechanisms of action to this combination may confer added benefit. Currently, other agents targeting [redacted]

[redacted]

[redacted]

The SRC will continue to review safety data regularly throughout the study and make recommendations about study continuation, dose modification, and establishment of a RP2D as appropriate. Enrollment in Part D may proceed concurrently with enrollment in the Part B and C expansion cohorts.

Other combinations of CC-95251 and antineoplastic agents in subjects with R/R AML and/or R/R or TN MDS may be explored at the recommendation of the SRC and will be added by subsequent protocol amendment.

1.3.3 Rationale for Dose, Schedule and Regimen Selection

The ongoing, Phase 1 study CC-95251-ST-001 has evaluated escalating doses of CC-95251 up to a dose level [redacted] mg/kg [redacted] administered as monotherapy, in combination with cetuximab in subjects with colorectal cancer and SCCHN and in combination with rituximab [redacted] non-Hodgkin's Lymphoma (NHL).

[redacted]

[redacted]

As the demonstrated mechanism of action of CC-95251 involves [redacted]

[redacted] based on review of the available safety, PK, PD, and preliminary efficacy data [redacted] The investigation of any other alternate dosing schedule beyond those stipulated in the current protocol version will be submitted in a protocol amendment.

The dosing of azacitidine will follow local prescribing information and institutional standard of care at 75 mg/m^2 with an exception to allow flexibility on the dosing schedule, either Days 1-7 or Days 1-5 and 8-9 in each 28-day cycle. [redacted]

1.3.4 Rationale for Choice of Combination Compounds

1.3.4.1 Rationale for Combination of CC-95251 with Azacitidine

The safety and clinical profile of azacitidine have been well-characterized in the setting of both AML and MDS. As detailed in Section 1.2.2, the use of azacitidine in the therapeutic treatment landscape for these myeloid malignancies makes it a preferred agent to pair in combination with CC-95251.

Preclinically, azacitidine treatment of an AML cell line has been shown to increase the surface expression of the pro-phagocytic ligand calreticulin which correlated with an increase in phagocytosis by monocyte-derived macrophages. Blockade of CD47 further augmented the phagocytosis of azacitidine-treated AML cells (Chao, 2020). [redacted]

Magrolimab (Hu5F9-G4), an anti-CD47 monoclonal antibody, in combination with azacitidine demonstrated preliminary clinical activity in a Phase 1b trial evaluating untreated patients with intermediate to very high risk MDS and chemotherapy ineligible AML and several additional trials are now underway which target the CD47/SIRPα axis in AML and MDS (Sallman, 2020a, Sallman, 2020b, Sallman, 2023). The early signals of clinical activity in AML and MDS seen by targeting of the CD47/SIRPα axis lend further support to the potential for CC-95251 plus azacitidine in these disease settings.

1.3.4.2 Rationale for Combination of CC-95251 with Azacitidine Plus Venetoclax

The safety and clinical profile of injectable azacitidine in combination with venetoclax has been well characterized in the setting of AML. As detailed in Section 1.2.3, injectable azacitidine and venetoclax has demonstrated improved OS and CR rates compared to azacitidine alone, and this combination is now approved by the FDA and European Commission as a standard of care (SOC) for adults with ND AML not eligible for intensive induction chemotherapy. Despite this improvement over prior regimens, CR rates and OS remain low, and this is not a curative therapy.

Outcomes of subjects with R/R AML are dismal, with a median OS of 3 to 7 months, and while there is no approved SOC, the combination of venetoclax with injectable azacididine has been used successfully in this population, albeit with low OR and CR rates. Therefore, these remain areas of high unmet therapeutic need, and the addition of agents to this regimen with a different mechanism of action may confer additional benefit. Preliminary results from recent studies combining agents targeting the CD47/SIRPα axis such as magrolimab and ALX148 in R/R and TN AML have demonstrated limited response, though with more promising results in the front-line setting (Daver, 2022, Garcia-Manero, 2022). These early results lend further support to the potential for CC-95251 plus azacitidine and venetoclax in these settings.

1.3.5 Rationale for Pharmacodynamics and Potential Predictive Biomarkers

The antitumor function of CC-95251 depends on the binding of SIRPα on monocytes, neutrophils, and dendritic cells, and some tumor cells (eg, AML blasts), promoting phagocytosis and killing of tumor cells. PD biomarkers will help to inform the appropriate dose and schedule of CC-95251 by providing measures of target engagement, immune activation status, cytokine release, disease progression, and tumor burden. Additionally, the sampling plan and downstream analyses of the exploratory endpoints aim to address open questions centered on the biology governing the activity and durability of the CC-95251 antitumor response, as well as potential resistance mechanisms that could include underlying immune status, the tumor microenvironment, or direct resistance by the tumor.

Multiple pharmacodynamic biomarkers will be explored to characterize dose-dependent CC-95251 activities as a single agent and in combination with azacitidine or azacitidine and venetoclax. These may include:

- Frequencies of leukemic blasts and monocytes in the bone marrow and periphery
- SIRPα target expression levels and coverage (receptor occupancy)
- [redacted]

Potential predictive markers of efficacy of CC-95251 alone or in combination with azacitidine or in venetoclax and azacitidine will be explored for correlates of response. Samples may be characterized using molecular and cellular assays potentially including, but not limited to:

- Baseline SIRPα expression on tumor and/or immune cells and presence of immune cell subsets
- [redacted]
- [redacted]

Resistance to the SIRPα-CD47 axis has not been characterized, although changes in the tumor microenvironment and acquired mutations within the tumor could be factors that drive resistance to therapeutic drugs. Potential pharmacodynamic biomarkers will be evaluated from samples collected pre- and post-treatment from bone marrow and peripheral blood, as applicable. Assessments will explore biomarkers related to safety, efficacy, and resistance to treatment with

CC-95251 alone or in combination. Biomarker assessments may include, but are not limited to, the following:

- SIRPα expression levels and spatial localization of immune cells from paired bone marrow biopsies; single cell expression levels on bone marrow aspirates
- Minimal residual disease (MRD) may be measured on bone marrow samples at time of response assessments, end of treatment (EOT) and/or time of CR using flow cytometry and/or molecular analyses (eg, next generation sequencing [NGS]).
- [redacted]
- [redacted]
- [redacted]

Other biomarkers of interest may be evaluated as determined by additional data.

Genetic variation may impact a subject's response to study intervention, susceptibility to disease, and severity and progression of disease. Variable response to study intervention may be due to genetic determinants that impact intervention absorption, distribution, metabolism, and excretion; mechanism of action of the intervention; disease etiology; and/or molecular subtype of the disease being treated.

DNA samples will be used for research related to the study intervention(s) and/or disease/condition under study and related conditions. The samples may also be used to develop tests/assays, including diagnostic tests related to the study intervention(s) and/or disease/condition under study and related conditions. Genetic research may consist of the analysis of 1 or more candidate genes or the analysis of genetic markers throughout the genome or analysis of the entire genome. Biomarker samples may also be used for research to develop methods, assays, prognostics, and/or diagnostics.

The biomarker assessments will be conducted according to the laboratory manual.

1.4 Risk/Benefit Assessment

1.4.1 Benefit Assessment

Patients with intermediate to very high-risk MDS and AML have a poor prognosis overall with a limited number of therapeutic options available to modify the course of the disease. As a result, there remains a significant need to develop novel therapeutics that can generate clinically meaningful responses in these therapeutic indications. Multiple lines of preclinical evidence and now emerging clinical trial data suggest the potential for therapeutic efficacy via targeting of the CD47-SIRPα macrophage checkpoint axis in the setting of HR-MDS and AML.

Azacitidine has an established role in the therapeutic management of both HR-MDS and AML and a well-characterized safety profile. As a result, it is commonly utilized as a core component of multi-drug regimens with partnered agents that carry distinct and potentially synergistic

mechanisms of action. CC-95251 is a first-in-class, [redacted]. The combination of CC-95251 with azacitidine provides the opportunity to [redacted]. In the Part C expansion, administration of CC-95251 in combination with azacitidine to newly diagnosed (IPSS-R [redacted]) MDS subjects ensures that study subjects are receiving the clinical standard-of-care hypomethylating agent with the added potential benefit for more robust disease-modifying activity due to the addition of CC-95251.

Recently, a randomized trial (VIALE-A) of injectable azacitidine plus either venetoclax or placebo in untreated AML subjects who were ineligible for standard induction therapy because of coexisting conditions, or because they were ≥ 75 years of age, demonstrated a 5.1-month increase in OS and higher CR rate (36.7% vs 17.9%) among subjects who received venetoclax in combination with injectable azacitidine compared to those who received azacitidine alone (DiNardo 2020). Systematic review and meta-analysis of venetoclax treatment in R/R AML, which included 7 studies with a total of 224 subjects, demonstrated an ORR of 38.7% and CR rate of 19% for R/RAML subjects treated with venetoclax plus HMA/LDAC (Bewersdorf 2020b). Moreover, the meta-analysis showed that prior treatment with HMA did not preclude a response to subsequent venetoclax-based treatment (Bewersdorf 2020b). Although the approved combination regimen of venetoclax and azacitidine has improved response rates in the above-mentioned AML populations compared with prior regimens, this remains a population without a curative treatment option. It is hypothesized that adding an investigational third agent such as CC-95251 which targets a different mechanistic pathway may increase remission rates and prolong survival, therefore addressing an important unmet medical need.

1.4.2 Risk Assessment

The proposed study design includes various components aimed at limiting potential risks to study subjects. The subject population will not include individuals, such as children or mentally disabled adults, who are not capable of expressing themselves in the same way as mentally competent adults, in order to detect any potential harm to the subjects as early as possible. Standard eligibility criteria are included to ensure acceptable baseline organ function (including hematopoietic function) and lack of clinically significant comorbid diseases. Specific precautions for early development include use of a study design with dose escalation and subsequent expansion, a defined DLT observation period and DLT monitoring, staggered enrollment, hospitalization for observations as specified in the study protocol, as well as SRC oversight built into the protocol. Subjects will be monitored for possible toxicity throughout the study by physical examination, vital sign and AE collection, through standard and specialized laboratory tests including complete blood counts, serum chemistries, and electrocardiogram (ECG), and observed for survival follow-up starting from the last dose of the investigational agent for up to [redacted] or until death, lost to follow-up, or the end of study, whichever occurs first. Study subject monitoring and guidelines for

management for select AEs of interest for the study drug are included in the study protocol (Section 7.2.7.8).

The [redacted] will be utilized to guide CC-95251 dose escalation/de-escalation decisions, with the final recommendation being made by the SRC. Additionally, the protocol defines the criteria in the dose escalation (Part A) that must be met prior to opening enrollment to cohorts testing CC-95251 in combinations with azacitidine or with venetoclax and azacitidine in the relapsed/refractory setting. The protocol also specifies that testing of combinations in newly diagnosed MDS or AML populations in dose expansion may only occur [redacted] Furthermore, the protocol also defines rules for monitoring of excess toxicities during the dose expansion cohorts outlined in the study. Review of the TEAEs to date with monotherapy CC-95251 does not suggest a high likelihood of overlapping toxicity with common AEs attributed to azacitidine or the combination of venetoclax and azacitidine. Furthermore, there is low potential for drug-drug interactions in this proposed pairing of a biologic monoclonal antibody with a nucleoside analog and small molecule inhibitor. Well-defined discontinuation criteria are established in the protocol for individual subjects for both safety and treatment futility with clear criteria for study intervention discontinuation, dose delay, and toxicity management.

The risks associated with treatment with CC-95251 are detailed in Table 1.

Table 1: Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention: CC-95251		
[redacted]		• This study protocol includes prophylaxis, monitoring and management guidance for [redacted] in Section 7.2.7.8 • [redacted] in this study as described in the study protocol. See Section 7.2.1.1
		• Subjects are being monitored for possible toxicity throughout the study by standard and specialized laboratory tests as described in the study protocol, Section 6.2.6, Table of Events (Section 5) • Management guidance including dose modification guidelines included in this study protocol (Section 7.2.6 and Section 7.2.7.7)

Table 1: Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
[redacted]		• Subjects are being monitored for possible toxicity throughout the study by physical examination, vital signs and AE collection, and through standard and specialized laboratory tests as indicated in this study protocol (Section 5 and Section 6.2.6) • Dose modification guidelines included in this study protocol (Section 7.2.7.7) • Permitted antimicrobial prophylaxis is described in Section 7.2.7.8.5 and Section 8.1
		• Subjects are being monitored for possible toxicity throughout the study by physical examination, vital signs and AE collection, and through standard and specialized laboratory tests as indicated in this study protocol (Sections 5 and 10.1) • Dose modification guidelines included in this study protocol (Section 7.2.7.7)
		• Subjects are being monitored for possible toxicity throughout the study by physical examination and AE collection, and through standard and specialized laboratory tests [redacted] (Sections 5 and Section 6.2.6) • Eligibility criteria [redacted] and dose modification guidelines included in this study protocol (Section 4.2 and 7.2.7.7)
		• This study protocol includes monitoring and management of CRS and MAS (Section 7.2.7.8.3) • Full emergency resuscitation facilities should be immediately available, and subjects should be under close supervision of the Investigator or appropriately trained staff at all times (Section 7.2.7.8.3) • [redacted]
		• Subjects with AML will be hospitalized for at [redacted] after the first dose of CC-95251 (C1D1) for IV

Table 1: Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	extensive bone marrow involvement/bone marrow blast percentage.	hydration [redacted] to monitor for adverse events (Sections 7.2.1.1, 8.1, and 8.2) • Subjects will be closely monitored for [redacted] by laboratory tests as described in Sections 5 and Section 6.2.6 • [redacted] monitoring and management guidelines included in Section 7.2.7.8.2, and dose modification guidelines in [redacted]
Study Intervention: Venetoclax		
[redacted] Neutropenia Lymphopenia Anemia Thrombocytopenia Serious and fatal infections	These events were commonly reported and are considered important identified risks. [redacted] results from on-target effects and occurs during the initial dosing/ramp-up period.	[redacted] • Low starting dose followed by gradual dose ramp-up • Subjects with AML receiving venetoclax will be hospitalized during ramp-up [redacted] for IV hydration [redacted] and to monitor for adverse events (See Sections 7.2.1.1, 8.1, and 8.2) • Subjects will be closely monitored for [redacted] by laboratory tests as described in Sections 5 and 6.2.6 • [redacted] monitoring and management guidelines included in Section 7.2.7.8.2, and dose modification guidelines in [redacted] Serious/Fatal Infections • Physical examination, vital sign and laboratory assessments, and monitoring for infections. Use of [redacted] as needed to treat infections. Neutropenia/Lymphopenia/Anemia/Thrombocytopenia • Dose modification guidelines included in this study protocol in Section7.2.7.7, [redacted] and [redacted] • Monitor for infections and bleeding • Hematologic toxicity monitoring and management guidance included in Section 7.2.7.8.4, Hematological Toxicity
Study Intervention: Azacitidine		
Anemia Bleeding Bone marrow suppression Neutropenia Febrile neutropenia Infections Leukopenia Pancytopenia	Serious and fatal hemorrhagic events (GI, intracranial), and serious and fatal infections have been reported.	Laboratory monitoring. Monitor for infections and bleeding. Use of [redacted] as needed to treat infections Azacitidine dose adjustment recommendations are provided in [redacted] as well as in the product label (note: dose increases will not be allowed)

Table 1: Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Procedures		
BMA or BMB, venipuncture	Planned study procedures (BMA or BMB, venipuncture) are consistent with routine care for AML subjects and do not pose additional risk to study subjects.	• Routine medical evaluation and AE assessment
Other		

Susceptibility of immunocompromised subjects with AML and MDS to SARS-CoV-2 infections	The global COVID-19 pandemic has been identified as a potential risk to clinical trial subjects in general. Immunocompromised subject populations, such as those with AML and MDS, may be more susceptible to infections, including SARS-CoV-2 infections. In addition, the potential impact of venetoclax and azacitidine administration on the frequency or severity of SARS-CoV-2 infections in subjects with AML or MDS is currently unknown.	• To mitigate this potential risk, RT-PCR testing for SARS-CoV-2 infection will be mandatory for all subjects. Subjects with recent or acute
		• SARS-CoV-2 infections will be excluded or delay the start of treatment as defined in Section 4.3 and 7.2.7.8.5.1
		• If a subject has a confirmed
		• SARS-CoV-2 infection while on study intervention, dose delay or interruption of study intervention is required as described in Section 7.2.7.8.5.1
		  • Testing for COVID-19 should follow local standard practice
		  • None-live COVID-19 vaccination is a simple concomitant medication within the study (Section 8.1)

Abbreviations: AE = Adverse event; [redacted]; AML = Acute myeloid leukemia; [redacted] BMA = Bone marrow aspirate; BMB = Bone marrow biopsy; C = cycle; [redacted]; D = day; [redacted] GI = Gastrointestinal, [redacted]; IV =intravenous; [redacted]; MDS = Myelodysplastic Syndromes; RT-PCR = Reverse transcription-polymerase chain reaction; [redacted] SARS-CoV-2 = Severe acute respiratory syndrome coronavirus 2; [redacted]

1.4.3 Overall Risk/Benefit Conclusion

As demonstrated by the clinical data summarized in Section 1.2.1.5, CC-95251 is well tolerated as monotherapy and in combination with cetuximab or rituximab in solid tumors, with a toxicity profile that supports its use in combination with azacitidine or in triple combination with venetoclax and azacitidine. Given the poor prognosis for MDS and AML subjects with R/R disease, and limited, noncurative therapeutic options for ND AML subjects not eligible for chemotherapy and ND MDS subjects ineligible for stem cell transplant, there remains a significant need to develop novel therapeutics that can generate clinically meaningful responses in these therapeutic indications. Multiple lines of preclinical evidence and now emerging clinical trial data

suggest the potential for therapeutic efficacy via targeting of the CD47-SIRPα macrophage checkpoint axis in the setting of HR-MDS and AML. Clinical experience with CC-95251 to date suggests a manageable safety profile with low expected risk to the subject populations while having a strong rationale for enhanced therapeutic activity in this difficult clinical setting. In summary, the benefits of CC-95251 alone and in combination with either azacitidine or venetoclax and azacitidine are expected to outweigh the risks for subjects treated with these compounds. The Sponsor will evaluate the benefit/risk profile of the study on an ongoing basis. This evaluation will be based on all available data with particular attention regarding (i) AEs or other safety trends in clinical studies involving CC-95251 in combination with azacitdine or venetoclax plus azacitidine, whose character, severity, and/or frequency suggest that subjects would be exposed to an unreasonable and significant risk of illness or injury; (ii) new nonclinical data suggesting unreasonable and significant risk of illness or injury. If such evaluation suggests that the benefit/risk profile of the study has become unfavorable to subjects, the Sponsor will take appropriate action to optimize and ensure study subjects safety.

Overall, based on the current available data, the defined safety management/monitoring plan specified in the protocol, the low expectation for overlapping toxicities, and the current therapeutic benefit versus risk ratio, there is an acceptable level of risk and potential therapeutic benefit to proceed with the current study in the subject population at the dose regimen specified in the protocol.

2 STUDY OBJECTIVES AND ENDPOINTS

Table 2: Study Objectives

Primary Objective(s)
The primary objectives of the study are: • To determine the safety and tolerability of CC-95251 alone and in combination with antineoplastic agents • To define the recommended Phase 2 dose (RP2D) of CC-95251 alone and in combination with antineoplastic agents in subjects with AML and MDS
Secondary Objective(s)
The secondary objectives are: • To assess the preliminary efficacy of CC-95251 as a single agent and in combination with antineoplastic agents in AML and MDS • To characterize the pharmacokinetics (PK) of CC-95251 as a single agent and in combination with antineoplastic agents in AML and MDS • To evaluate the presence, frequency and functional impact of anti-CC-95251 antibodies (anti-drug antibodies [ADA])

Table 2: Study Objectives

Exploratory Objective(s)
The exploratory objectives are: • To explore the relationship between dose and systemic exposure of CC-95251 and measures of toxicity, efficacy, and PD biomarkers. • To evaluate molecular and/or cellular biomarkers in the bone marrow and blood that may be associated with efficacy of CC-95251 • To evaluate the minimal residual disease (MRD) status, by flow cytometry and/or relevant gene sequencing methods

Abbreviations: ADA = anti-drug antibodies; AML = acute myeloid leukemia; MDS = myelodysplastic syndromes; MRD = minimal residual disease; PD = Pharmacodynamics; PK = pharmacokinetics.

Table 3: Study Endpoints

Endpoint	Name	Description	Timeframe
Primary	Safety	DLTs evaluated using the NCI CTCAE criteria, Version 5.0. Adverse events, including TEAEs, laboratory assessments, ECG results, ECOG performance status, and vital signs	Dose escalation and dose expansion Screening to [redacted] after the last dose of study treatment
Secondary	Preliminary efficacy[a]	Complete remission rate (CRR) (as assessed by the Investigator) for AML according to the modified European Leukemia Net (ELN) response criteria (CR + CRh + CRi), ORR (CR + CR_{MRD-} + CRh + CRi + MLFS + PR) CRR (as assessed by the Investigator) for MDS according to the modified IWG Response Criteria (CR), ORR (CR + CRh + marrow CR + PR) Duration of remission, duration of response, stable disease rate (MDS only), relapse-free survival, event-free survival, progression-free survival, time to remission/response, transfusion independence, time to AML transformation for MDS subjects, OS rates at 6 and 12 months	Dose expansion Day 1 to end of follow up
Secondary	Pharmacokinetics (PK)	Estimate parameters including but not limited to C_{max}, C_{min}, C_{trough}, $AUC_{(0-T)}$, $AUC_{(TAU)}$, t_{max}, CLT, and accumulation index of CC-95251, when feasible as a single agent and in combination with antineoplastic agents in AML and MDS	Dose escalation and dose expansion Day 1 to 8 weeks post-dose of CC-95251
Secondary	Anti-drug Antibody (ADA)	Determine the presence and frequency of anti CC-95251 antibodies (ADAs) using a validated electrochemiluminescence (ECL) assay	Dose escalation and dose expansion Day 1 to 8 weeks post-dose of CC-95251
Exploratory	Pharmacodynamics (PD)	Potential pharmacodynamic biomarkers will be explored in blood at baseline and on study treatment and may include: • [redacted] • [redacted]	Dose escalation and dose expansion Day 1 to end of follow up

Table 3: Study Endpoints

Endpoint	Name	Description	Timeframe
		• [redacted] • [redacted]	
Exploratory	PD	Potential pharmacodynamic biomarkers will be explored in bone marrow at baseline and on study treatment and may include: • [redacted] • [redacted] • [redacted] • [redacted] • [redacted]	Dose escalation and dose expansion Day 1 to end of follow up
Exploratory	Mechanisms of Response/Resistance	Molecular and/or cellular biomarkers in the bone marrow will be explored as potential predictors of response to CC-95251 [redacted]	Dose escalation and dose expansion Day 1 to end of follow up
Exploratory	Preliminary efficacy (MRD)[b]	Proportion of subjects achieving MRD negativity at any time on/after treatment with CC-95251 alone and in combination with azacitidine or azacitidine and venetoclax	Dose escalation and dose expansion Day 1 to end of follow up

Abbreviations: ADA = anti CC-95251 antibodies; AML = acute myeloid leukemia; $AUC_{(0-T)}$ = area under the concentration time-curve from time zero to time of last quantifiable concentration; $AUC_{(TAU)}$ = area under the concentration-time curve in a dosing interval; CLT = total body clearance of the drug from the serum; C_{max} = maximum serum concentration of drug; C_{min} = minimum serum concentration of drug; CR = complete remission; CRh = morphologic complete remission with partial hematologic recovery; CRi = morphologic complete remission with incomplete blood recovery; CR_{MRD-} = Morphologic complete remission without minimal residual disease; CRR = complete remission rate; C_{trough} = trough observed serum concentration; DLT = dose-limiting toxicity; ECG = electrocardiogram; ECL = electrochemiluminescence; ECOG = Eastern Cooperative Oncology Group; ELN = European Leukemia Net; IWG = International Working Group; MDS = myelodysplastic syndromes; MLFS = morphologic leukemia-free state; MRD = minimal residual disease; NCI CTCAE = National Cancer Institute

common terminology criteria for adverse events; [redacted]; ORR = objective response rate; OS = overall survival; PD = pharmacodynamics; PK = pharmacokinetics; [redacted] TEAE = treatment-emergent adverse events; t_{max} = time to peak (maximum) serum concentration.

a [redacted]

b [redacted]

3 OVERALL STUDY DESIGN

3.1 Study Design

Study CA059-001 is an open-label, multicenter, Phase 1 study testing the safety and efficacy of CC-95251, a monoclonal antibody directed against SIRPα, alone and in combination with antineoplastic agents in subjects with R/R AML and R/R or treatment-naïve MDS. This protocol is intended to evaluate various drug combinations with CC-95251, as separate arms, over the life of the protocol, using the same objectives. CC-95251 as a single agent and as part of each of the combinations will be evaluated separately (ie, the intention is not to compare between monotherapy or combinations) for the purposes of the objectives, trial design, and statistical analysis.

The study will consist of 4 parts with a dose escalation (Part A) and dose expansion (Parts B, C, and D) as detailed below [redacted]

- Part A: Dose escalation with CC-95251 alone and in combination with injectable azacitidine in subjects with relapsed/refractory (R/R) AML and R/R intermediate, high or very high risk (ie, IPSS-R [redacted] MDS.
- Dose escalation with CC-95251 in combination with injectable azacitidine and venetoclax (triple combination) in subjects with R/R AML.
- Part B: Dose expansion testing CC-95251 alone and in combination with injectable azacitidine in R/R AML and R/R intermediate, high or very high risk (ie, IPSS-R [redacted] MDS.
- Part C: CC-95251 dose expansion in combination with injectable azacitidine in treatment-naïve subjects with intermediate, high or very high risk (ie, IPSS-R [redacted]) MDS.
- Part D: CC-95251 dose expansion in combination with injectable azacitidine and venetoclax (triple combination) in subjects with TN AML ineligible (IE) for intensive chemotherapy (IC).
- Other combinations of CC-95251 and antineoplastic agents in subjects with R/R AML and/or R/R or treatment-naïve MDS may be explored at the recommendation of the SRC and will be added by subsequent protocol amendment.

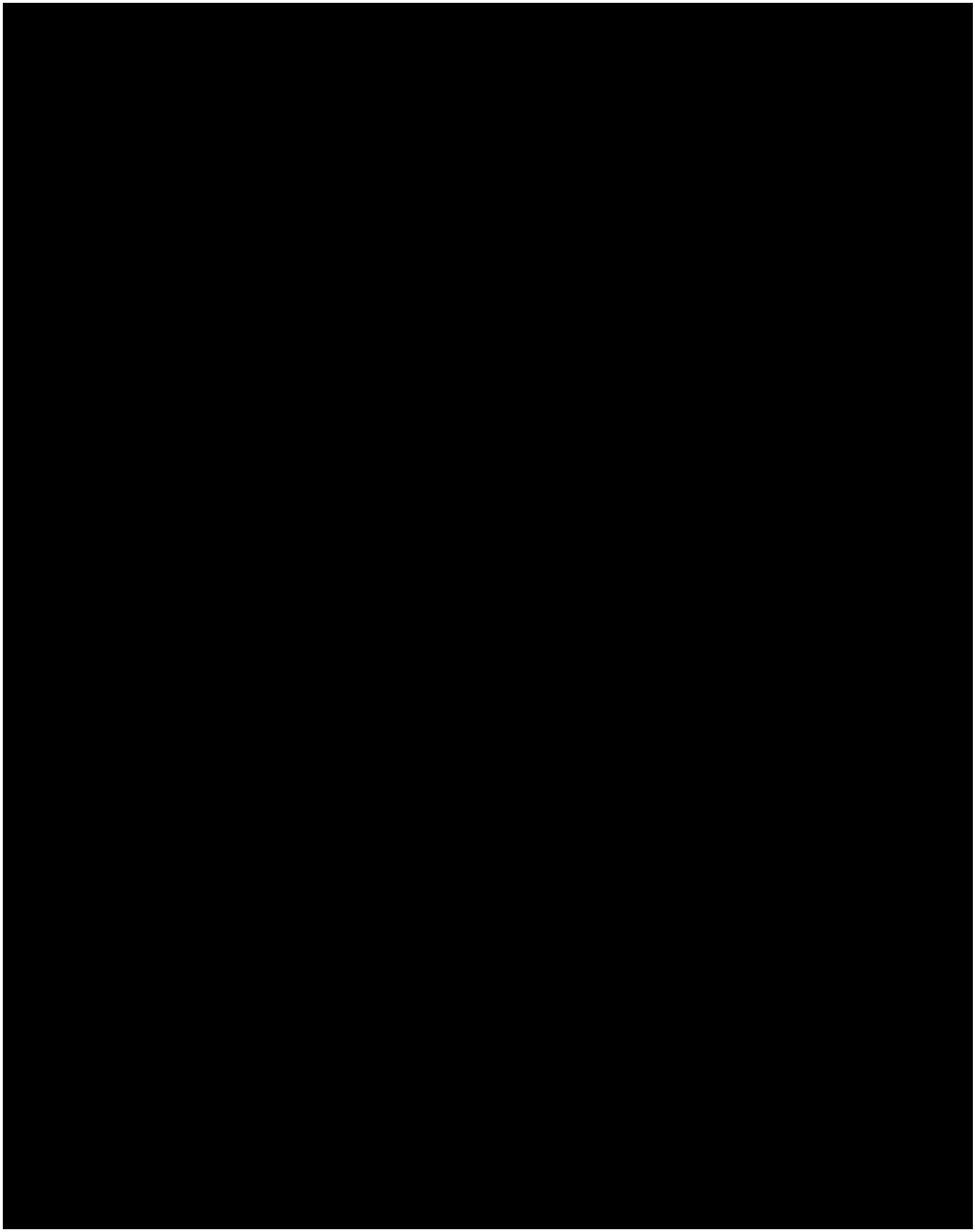
The Study Population will be subjects ≥ 18 years of age and defined as follows:

- R/R AML (Parts A and B): AML as defined by the 2016 World Health Organization (WHO) Classification (Appendix B) who have failed or who are ineligible for all available therapies for AML which may provide clinical benefit.
- R/R MDS (Parts A and B): MDS as defined by the 2016 WHO Classification (Appendix D) with intermediate, high or very high risk by IPSS-R (IPSS-R [redacted] and who have failed or who are ineligible for all available therapies for MDS which may provide clinical benefit.
- TN MDS (Part C): Treatment-naïve (TN) MDS as defined by the 2016 WHO Classification (Appendix D) with intermediate, high or very high risk by IPSS-R (IPSS-R [redacted]).
- TN AML (Part D): Treatment-naïve/ND AML as defined by the 2016 WHO Classification, including secondary AML and therapy-related AML in subjects who are ineligible (IE) for intensive chemotherapy (IC) and allogeneic [redacted] due to having one of the following:

- ♦ Severe cardiac comorbidities (including congestive heart failure, left ventricular ejection fraction [LVEF] <45%, and chronic stable angina)
- ♦ Pulmonary comorbidity (diffuse capacity of the lung for carbon monoxide [DLCO] ≤ 65% or forced expiratory volume in 1 second [FEV1] ≤ 65%)
- ♦ Any other comorbidity incompatible with intensive chemotherapy upon approval of the Sponsor Medical Monitor.
- ♦ Age ≥ 75 years, regardless of the presence of any of the above comorbidities

– Subjects must have a projected life expectancy of ≥ 12 weeks.

– TN AML subjects who have not received HMA, venetoclax, or chemotherapy in the setting of antecedent MDS are eligible. Prior treatment for MDS including, but not limited to, growth factors (eg, erythyropoiesis-stimulating agents), hydroxyurea, and lenalidomide is allowed.



[redacted]

3.1.1 Part A

[redacted] will be utilized to guide CC-95251 dose escalation/de-escalation decisions, with the final decisions being made by the SRC.

The proposed dose levels for testing the CC-95251 monotherapy include a starting dose [redacted] 20 mg/kg QW and [redacted] of 30 mg/kg to be administered by IV infusion. A 20 mg/kg QW dose of CC-95251 has been demonstrated to be tolerated in subjects with advanced solid cancers in the CC-95251-ST-001 study (NCT03783403). In the event that [redacted] is not tolerated in the CC-95251 monotherapy cohort, [redacted] of 10 mg/kg CC-95251 may be recommended by the SRC.

The proposed starting dose (DL1a) for CC-95251 in combination with injectable azacitidine is 10 mg/kg QW, [redacted]. The Part A dose escalation may enroll subjects in the CC-95251 plus azacitidine- cohorts in parallel with the CC-95251 monotherapy cohorts. However, cohorts of CC-95251 plus azacitidine will only open to enrollment after the corresponding or a higher dosing cohort of CC-95251 monotherapy is determined to be tolerated by the SRC.

The proposed starting dose (DL1b) for CC-95251 in combination with azacitidine and venetoclax (triple combination) is 20 mg/kg QW, [redacted] (10 mg/kg QW) may be recommended by the SRC if the starting dose is

not tolerated or to explore a lower dose level based on the available safety, PK, and PD data. The Part A dose escalation may enroll subjects in the CC-95251 plus azacitidine and venetoclax cohorts in parallel with the CC-95251 monotherapy and double combination cohorts. [redacted]

All subjects within each dose level will be observed [redacted] initiation of the next dose level. Subject treatment on Cycle 1 Day 1 (C1D1) will be staggered with [redacted] between subjects in a given cohort during Part A.

A decision table ([redacted]) based on [redacted] are provided to guide CC-95251 dose escalation/de-escalation decisions for monotherapy, double combination cohorts, and triple combination cohorts. The SRC will make dose escalation/de-escalation recommendations based on real-time integrated assessment of available safety, efficacy, PK and PD in each dose cohort. For a dose level to be selected by the SRC for dose expansions (Part B, C, or D), [redacted] should be evaluated for DLT in Part A to declare a tolerable dose level. Additional subjects may be enrolled in 1 or more cohorts at the recommendation of the SRC. Subjects non-evaluable for DLT may be replaced.

After enrollment has been completed in the corresponding Part A cohorts, the SRC will undertake an evaluation of the available safety, PK, PD, and preliminary efficacy data to make a determination of the preliminary RP2D of CC-95251 within a respective indication to test in the expansion cohorts (Parts B, C, and D). [redacted] The preliminary [redacted] and may differ based on indication (ie MDS versus AML). An intermediate dose level of CC-95251 or a variable dose schedule [redacted] may be evaluated to accurately determine the RP2D at the recommendation of the SRC. The investigation of any other alternate dosing schedule beyond those stipulated in the current protocol version will be submitted in a protocol amendment.

3.1.2 Part B

[redacted] The expansion cohorts of each individual treatment may start after a dose and schedule is shown to be tolerated in the corresponding Part A cohort and the SRC has selected the Part B dose and schedule.

Approximately [redacted] subjects per cohort will be enrolled to further evaluate the safety and assess the efficacy of:

1) CC-95251 alone in R/R AML
2) CC-95251 in combination with azacitidine in R/R AML

3) CC-95251 alone in R/R MDS (IPSS-R [redacted]
4) CC-95251 in combination with azacitidine in R/R MDS (IPSS-R [redacted]

at the preliminary RP2D of CC-95251 monotherapy or RP2D of CC-95251 in combination with azacitidine established in Part A. [redacted] and will regularly review safety and emerging response data during expansion to make recommendations about continuation and dose modification, as appropriate (Section 7.2.7). The subjects will be assigned to treatment cohorts (monotherapy vs double combination with azacitidine) based on the slot availability, not based on randomization.

Additional cohorts of subjects testing CC-95251 in combination with additional antineoplastic agents in subjects with R/R AML or R/R MDS may be considered at the recommendation of the SRC and will be included by protocol amendment.

3.1.3 Part C

Part C will evaluate subjects with treatment-naïve (ie, previously untreated), intermediate, high or very high risk (ie, IPSS-R [redacted] MDS with CC-95251 in combination with standard of care injectable azacitidine.

Enrollment in Part C [redacted] The SRC will review the safety data from this group of subjects utilizing [redacted] prior to the opening of the Part C expansion. The dose of CC-95251 selected for Part C may occur [redacted] based on review of available safety, PK, PD, and preliminary efficacy data.

The Part C expansion will initially evaluate at [redacted] with treatment-naïve MDS treated [redacted] of CC-95251 plus azacitidine. The SRC will review the available safety utilizing [redacted] PK, PD and preliminary efficacy data in the initial [redacted] to determine if the dose and schedule is tolerated prior to escalating the CC-95251 dose to the proposed Part C expansion dose and schedule. [redacted] Thereafter, a total of approximately [redacted] additional subjects with treatment-naïve MDS may be enrolled in Part [redacted] During enrollment in Part C the SRC will review available safety data from Cycle 1 of every [redacted] subjects treated in the cohort to evaluate for excessive toxicity. Enrollment in Part C may proceed concurrently with enrollment in the Part B expansion cohorts.

The SRC will continue to review safety data regularly throughout the study and make recommendations about study continuation, dose modification and establishment of a RP2D as appropriate.

3.1.4 Part D

Part D will evaluate subjects with TN AML with CC-95251 in combination with standard of care azacitidine and venetoclax. Enrollment in Part D may start [redacted] of CC-95251 plus azacitidine and venetoclax. The SRC will review the safety data from this group of subjects utilizing the [redacted] prior to the opening of the Part D expansion.

The Part D expansion will initially evaluate [redacted] An additional [redacted] subjects may be enrolled based on the response seen in the initial [redacted] subjects ([redacted] and Section 9.3: Sample Size and Power Considerations). During enrollment in part D, the SRC will review available safety data from Cycle 1 of every [redacted] subjects treated in the cohort to evaluate for excessive toxicity.

The SRC will continue to review safety data regularly throughout the study and make recommendations about study continuation, dose modification, and establishment of a RP2D as appropriate.

3.1.5 Study Treatments

CC-95251 will be administered intravenously in two phases starting with a more frequently dosed induction phase followed by a maintenance phase.

- During induction phase, subjects will be dosed weekly for Cycles 1 through 4 (QW, eg, on Day 1, Day 8, Day 15, and Day 22 of each cycle). After Cycle 4, subjects will enter the maintenance phase.
- During the maintenance phase, CC-95251 will be administered every two weeks (Q2W, eg, on Day 1 and Day 15 of each cycle).

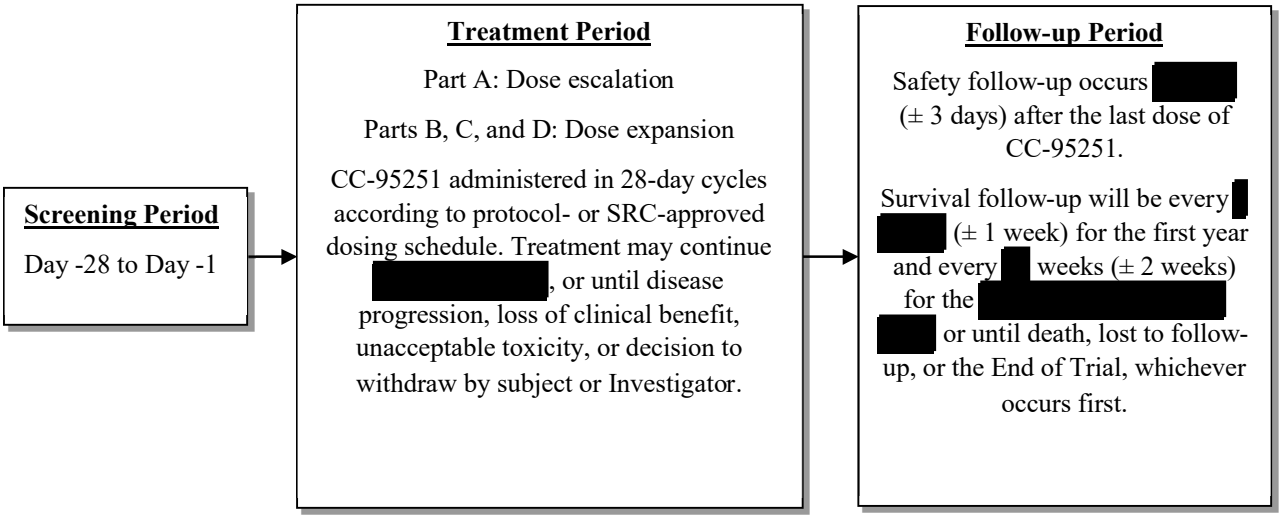
The SRC may change the frequency of dosing [redacted] based on review of the available safety, PK, PD, and preliminary efficacy data [redacted] The investigation of any other alternate dosing schedule beyond those stipulated in the current protocol version will be submitted in a protocol amendment.

Azacitidine will be administered at 75 mg/m^2 on Days 1-7 (or Days 1-5 and 8-9) of each 28-day cycle as an IV or SC injection throughout the course of the study treatment per local prescribing information and institutional standard of care.

[redacted] Subjects will be admitted as inpatients during venetoclax dose ramp-up for IV hydration and monitoring of toxicities including TLS. [redacted] (Table 12). The duration of venetoclax dosing may be shortened based on evaluation of a bone marrow aspirate and biopsy on [redacted] to evaluate clearance of blasts and overall cellularity (see Section 7.2.7.7 and [redacted] In subsequent cycles, the shortened venetoclax dosing may be continued at the discretion of the investigator. The investigator may also choose to follow the algorithm in [redacted] in [redacted]

Parts A, B, C, and D will consist of 3 periods: Screening, Treatment, and Follow-up (refer to Figure 4).

Figure 4: Overall Study Design



Abbreviations: SRC = safety review committee.

3.1.5.1 Screening Period

The Screening Period starts 28 days prior to first dose of study intervention. The informed consent form (ICF) must be signed and dated by the subject and the administering staff prior to the start of any other study procedures. All screening tests and procedures must be completed within the 28 days prior to the first dose of study treatments.

3.1.5.2 Treatment Period

Upon confirmation of eligibility, subjects will be enrolled and begin treatment in the assigned dose level cohort.

The Sponsor will supply the investigational product (IP), CC-95251, for IV administration (Section 7.1.1).

Azacitidine will be supplied or obtained according to local clinical study agreement and in accordance with local guideline. When provided by the Sponsor, azacitidine for Injection will be supplied as a lyophilized powder in 100 mg single-dose vials for reconstitution and administration.

Venetoclax will be supplied or obtained according to local clinical study agreement and in accordance with local guidelines. When provided by the Sponsor, venetoclax will be supplied as tablets in 10 mg, 50 mg, and 100 mg blister/bottles for administration.

In Part A, subjects with AML in CC-95251 monotherapy and double combination (CC-95251 and azacitidine) cohorts will be hospitalized for [redacted] after the first dose of CC-95251 (C1D1) for IV hydration [redacted] and to monitor for adverse events. Subjects with AML in triple combination (CC-95251 plus azacitidine and venetoclax) cohorts will be hospitalized during venetoclax dose ramp-up ([redacted]) for hydration [redacted] and to monitor for adverse events. [redacted] Full emergency resuscitation facilities should be immediately available, and subjects should be under close supervision of the Investigator or designated staff during and for [redacted] following CC-95251 administration with serial vital signs obtained and pulse oximetry performed.

[redacted]

CC-95251 infusion will be started at [redacted] mg/hr [redacted] mg/hr [redacted] mg/hr. Further changes to the rate of infusion may be considered during the course of the trial based on review of clinical data and approval from the SRC.

For subjects receiving azacitidine in combination with CC-95251, subjects will receive azacitidine prior to starting CC-95251 infusion on days receiving both treatments. Subjects should be observed for at least [redacted] between administrations.

For subjects receiving triple combination, on Day 1 of each cycle, CC-95251, azacitidine, and venetoclax will be administered on the same day. [redacted]

For subjects receiving CC-95251 monotherapy and double combination (CC-95251 and azacitidine), in the absence of residual morphologic leukemia and in the presence of ongoing

cytopenias at the completion of the DLT evaluation period, study interventions could be interrupted for up to [redacted] to allow for hematologic recovery. [redacted]

For subjects receiving triple combination (CC-95251 plus azacitidine and venetoclax), [redacted]

If the venetoclax dosing schedule is shortened based on bone marrow evaluation and the algorithm above, the shortened schedule may be continued in subsequent cycles at the discretion of the investigator. The investigator may also choose to follow the algorithm in [redacted]

Dose modification guidance is provided in Section 7.2.7.7, [redacted] and [redacted]

[redacted]

Thus, in Part A dose escalation, the window for evaluation of DLT during Cycle 1 will be up to [redacted] Cycles 2 and higher will be 28 days in length. In dose expansion, all cycles will be 28 days in length. [redacted] Subjects will only be considered DLT evaluable during the first cycle of their initial enrollment in Part A (dose escalation).

In dose expansion (Parts B, C, and D), a non-binding [redacted] safety monitoring method will be used to continuously monitor for excess toxicities defined as the occurrence of AEs [redacted] (Section 9.9.2). After a minimum of [redacted] subjects have enrolled and completed at least one cycle of study treatment, the non-binding [redacted] stopping criterion [redacted] will be calculated (refer to [redacted]). If the stopping rule is triggered, the SRC will conduct a comprehensive review of available safety, PK, PD, and preliminary efficacy data to make continuation decisions.

In both Parts B, C, and D, a [redacted] will be performed. In Part B, at least [redacted] efficacy evaluable subjects who complete at least one cycle of study treatment for each cohort will initially be accrued; [redacted] In Part C, at least [redacted] efficacy evaluable subjects who complete at least one cycle of study treatment at RP2D will initially be accrued; [redacted]. In Part D, at least [redacted] evaluable subjects who complete at least one cycle of study treatment at RP2D will initially be

accrued; [redacted]

The [redacted] decision will be made by the SRC upon reviewing all available safety, PK, PD, and any efficacy results in dose expansion phase, including considerations on adjustment of the RP2D dose. Otherwise, the cohort will be expanded to up to approximately [redacted] evaluable subjects in Part B, approximately [redacted] evaluable subjects in Part C, and approximately [redacted] evaluable subjects in Part D (Section 9.9.2).

All treatments will be administered in 28-day cycles. Subjects may continue treatment if they are deriving benefit from treatment without unacceptable toxicity (any CR, MLFS, partial remission (PR), or stable disease (SD) with demonstrated clinical benefit eg, reduction in transfusion burden), as judged by the Investigator, [redacted]), or until disease progression, loss of clinical benefit, unacceptable toxicity, or decision to withdraw by subject or Investigator. Subjects who discontinued one study treatment in a combination arm for reasons other than relapse or resistant disease may continue on the non-discontinued drug(s) if they are receiving benefits as per Investigator's discretion until there is evidence of relapse or resistant disease, or until they are no longer able to tolerate treatment due to an adverse event.

[redacted]
The subject cannot have had another systemic anti-cancer therapy upon relapse.
[redacted] The subject will not be re-considered in the efficacy evaluation.

3.1.5.3 Follow-up Period

All subjects will be followed for [redacted] after the last dose of study drug for AE reporting. In addition, serious AEs (SAEs) made known to the Investigator at any time thereafter that are suspected of being related to study drug are to be reported until such SAEs have recovered (returned to baseline), recovered with sequelae, or death (due to the SAE). Subjects will also be followed for all AEs (SAEs and non-serious AEs) associated with confirmed or suspected SARS-CoV-2 infection until resolution, the condition stabilizes, the event is otherwise explained, the event is deemed irreversible, the subject is lost to follow-up, or for suspected cases, until SARS-CoV-2 infection is ruled-out (Section 6.3.1).

Subjects who discontinue treatment for reasons other than disease progression (or relapse) or start of a new anticancer therapy will have efficacy evaluations of CBC and PBS performed every

subsequent [redacted] up to a [redacted]. A bone marrow evaluation will be completed [redacted] and as clinically indicated during the Follow-up Period.

All subjects will be followed starting from the end of treatment according to the schedule for the efficacy long term follow-up (refer to Section 6.3.2) for survival for [redacted] or until death, lost to follow-up, or the End of Trial, whichever occurs first. Survival follow-up may be conducted by record review (including public records) and/or telephone contact with the subject, family, or the subject's treating physician.

During follow-up, information (including dates) on new anticancer therapies will be collected until withdrawal from the study, death, or the End of Trial, whichever comes first.

The study will be conducted in compliance with the International Council on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use/Good Clinical Practice (GCP) and applicable regulatory requirements.

3.2 Study Duration for Subjects

Enrollment is expected to take approximately 24 to 36 months to complete (approximately 16 to 19 months for dose escalation and approximately 12 to 18 months for dose expansion). The entire study is expected to last up to approximately 3 to 4 years.

An individual subject will be in the study for [redacted] including treatment and follow up unless, the SRC decides to extend the treatment period.

3.3 End of Trial

The end of Trial is defined as either the date of the last visit of the last subject to complete the post-treatment follow-up, or the date of receipt of the last data point from the last subject that is required for primary, secondary and/or exploratory analysis, as prespecified in the protocol, whichever is the later date. Survival Follow-up may be terminated at the Sponsor's discretion.

4 STUDY POPULATION

4.1 Number of Subjects

This is a multicenter, open-label study which will enroll approximately [redacted] subjects. Approximately [redacted] subjects will be enrolled in Part A dose escalation, [redacted] subjects in Part B dose expansion ([redacted] per cohort), [redacted] subjects in Part C dose expansion, and [redacted] subjects in Part D dose expansion.

4.2 Inclusion Criteria

Subjects must satisfy the following criteria to be enrolled in the study:

1) Subject is ≥ 18 years of age, at the time of signing the ICF.
2) Subject must understand and voluntarily sign an ICF prior to any study-related assessments/procedures being conducted.

3) Subject is willing and able to adhere to the study visit schedule and other protocol requirements.
4) Parts A and B:
   a. R/R AML: AML as defined by the 2016 WHO Classification (Appendix B) who have failed or who are ineligible for all available therapies for AML which may provide clinical benefit.
   b. R/R MDS: MDS as defined by the 2016 WHO Classification (Appendix D) with intermediate, high or very high risk by IPSS-R (IPSS-R [redacted] and who have failed or who are ineligible for all available therapies for MDS which may provide clinical benefit.
5) Part C: Treatment-naïve (ie, previously untreated) MDS as defined by the 2016 WHO Classification (Appendix D) with intermediate, high or very high risk by IPSS-R (IPSS-R [redacted]. Prior administration of erythroid or myeloid growth factors and/or supportive transfusions is permitted unless otherwise specified (eg, in Section 4.3 and Section 8).
6) Part D: TN AML as defined by the 2016 WHO Classification (APPENDIX B), including secondary AML and therapy-related AML in subjects who are IE for IC and allogeneic [redacted] due to having one of the following:
   a. Severe cardiac comorbidities (including congestive heart failure, left ventricular ejection fraction [LVEF] <45%, and chronic stable angina).
   b. Pulmonary comorbidity (diffuse capacity of the lung for carbon monoxide [DLCO] ≤ 65% or forced expiratory volume in 1 second [FEV1] ≤ 65%).
   c. Any other comorbidity incompatible with intensive chemotherapy upon approval of the Sponsor Medical Monitor.
   d. Aged ≥ 75 years, regardless of the presence of any of the above comorbidities.
      i. Subjects must have a projected life expectancy of ≥ 12 weeks.
      ii. TN AML subjects who have not received HMA, venetoclax, or chemotherapy in the setting of antecedent MDS are eligible. Prior treatment for MDS including, but not limited to growth factors (eg, erythropoiesis-stimulating g agents), hydroxyurea, and lenalidomide is allowed.
7) Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 to 2.
8) Subjects must have the following laboratory values:
   - Total White Blood Cell Count (WBC) [redacted]
   - Potassium and magnesium within normal limits or correctable with supplements.
   - Aspartate aminotransferase/serum glutamic oxaloacetic transaminase (AST/SGOT) and alanine aminotransferase/serum glutamic pyruvic transaminase (ALT/SGPT) [redacted], unless considered due to leukemic organ involvement, in which case AST and ALT can be [redacted]
   - Uric acid [redacted] mg/dL ([redacted] µmol/L). Prior and/or concurrent treatment with hypouricemic agents (eg, allopurinol, rasburicase) are allowed.

- Serum bilirubin [redacted], or primary unconjugated bilirubin [redacted] if individual has a documented history of Gilbert's syndrome (eg, a gene mutation in UGT1A1) or genetic equivalent.
- Estimated serum creatinine clearance of [redacted] mL/min using the Cockcroft-Gault equation. Measured creatinine clearance from a 24-hour urine collection is acceptable if clinically indicated.
- [redacted] and partial thromboplastin time (PTT) [redacted].

9) Subject of childbearing potential (SCBP)[1] must:

- Either commit to true abstinence[2] from heterosexual contact (which must be reviewed on a monthly basis and source documented) or agree to use, and be able to comply with, at least one highly effective contraceptive methods (oral, injectable, or implantable hormonal contraceptive; tubal ligation; intra-uterine device; or vasectomized partner), from signing the ICF, while participating in the study, during dose interruptions, and for up to [redacted] following the last dose of CC-95251 and 6 months (or longer if required by local regulations) after the last dose of azacitidine, and 30 days after the last dose of venetoclax (It is currently unknown whether venetoclax may reduce the effectiveness of hormonal contraceptives, and therefore women using hormonal contraceptives should add a barrier method.); and
- Have two negative quantitative serum or urine pregnancy tests as verified by the Investigator, one must be at Screening and one performed within 72 hours prior to starting study treatment (Section 6.1). Subject must agree to ongoing pregnancy testing during the course of the study, and [redacted] after end of CC-95251 and 6 months (or longer if required by local regulations) after azacitidine, and 30 days for venetoclax. This applies even if the subject practices true abstinence[2] from heterosexual contact. The subject may not receive study treatment until the Investigator has verified that the result of the pregnancy test is negative; and
- Have a negative quantitative serum pregnancy test (sensitivity of at least 25 mIU/mL) at Screening.
- Have a negative serum or urine pregnancy test (Investigator's discretion) within 72 hours prior to C1D1 of study treatment, and within 72 hours prior to Day 1 of every subsequent cycle. A serum or urine pregnancy test (Investigator's discretion) must also be performed at the end of study for each SCBP; and
- Avoid conceiving and blood or egg donation from signing the ICF, while participating in the study, during dose interruptions, and for [redacted] after the last dose of CC-95251 and 6 months (or longer if required by local regulations) after the last dose of azacitidine, and 30 days after the last dose of venetoclax.

[1] A subject of childbearing potential is a sexually mature individual who 1) has not undergone a hysterectomy (the surgical removal of the uterus) or bilateral oophorectomy (the surgical removal of both ovaries) or 2) has not been naturally postmenopausal for at least 24 consecutive months (eg, has had menses at any time during the preceding 24 consecutive months).

[2] True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception.)

10) Subjects who are able to impregnate their partner must practice true abstinence[2] (which must be reviewed on a monthly basis and source documented) or agree to use a condom (a latex condom is recommended) during sexual contact with a pregnant partner or a partner with childbearing potential and must avoid blood or semen or sperm donation from signing the ICF, while participating in the study, during dose interruptions, and for at least [redacted] following CC-95251 discontinuation and 3 months (or longer if required by local regulations) after the last dose of azacitidine, even if subject has undergone a successful vasectomy.

4.3 Exclusion Criteria

The presence of any of the following will exclude a subject from enrollment:

1) [redacted] Evaluation of cerebrospinal fluid is only required if there is clinical suspicion of CNS involvement by leukemia during screening.
2) Subjects with immediately life-threatening, severe complications of leukemia such as disseminated/uncontrolled infection, uncontrolled bleeding, and/or uncontrolled disseminated intravascular coagulation (DIC).

[redacted]

5) Subjects who have received prior treatment with a [redacted]
6) An exception is subjects who are considered for retreatment in the study. Impaired cardiac function or clinically significant cardiac diseases, including any of the following:

[redacted]

8) Prior autologous [redacted] prior to starting study treatment, or who, in the Investigator's judgment, have not fully recovered from the effects of the last transplant.
9) Prior allogeneic [redacted] with either standard or reduced intensity conditioning [redacted] prior to starting study treatment.
10) Subjects on [redacted] The use of topical steroids for ongoing

skin or ocular [redacted] is permitted. [redacted]

11) Subject is on chronic systemic immunosuppressive therapy or corticosteroids [redacted] mg [redacted]). Intranasal, inhaled, topical, or local corticosteroid injections (eg, intra-articular injection), or steroids as premedication for hypersensitivity reactions (eg, computed tomography [CT] scan premedication) are exceptions to this criterion.
12) Prior systemic cancer-directed treatments or investigational modalities [redacted]
13) Major surgery [redacted] prior to starting CC-95251. Subjects must have recovered from any clinically significant effects of recent surgery.
14) Pregnant or nursing subjects.
15) Subject has active [redacted] infection.
    - [redacted]
16) Subject has active [redacted] infection.

[redacted]

17) [redacted]
18) History of concurrent second cancers requiring active, ongoing systemic treatment.
19) Subject has any significant medical condition, laboratory abnormality, or psychiatric illness that would prevent the subject from participating in the study.
20) Subject has any condition including, active or uncontrolled infection, or the presence of laboratory abnormalities, which places the subject at unacceptable risk if he/she were to participate in the study.
21) Subject has any condition that confounds the ability to interpret data from the study.
22) Previous SARS-CoV-2 infection [redacted] for mild or asymptomatic infections or 20 days for severe/critical illness prior to C1D1.
    - Acute symptoms must have resolved and based on Investigator assessment in consultation with the Sponsor's Medical Monitor, there are no sequelae that would place the subject at a higher risk of receiving study treatment.
23) Previous non-live COVID-19 vaccine [redacted]. For vaccines requiring more than one dose, the full series (eg, both doses of a two-dose series) should be completed at least [redacted] when feasible and when a delay in C1D1 would not put the study subject at risk.

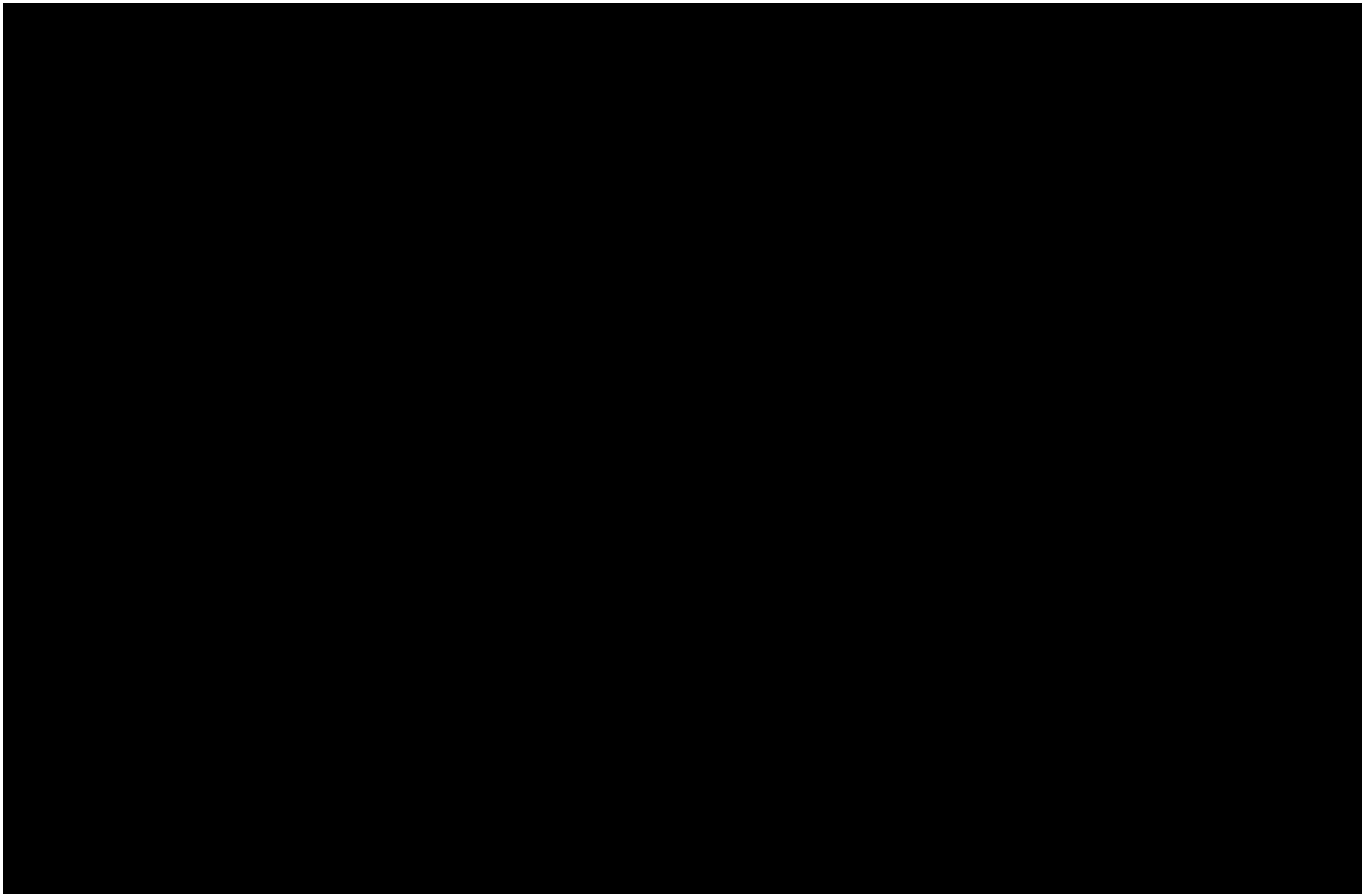
24) Previous live COVID-19 vaccine [redacted] of C1D1. For live vaccines requiring more than one dose, the full series (eg, both doses of a two-dose series) should be completed at least [redacted] to C1D1 when feasible and when a delay in C1D1 or study treatment would not put the study subject at risk.
25) Treatment-naïve MDS subjects who are determined by the investigator [redacted]
26) Subjects with known dysphagia, short-gut syndrome, gastroparesis, or other conditions/surgery that limit the ingestion or gastrointestinal absorption of drugs administered orally.
27) Prior/Concomitant Therapy Treatment naive/ND AML subjects:

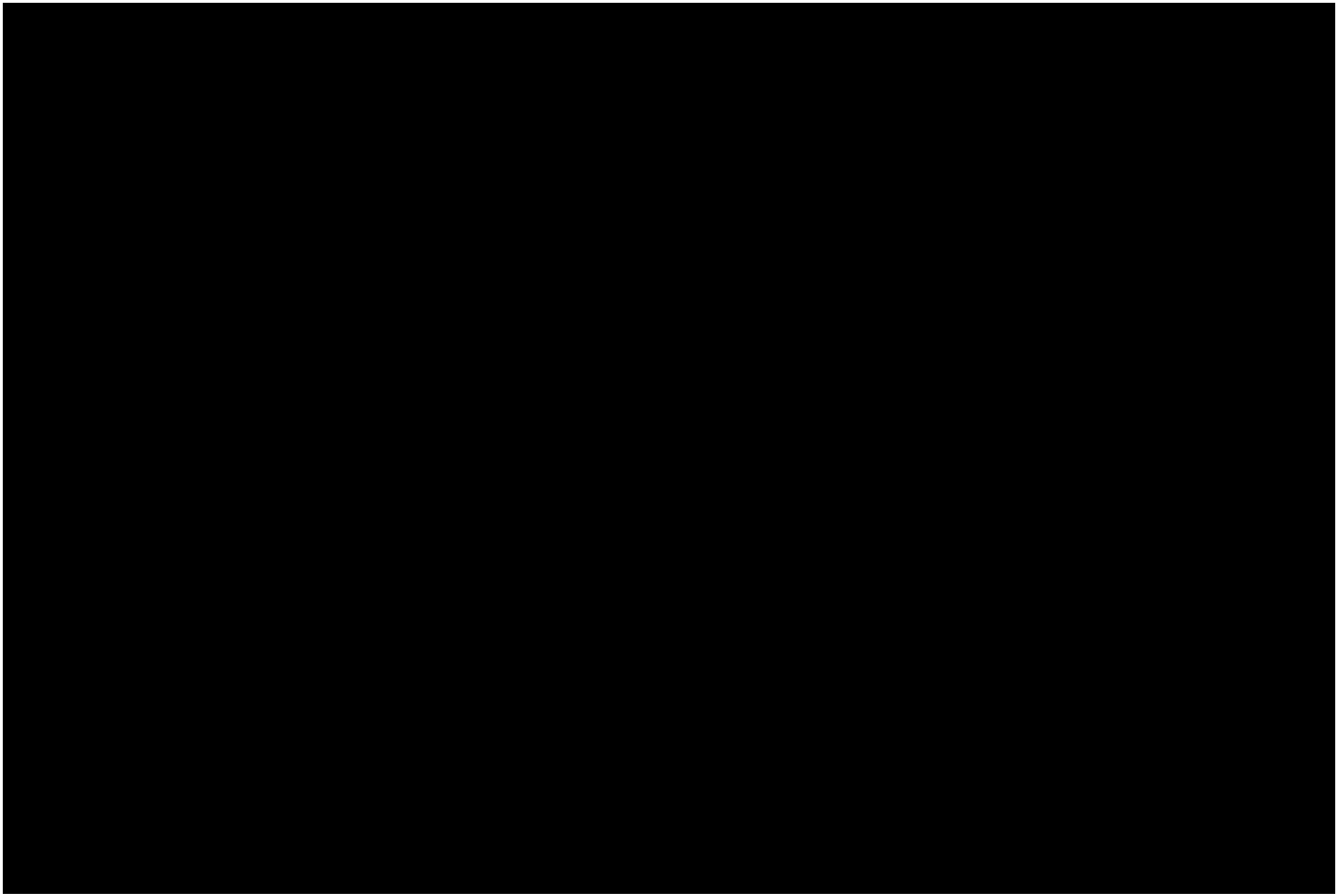
[redacted]

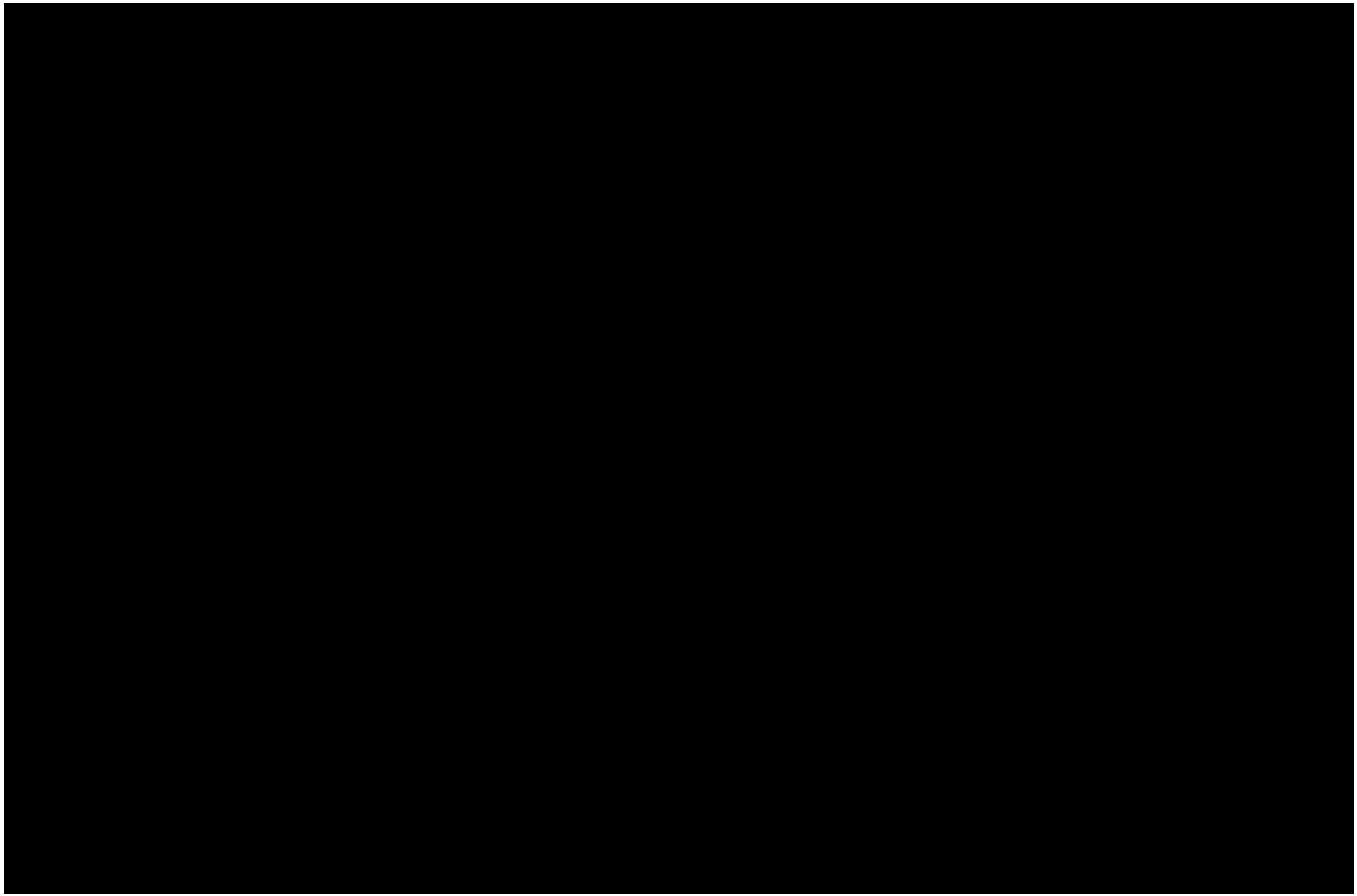
4.4 Lifestyle Restrictions

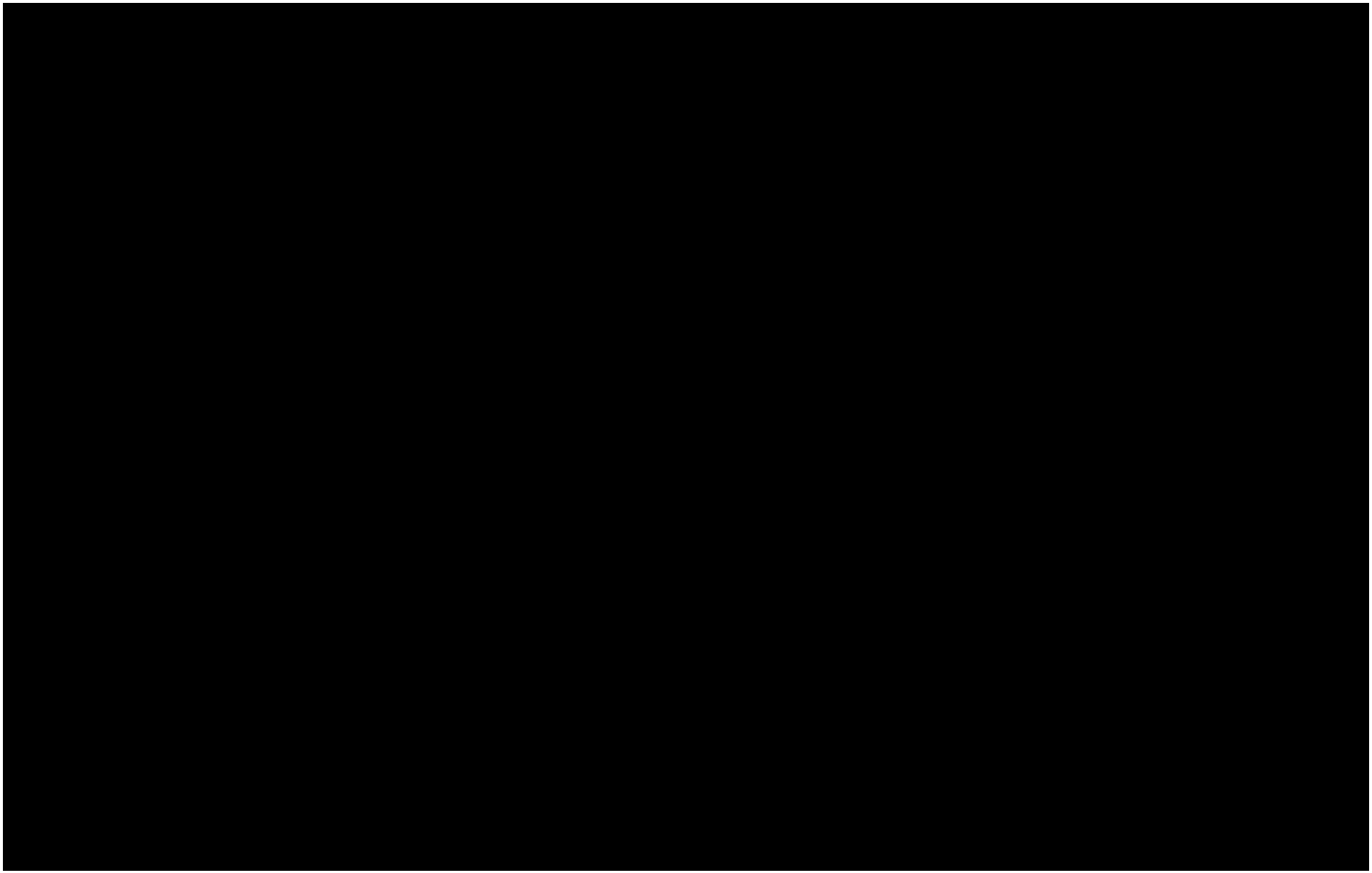
4.4.1 Meals and Dietary Restrictions

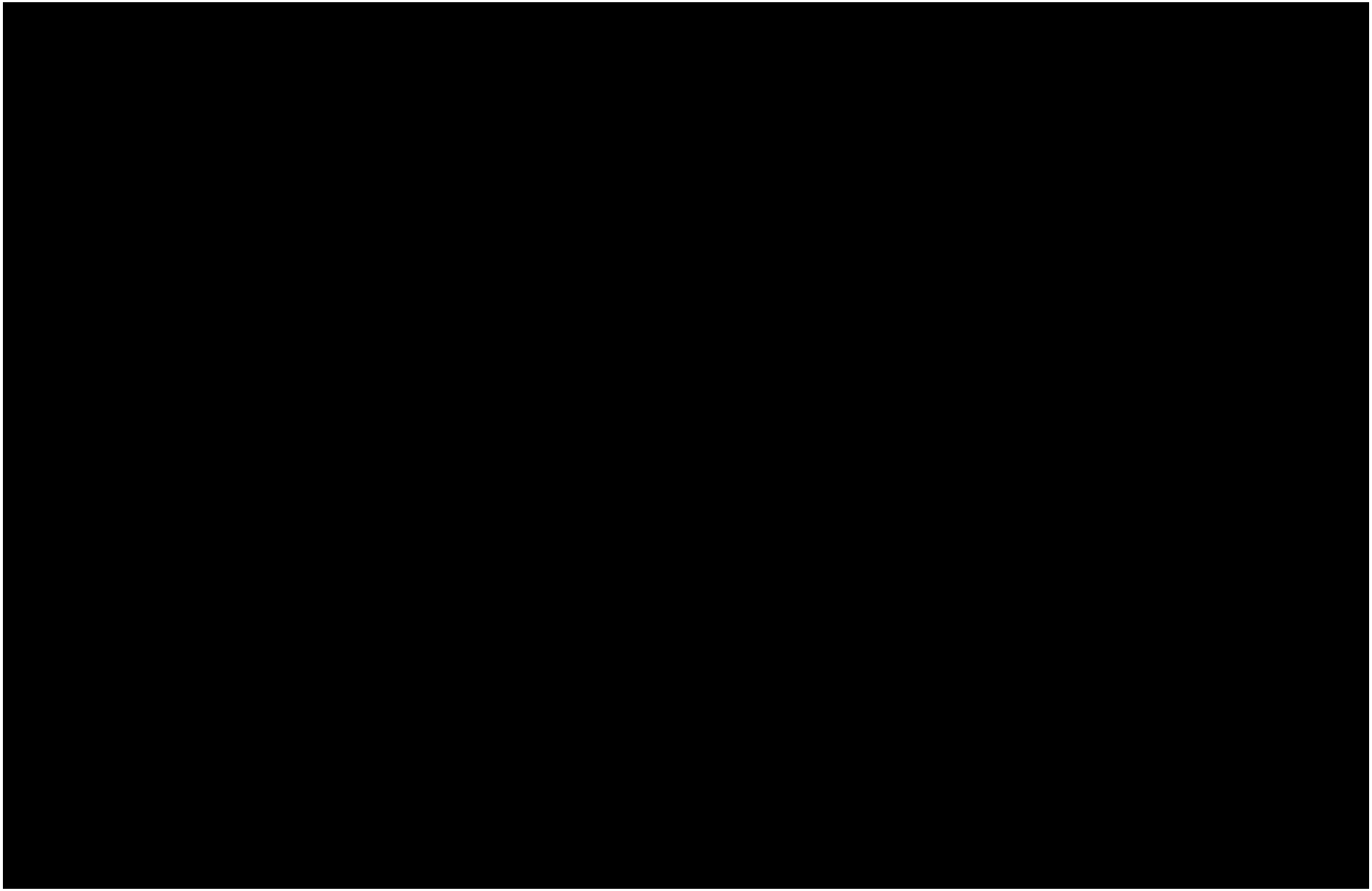
No restrictions are required for CC-95251. [redacted]

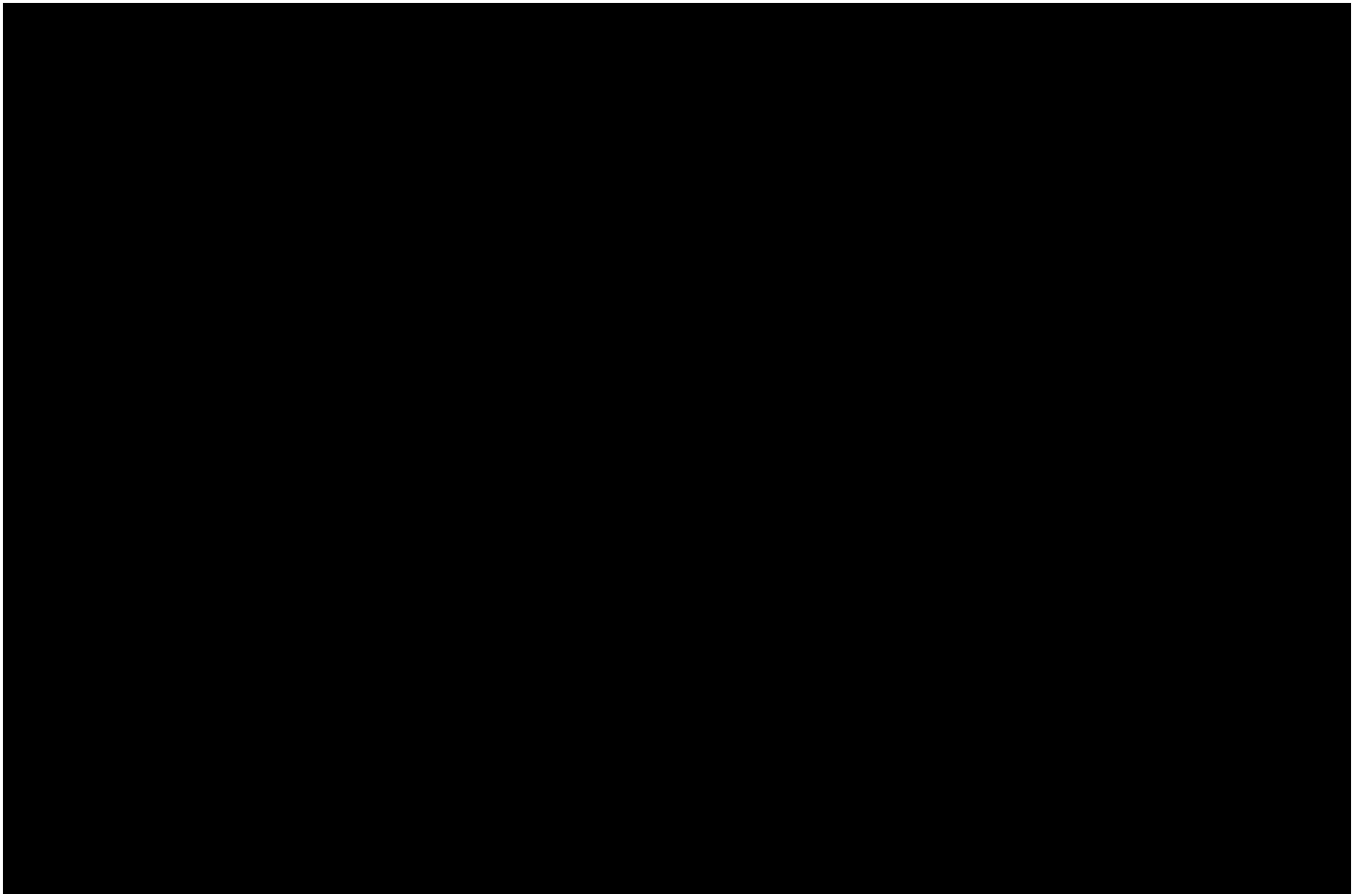


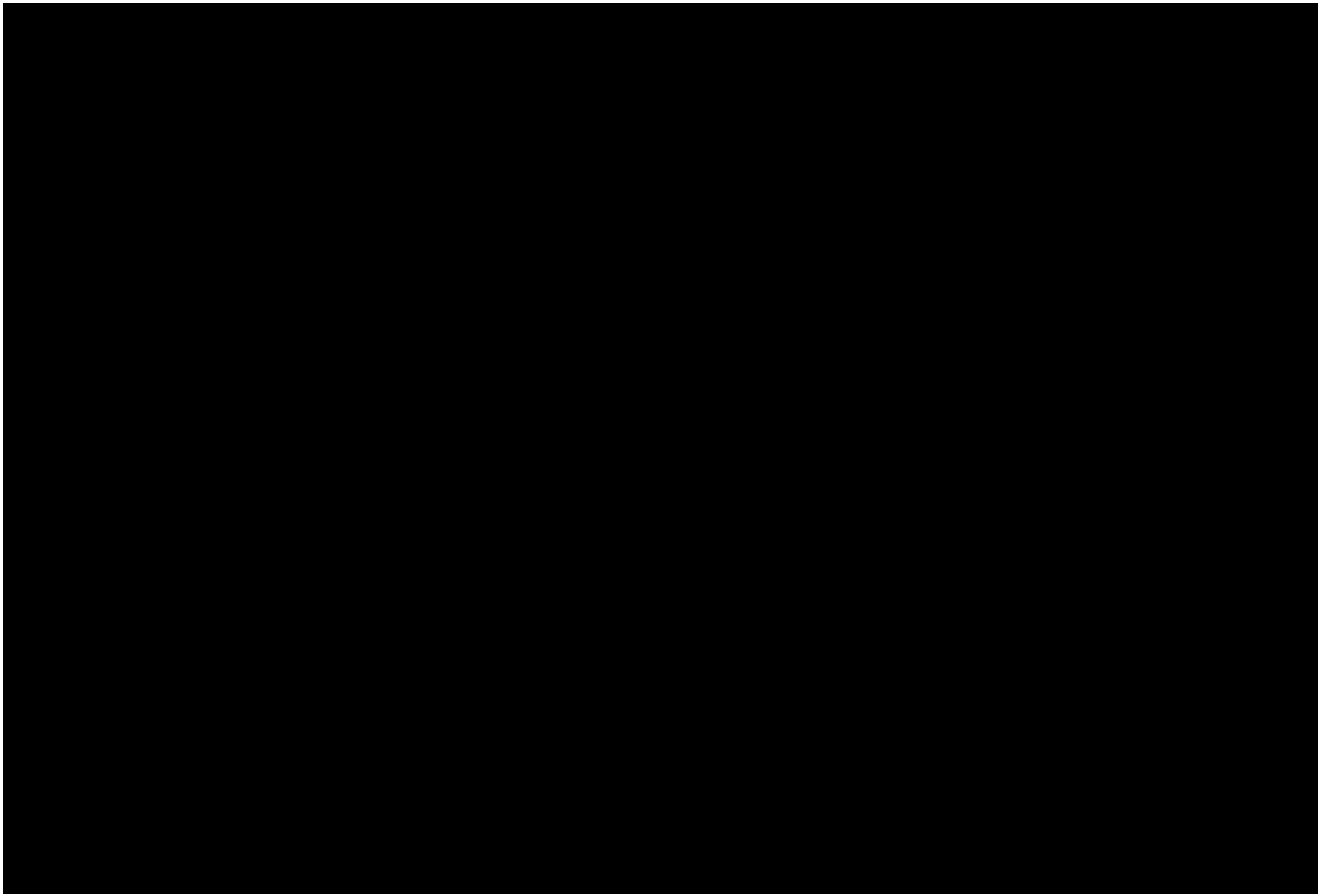


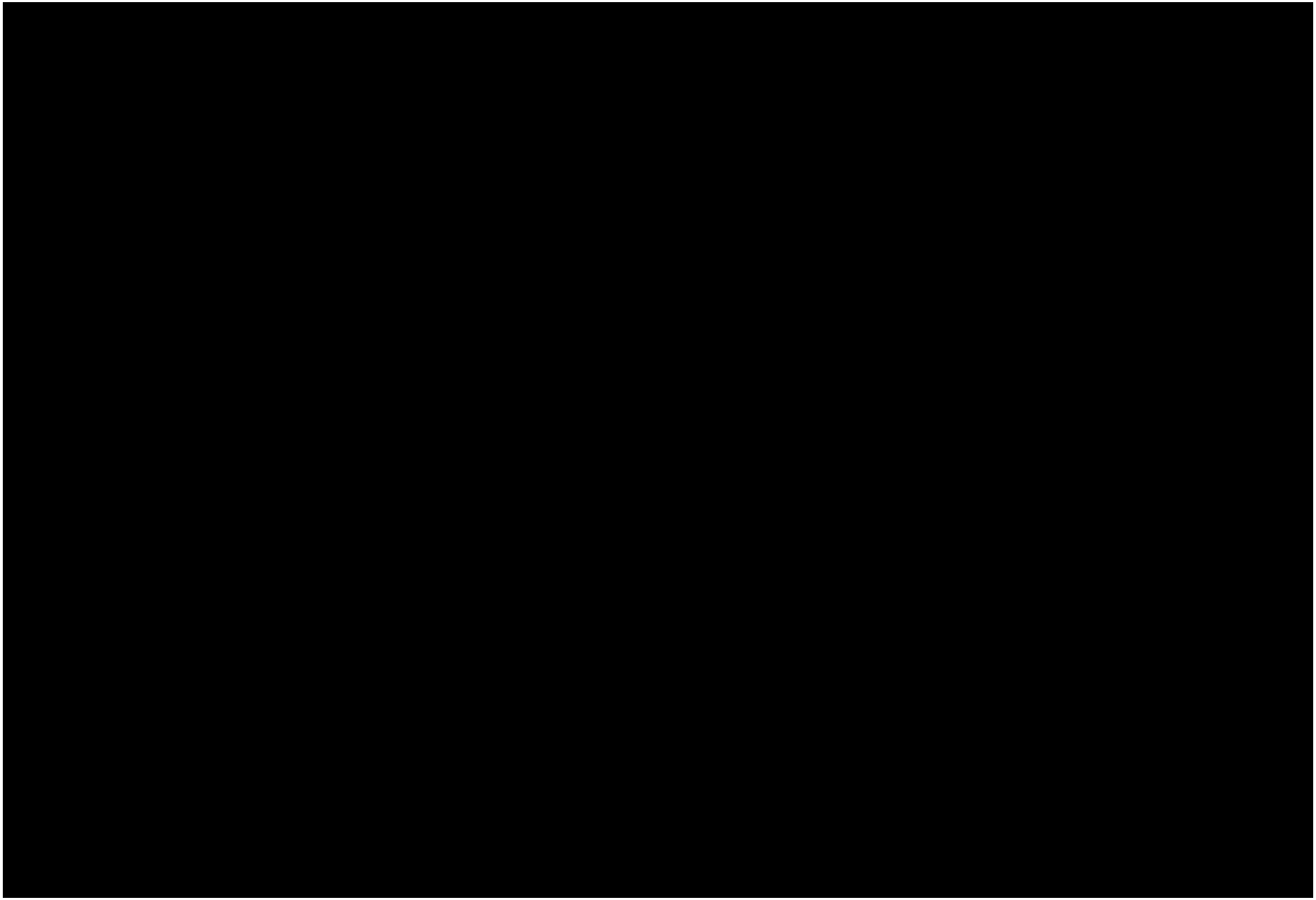


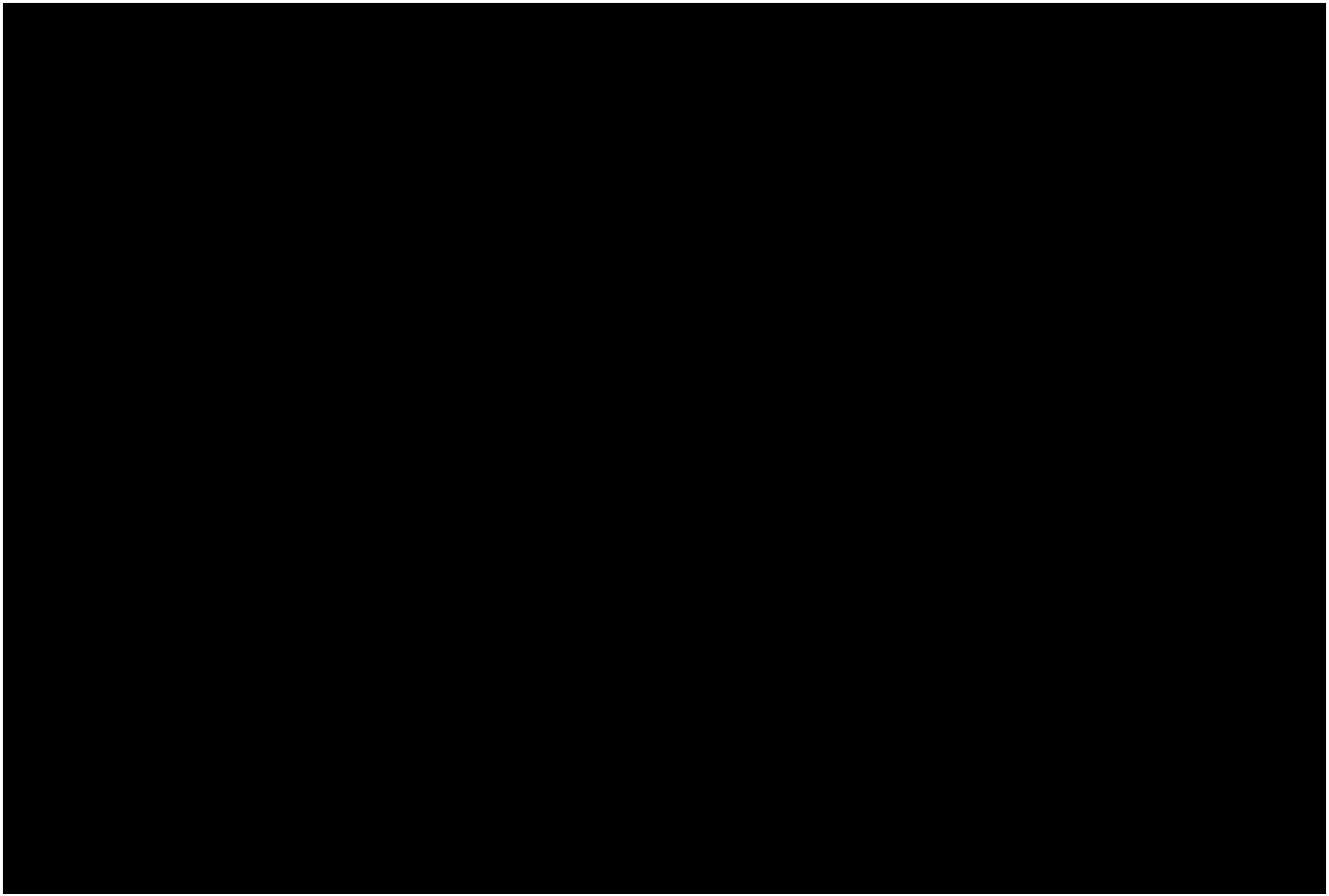












[redacted]

6 PROCEDURES

Any questions regarding the protocol should be directed to the Sponsor's Medical Monitor (MM) or designee. The procedures conducted for each subject enrolled in the study are outlined in [redacted], and Section 6.2.

All study treatment visits/procedures will have a [redacted] unless otherwise specified (eg, PK sampling) below or in [redacted], and [redacted] All laboratory blood samples should be drawn predose unless otherwise specified (eg, PK samples). Specific laboratory tests that must be completed [redacted] prior to the first dose of study drug are identified in Section 6.1.

The study procedures should be recorded in the source document and the electronic case report forms (eCRF). In the event subjects fail screening, minimal information will be documented on the eCRFs, per database instructions.

6.1 Screening Period

For all treatment arms, the Screening window starts [redacted] prior to first dose of study drug. Refer to [redacted], and Section 6.2 through Section 6.7 for detailed information on procedures performed and the schedule.

Waivers to the protocol will not be granted during the conduct of this trial, under any circumstances.

Safety laboratory analyses will be performed locally. Screening laboratory values must demonstrate subject eligibility, but may be repeated within the screening window, if necessary.

The ICF will be administered at the Screening visit to all subjects by qualified study staff. It must be signed and dated by the subject and the administering staff prior to the start of any other study procedures and its completion documented in source documents and in the eCRF. All screening tests and procedures must be completed within [redacted] prior to the first dose of study drug according to the schedule shown in [redacted].

The following will be performed at Screening (as specified in [redacted]) after informed consent has been obtained.

Inclusion and exclusion criteria will be assessed at Screening and recorded in the source documents and the eCRF.

- Medical [redacted] will be collected during Screening as consistent with local regulations. If full date of birth will not be collected, year of birth and age are required. Oncologic history will include a detailed history of the primary diagnosis and date, therapies and responses and transfusion dependence history if applicable.
- Information on prior and concomitant medications and procedures will be collected (refer to Section 6.2.1).
- Registration in the interactive response technology system (IRT)

- Adverse event (AE) monitoring (refer to Section 6.2.2).
- Vital signs assessed (refer to Section 6.2.3)
- Physical examination (source documented only), height, weight, and ECOG performance status (refer to Section 6.2.4).

[redacted]

- Viral serologies for [redacted] will be collected at Screening. [redacted]

- Pregnancy testing (refer to Section 6.2.5) for SCBP. Appropriate methods of contraception will be discussed with subjects during Screening. One highly effective contraceptive method for SCBP (eg, oral, injectable, or implantable hormonal contraceptive; tubal ligation; intra-uterine device; or vasectomized partner) and a single contraceptive method (a condom [a latex condom is recommended]) for subjects who are able to impregnate their partner must be used from the time the ICF is signed, throughout the study by subjects, and for [redacted] after the last dose of CC-95251 and 6 months (or longer if required by local regulations) for SCBP or 3 months (or longer if required by local regulations) for subjects who are able to impregnate their partner, after the last dose of azacitidine.
- True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. This will be documented in the source documents.

- Pregnancy β-subunit of human chorionic gonadotropin (β-hCG) test for SCBP (refer to Section 6.2.5).
  - A SCBP must have two negative pregnancy tests (sensitivity of at least 25 mIU/mL) prior to starting study treatment. The first pregnancy test must be performed at Screening and the second pregnancy test performed within 72 hours prior to the start of study treatment. The results must be confirmed to be negative prior to dosing.
- Clinical laboratory tests (refer to Section 6.2.6).
- Single [redacted] (refer to Section 6.2.7) will be performed to fulfill eligibility criteria.
- Left Ventricular Ejection Fraction (LVEF) assessment (refer to Section 6.2.8).
- Disease (efficacy) assessments (refer to Section 6.4) with the bone marrow aspiration and biopsy, peripheral blood smear (PBS), and complete blood count (CBC) are collected during [redacted] prior to the first dose of study drug. Pharmacodynamic bone marrow biomarker samples should be obtained at the same time (refer to Section 6.6).

[redacted]

6.2 Treatment Period

Procedures in this section occur during treatment and specific timing is described in [redacted] The subject will begin treatment upon confirmation of eligibility. The subject must start treatment [redacted] of signing the ICF (refer to Section 7.2). If screening assessments are performed [redacted] of C1D1, safety laboratory (except hematology) and physical examinations need not be repeated at C1D1. Subjects with AML receiving CC-95251 monotherapy or double combination (CC-95251 with azacitidine) [redacted] Subjects with AML receiving triple combination (CC-95251 with azacitidine and venetoclax) [redacted]

All subjects who fulfill the inclusion/exclusion criteria who are continuing in the study will be registered in the IRT system prior to receiving study drug(s) on C1D1.

6.2.1 Prior and Concomitant Medications and Procedures

All prior and concomitant medications and procedures taken or conducted beginning when the subject signs the ICF, throughout the study, and [redacted] after the last dose of study drug will be recorded in the source documents and eCRF.

Packed red cell and platelet transfusion history [redacted]

6.2.2 Adverse Event Monitoring

Adverse events and serious adverse events (SAEs) will be recorded from the time a subject signs the ICF [redacted] after the last dose of study drug. Refer to Section 10 for detailed information. Subjects experiencing AEs will be monitored with relevant clinical assessments and laboratory tests, as determined by the Investigator. Every attempt will be made to document resolution dates for ongoing AEs. The AE will be recorded on the AE page of the eCRF and in the subject's source documents. Photographs of skin rashes should be obtained whenever possible, anonymized, and stored appropriately for future retrieval.

6.2.3 Vital Signs and Oxygen Saturation

Vital signs include body temperature, blood pressure, pulse rate, and respiration rate will be recorded at screening and during the study at various time points for safety monitoring as described in the Table of Events [redacted]

Serial vital signs will be obtained during each CC-95251 [redacted] and at 30 (s 10 minutes) after the EOI and recorded with vital signs time points. [redacted]

Additional vital signs should be obtained as clinically indicated per the Investigator's assessment. All measurements will be captured in the source documents and eCRF.

6.2.4 Physical Examination and ECOG Performance Status

Physical examination, including height and weight, and Eastern Cooperative Oncology Group (ECOG) performance status will be performed at the visits listed in [redacted], and [redacted]. Results for both will be recorded in the source documents and results for height, weight and the ECOG PS will also be collected on the eCRF.

Physical examination findings will be classified as either normal or abnormal. If abnormal, a description of the abnormality and clinical significance will be provided in the source documents. Clinically significant changes from baseline will be recorded in the AE section of the eCRF.

6.2.5 Pregnancy Test

All subjects will be informed about pregnancy-related risks prior to the first dose of study drug to ensure compliance with all requirements for pregnancy prevention.

A SCBP is defined as a sexually mature individual who has:

- Not undergone a hysterectomy (the surgical removal of the uterus) or bilateral oophorectomy (the surgical removal of both ovaries), or
- Not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (eg, has had menses at any time in the preceding 24 consecutive months).

The Investigator will classify a subject as a SCBP according to this definition. Pregnancy testing is not required for non-SCBP subjects, but justification must be recorded in the eCRF and the source document. Pregnancy testing will be conducted by the local laboratory.

For a SCBP, pregnancy testing will be conducted at the visits listed in [redacted]

A serum pregnancy (β-hCG) test with sensitivity of at least 25 mIU/mL is to be obtained at Screening and serum or urine pregnancy test (based on Investigator's discretion) within 72 hours prior to C1D1 of study treatment. The subject may not receive study drug until the Investigator has verified the two screening pregnancy tests to be negative.

- A quantitative serum or urine pregnancy test (based on Investigator's discretion and minimum test sensitivity [25 mIU/mL]) should be done within 72 hours prior to Day 1 of every cycle, and at the EOT visit. The subject may not receive study drug until the Investigator has verified the pregnancy test to be negative.
- A SCBP or a subject who is able to impregnate their partner must avoid blood/egg/semen/sperm donation and activities that could lead to conception for at least [redacted] after the last dose of CC-95251 and 6 months (or longer if required by local regulations) for SCBP or 3 months (or longer if required by local regulations) for subject who is able to impregnate their partner, after the last dose of azacitidine.

Results for pregnancy tests will be recorded in the source document and eCRF.

6.2.6 Clinical Laboratory Tests

The following laboratory assessments will be performed at the Screening visit and/or during the study at the time points as described in [redacted] All samples on dosing days should [redacted]. Laboratory assessments will be recorded in the source document and eCRF and are the following:

- Hematology: [redacted]
- Serum chemistry: [redacted]

[redacted]

  - For an individual subject, the type of sample drawn (either serum or plasma) for chemistry assessment should be consistent across all collection time points.
- Special chemistry: [redacted]

[redacted]

- Coagulation: [redacted]
- Urinalysis or dipstick
  - microscopy in the event of a positive (1+ or greater) blood or protein
  - 24-hour collection for creatinine clearance and protein quantification in the event of 2+ or greater protein
- Creatinine clearance determination using the Cockcroft-Gault equation required at Screening to fulfill inclusion criteria (refer to Section 4.2).

[redacted]

6.2.7 12-Lead Electrocardiograms

[redacted] When subjects are being treated with CC-95251 in combination with azacitidine, the ECG will be done prior to CC-95251 administration.

[redacted]

Investigators will make clinical decisions based on their interpretation of the ECG results and provide their overall assessment of the ECG in the eCRF. Clinically significant changes from baseline will be recorded in the AE section of the eCRF.

6.2.8 Left Ventricular Ejection Fraction

[redacted] will be conducted at Screening in all subjects, and as clinically indicated. If clinically indicated, follow-up assessments should use the same procedure used at the screening assessment. [redacted] Clinically significant changes for these assessments will be documented on the AE section of the eCRF.

6.2.9 End of Treatment

An EOT evaluation (refer [redacted] for procedures) should be performed for subjects who are discontinued from treatment for any reason as soon as possible after the decision to permanently discontinue treatment has been made [redacted].

6.3 Follow-up Period

6.3.1 Safety Follow-up

All subjects will be followed for [redacted] after the last dose of study drug for AE reporting. In addition, concomitant medication use, SAEs made known to the Investigator at any time thereafter that are suspected of being related to study drug are to be reported until such SAEs have recovered (returned to baseline), recovered with sequelae, or death (due to the SAE) as described in Section 10.1. Subjects will also be followed for all AEs (SAEs and non-serious AEs) associated with confirmed or suspected SARS-CoV-2 infection until resolution, the condition stabilizes, the event is otherwise explained, the event is deemed irreversible, the subject is lost to follow-up, or for suspected cases, until SARS-CoV-2 infection is ruled-out.

The [redacted] safety follow-up contact may be done by telephone if the subject is unable or unwilling to come in for the PK and ADA sampling.

6.3.2 Efficacy Long Term Follow up

After EOT visit, subjects without documented progression of disease (or relapse) or start of a new anticancer therapy will have efficacy evaluations [redacted] or until progression of disease (or relapse), initiation of a new anticancer therapy, withdrawal from the study, death, or the End of Trial, whichever comes first. A bone marrow evaluation will be completed [redacted] and as clinically indicated during the Follow-up Period.

Information (including dates) on new anticancer therapies initiated will be collected until withdrawal from the study, death, or the End of Trial, whichever comes first.

6.3.3 Survival Follow up

After EOT visit, all subjects will be followed according to the schedule for the efficacy long term follow-up (refer to Section 6.3.2) for survival [redacted] or until death, lost to follow-up, or the End of Trial, whichever occurs first. Survival follow-up [redacted]

The Follow-up Period will document survival and new anticancer therapies [redacted]

6.4 Efficacy Assessment

Blood and Bone Marrow Aspirate and/or Biopsy

Bone marrow (BM) aspiration and/or biopsy for disease burden assessments will be collected to be evaluated for [redacted] at Screening, end [redacted] In addition, bone marrow aspirates (BMA) or biopsies (BMB) are performed to confirm complete remission (CR) or morphologic CR with incomplete hematologic recovery (CRi) or morphologic CR with partial hematologic recovery (CRh), relapse after CR, CRi, or CRh (as assessed by the Investigator based on CBC with WBC differential results), or disease progression. Additional aspirates and/or biopsies will be collected as clinically indicated, based on Investigator's medical judgement. Both bone marrow aspirate and biopsy samples are mandatory at Screening [redacted] thereafter, a bone marrow aspirate alone is sufficient, but a biopsy must be collected if the aspirate is not available and may be collected in addition to the aspirate per institutional practice. [redacted]

Response to treatment will be assessed by Investigator using local laboratory results according to modified 2017 European Leukemia Network (ELN) AML Response Criteria (Döhner, 2017) for AML and modified IWG Response Criteria (Cheson, 2006) for MDS based on reported hematology laboratory parameters, peripheral blood smear, bone marrow aspirates and/or biopsies. Hematologic response/transfusion dependence will also be evaluated. In addition, CR with partial hematologic recovery (CRh) will be reported for both AML and MDS (Bloomfield, 2018).

AML response criteria will be summarized by best overall response categories: complete remission rate (CRR) defined as CR + CRi + CRh, and objective response rate (ORR, all responses of CR [ie, CR_{MRD-}, morphologic CR, CRh, CRi] + morphologic leukemia free state [MLFS] + partial remission [PR]). For MDS, the CRR is defined as CR, ORR includes all responses (CR + CRh + marrow CR + PR). The efficacy variable of focus will be CRR and ORR. Other measures of clinical activity include duration of remission, duration of response, stable disease rate (MDS only), relapse-free survival, event-free survival, progression-free survival, time to remission/response, transfusion independence, time to AML transformation for MDS subjects, and overall survival (OS) rates at 6 and 12 months.

The site will ensure peripheral blood, plasma and BMA/ BMB samples are collected and sent to the central lab for exploratory testing at the time of each bone marrow collection as detailed in the Biomarkers Section 6.6.

Progressive disease for AML will be defined as:

- A > 50% increase in bone marrow blast count percentage from the baseline (screening) bone marrow blast count (a minimum 15% point increase is required in cases with <30% blasts at baseline; or persistent bone marrow blast count > 70%, over at least 3 months; without at least a 100% improvement in ANC to an absolute level (> 0.5 x 10^9/L) and/or platelet count > 50 x 10^9/L non-transfused), or
- A > 50% increase in peripheral blasts (WBC × % blasts) to > 25 x 10^9/L (> 25,000/μL) (in the absence of differentiation syndrome), or
- New extramedullary disease.

The date of progressive disease is defined as the first date that there was either a > 50% increase in BM blast count from baseline, a persistence of BM blasts > 70% in subjects with a baseline BM blast count of > 70%, or a doubling of the peripheral blood (PB) blast count.

Treatment failure will be defined as progressive disease or not achieving at least partial remission (PR) by the end of the treatment period. Subjects may continue treatment if they are deriving benefit from treatment without unacceptable toxicity (any CR, MLFS, PR, or SD with demonstrated clinical benefit eg, reduction in transfusion burden), as judged by the Investigator, [redacted], or until disease progression, loss of clinical benefit, unacceptable toxicity, or decision to withdraw by subject or Investigator. Failure to achieve a response while simultaneously not meeting the criteria for progressive disease will be considered stable disease.

Subjects who discontinue study treatment for reasons other than disease progression (or relapse) or start of a new anticancer therapy will have disease assessments according to the specified

assessment schedule (refer to Section 6.3.2) until progression (or relapse) and/or initiation of new anticancer therapies. For subjects who have discontinued study treatment due to relapse or progression or start of a new anticancer therapy, follow up can be performed by site visits or phone calls. Subjects will be followed [redacted] they have died, are lost to follow up, withdraw consent for further data collection, or until study closure.

Molecular and cytogenetic studies in BM may be omitted:

- At the Screening, if they were completed within the [redacted] and the results are available to enter on the eCRFs.
- [redacted]

The bone marrow aspiration and core sampling (biopsy) should be performed according to the standard of care and analyzed at the local site's laboratory in accordance with the International Council for Standardization in Hematology Guidelines (Lee, 2008).

Minimal residual disease

The minimal residual disease (MRD) response rate and MRD conversion rate will also be assessed as efficacy variables. MRD negative CR (CR_{MRD-}), combined rate of CRs (cCRR = CR + CR_{MRD-} + CRi + CRh in AML and CR + CR_{MRD-} in MDS) will be assessed (Bloomfield, 2018).

MRD assessments will be performed in BMA or BMB at disease assessment timepoints using a flow cytometry-based and/or NGS-based method performed by central laboratory (refer to Biomarkers Section 6.6). [redacted]

Testing for MRD will be performed locally, as applicable, per institutional guidelines in AML subjects with complete response in order to permit efficacy assessment according to ELN response criteria (Dohner, 2017).

Packed red blood cell and platelet transfusions

Transfusion dependence is defined as [redacted]

Transfusion independence for hematologic response [redacted]

Packed red cell and platelet transfusion history [redacted] before beginning the study treatment, continuous, and until End of Treatment or efficacy follow-up, whichever occurs later will be collected.

6.5 Pharmacokinetics

Samples will be collected for PK and immunogenicity assessment for subjects at the time points indicated in [redacted] ([redacted]) for each study part.

All on-treatment PK time points are intended to align with days on which study treatment is administered. All predose samples should be taken prior to the start of CC-95251 infusion. If it is known that a dose is going to be delayed, then collect the predose sample just prior to the delayed dose. However, if a predose sample is collected but the dose is subsequently delayed, do not collect an additional predose sample.

[redacted]

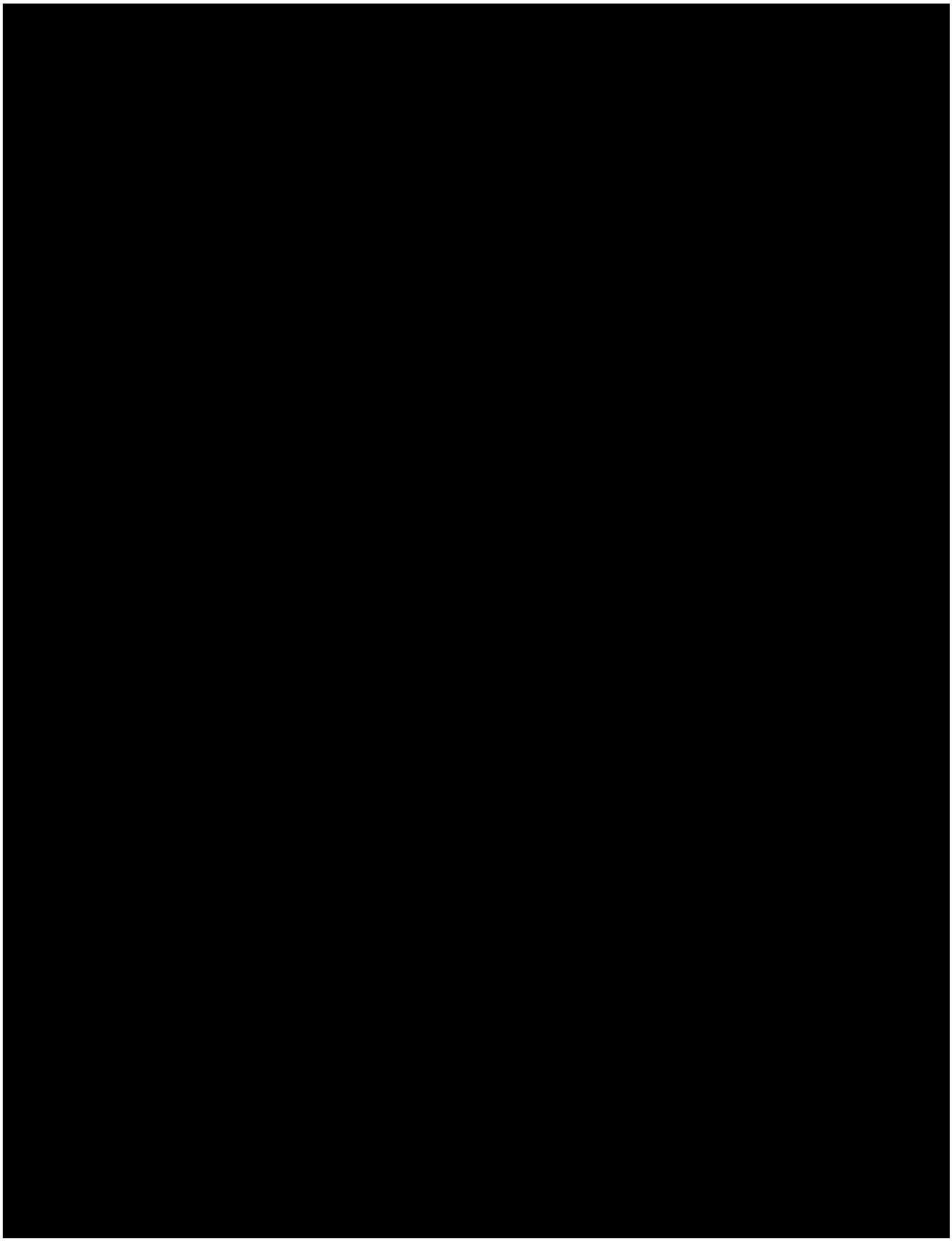
Dosing and sample collection information, including CC-95251 dose level, dosing date, dosing time, infusion time, and actual PK blood sampling time, should be accurately documented on the appropriate source documents and eCRF (refer to Table 5). If the infusion was interrupted, the interruption details will also be documented on the eCRF.

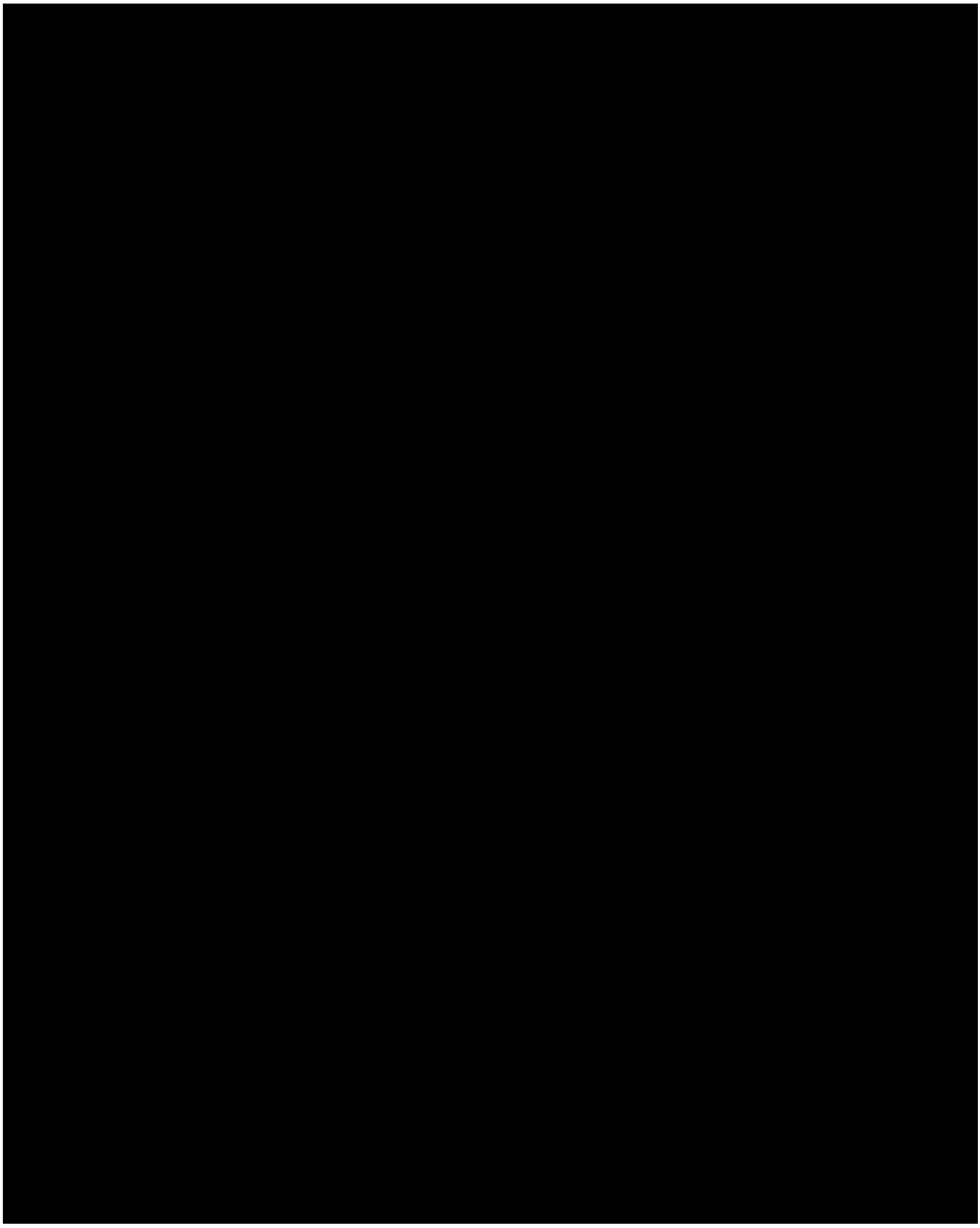
Pharmacokinetics of CC-95251 will be derived from serum concentration versus time. The pharmacokinetic parameters including but not limited to the ones shown in Table 5 will be assessed where feasible.

Table 5: Pharmacokinetic Parameters

C_{max}	Maximum observed serum concentration
C_{min}	Minimum observed serum concentration
T_{max}	Time of maximum observed serum concentration
$AUC_{(0-T)}$	Area under the concentration-time curve from time zero to time of last quantifiable concentration
C_{trough}	Trough observed serum concentration
AUC(TAU)	Area under the concentration-time curve in a dosing interval
CLT	Total body clearance

[redacted]





[redacted]

Concentration analyses for CC-95251 will be performed by validated bioanalytical method(s).

[redacted]

Additionally, residual bioanalytical samples will be archived and may be used for potential exploratory bioanalysis (including but not limited to: [redacted]

Detailed instructions for the PK and immunogenicity blood collection, labeling, processing, storage, and shipping will be provided to the site in the laboratory manual.

6.6 Biomarkers, Pharmacodynamics, Pharmacogenomics

Biomarker assessments will include analyses of peripheral blood and a portion of bone marrow tissue (aspirate and biopsy), collected before treatment and at several times after treatment has begun. Assessments will be performed centrally to evaluate potential associations with safety and efficacy, and to explore mechanisms of resistance and response to the specified treatment.

[redacted]

Minimal residual disease has been proposed as a marker of potential relapse; therefore, we will assess MRD in bone marrow using next generation sequencing and/or flow cytometry methods. [redacted]

Sample specimens will be collected for these studies as indicated in [redacted] and outlined in [redacted]. Biomarker specimens will be collected predose of study treatment unless otherwise specified to evaluate the following:

- Frequencies of bone marrow and peripheral blast cells and monocytes and SIRPα target expression levels and coverage (receptor occupancy)

[redacted]

[redacted]

Consent for biomarker sampling procedures will be obtained through signature of a biomarker specific component of the informed consent form. All subjects participating in this study will consent to biomarker sampling procedures, as described. The sponsor may conduct additional analyses on the PD samples to evaluate the safety of the study treatment or to better understand the progression of the disease or the disease's response to the study treatment. See the Laboratory Manual for sample collection, labeling, processing, storage, and shipping instructions.

[redacted]

6.7 Additional and Optional Research

Additional and optional research as described below may be performed using left-over samples originally collected for another test required in this study or using samples collected specifically for biomarker testing. The research may involve genetic tests using DNA or RNA and may lead to the development of new diagnostic tests.

6.7.1 Additional Research

Additional research related to the study drug and/or disease may be performed. The results of this additional research could help to improve the diagnosis and/or the treatment of this disease in the future.

6.7.2 Optional Research

Optional research not related to the study drug or the subject's disease may be performed. The subject's decision to participate in this optional research will not impact their ability to participate in the main study.

6.8 Subject Reported Outcomes

Not Applicable.

7 DESCRIPTION OF STUDY TREATMENTS

7.1 Description of Investigational Products

7.1.1 CC-95251

CC-95251 (as also known as BMS-986351) will be supplied as investigational product by the sponsor in 2 presentations: [redacted] CC-95251 should be prepared according to the CC-95251 Pharmacy Manual and local practice regulations.

7.1.2 Azacitidine

Azacitidine will be supplied or obtained according to local clinical study agreement and in accordance with local guidelines.

When provided by the Sponsor, azacitidine for Injection will be supplied as a lyophilized powder in 100 mg single-dose vials for reconstitution and administration.

Material supplied by the Sponsor will be labeled appropriately for investigational use as per the regulations of the relevant country health authority.

Please refer to the locally approved azacitidine label or Pharmacy Manual for preparation, administration, and storage information.

7.1.3 Venetoclax

Venetoclax will be supplied or obtained according to local clinical study agreement and in accordance with local guidelines. When provided by the Sponsor, venetoclax will be supplied as tablets in 10 mg, 50 mg, and 100 mg blister/bottles for administration. Material supplied by the Sponsor will be labeled appropriately for investigational use per the regulations of the relevant country health authority.

7.2 Treatment Administration and Schedule

7.2.1 Study Drug Preparation and Administration

7.2.1.1 CC-95251

[redacted] Subjects with [redacted] Full emergency resuscitation facilities should be immediately available, and subjects should be under close supervision of the Investigator or designated staff during and [redacted] following CC-95251 administration. For subjects receiving injectable azacitidine in combination with CC-95251, subjects will receive azacitidine prior to starting CC-95251 infusion on days receiving both treatments. Subjects should be observed [redacted] between administrations.

CC-95251 preparation and infusion will be described in the Pharmacy Manual.

[redacted]

[redacted]

The initial CC-95251 infusion will be started at [redacted] mg/hr [redacted] mg/hr [redacted] mg/hr. Further changes to the rate of infusion may be considered during the course of the trial based on review of clinical data and approval from the SRC.

Serial vital signs and oxygen saturation should be measured as described in Section 6.2.3.

After the end of each CC-95251 infusion, IV access should be maintained and the subject should remain under close supervision [redacted]

CC-95251 will be administered intravenously in two phases starting with a more frequently dosed induction phase followed by a maintenance phase. Treatments will be administered in 28-day cycles. During induction phase, subjects will be dosed weekly for Cycles 1 through 4 (eg, on Day 1, Day 8, Day 15, and Day 22 of each cycle).

After Cycle 4, subjects will enter the maintenance phase. During the maintenance phase, treatments will be administered in 28-day cycles with dosing every two weeks (eg, on Day 1 and Day 15 of each cycle).

An intermediate dose level of CC-95251 or a variable dose schedule [redacted] may be evaluated to accurately determine the RP2D at the recommendation of the SRC. The investigation of any other alternate dosing schedule beyond those stipulated in the current protocol version will be submitted in a protocol amendment.

Subjects may continue CC-95251 for [redacted], or until disease progression, loss of clinical benefit, unacceptable toxicity, or decision to withdraw by subject or Investigator.

7.2.1.2 Azacitidine

Azacitidine at 75 mg/m^2 is administered on Days 1-7 (or Days 1-5 and 8-9) of each 28-day cycle as an IV or SC injection per local prescribing information and institutional standard of care.

BSA for subject dosing should be calculated on the first day of each dosing cycle. BSA should be calculated per institutional standard, however, the Dubois formula [redacted]

[redacted] is preferred. If a subject's body weight changes by more than 10% compared with baseline body weight, or compared with a previous body weight value that required a dose adjustment, then the dose of azacitidine should be recalculated. The dose during a treatment cycle should not be amended.

Subjects may receive best supportive care as needed (please refer to local prescribing information and local therapeutic guidelines for more details on available formulations, preparation, storage conditions [eg, refrigeration], the approved indications, known precautions, warnings, and adverse reactions of best supportive care; see current version of Prescribing Information), including antibiotics and transfusions, per Investigator's discretion.

[redacted]

7.2.1.3 Venetoclax

[redacted] (Table 12). Subjects should be instructed to take their daily dose at approximately the same time each day [redacted]

On Day 1 of each cycle, CC-95251, azacitidine, and venetoclax will be administered [redacted] and subjects should be observed for [redacted] between infusions. [redacted] will be taken orally [redacted] hours [redacted]

Each dose should be taken with a meal and water and consumed over as short of a time as possible. Subjects should be instructed to swallow tablets whole and to not chew or crush the tablets. [redacted]

Subjects will be given a medication diary to record the time of venetoclax administration for at-home administration. All efforts should be made to administer venetoclax on all scheduled days of each 28-day treatment cycle. [redacted] Any missed doses should be documented in the subject's medication diary and not be taken beyond the last scheduled day of venetoclax administration.

If vomiting occurs shortly after a dose of venetoclax is administrated, that dose should not be made up later that day. The subject should continue with the dosing schedule on the next day and inform the investigator about the vomiting event at the next visit and document this in the subject medication diary. Dosing and dosing modifications should follow the approved labels, as summarized in the dose modification guidance, [redacted] and Table 12. Subject-specific factors for level of risk of [redacted] should be assessed, and [redacted] and anti-hyperuricemics to subjects prior to first dose of venetoclax should be given, per locally approved label (see Section 7.2.7.8.2: Prophylaxis and Management of Tumor Lysis Syndrome).

Material supplied by Bristol-Myers Squibb Company (BMS) will be labeled appropriately for investigational use per the regulations of the relevant country health authority. Please refer to the locally approved venetoclax package insert, SmPC, or Pharmacy Manual for dosing and storage information

7.2.2 Dose Escalation Criteria

In Part A, CC-95251 will be given at doses that will increase according to the dose levels in [redacted] The number of cohorts depends on incidence of DLT. [redacted] The initial dose of CC-95251 will be 20 mg/kg [redacted] A sample decision table is shown in [redacted].

The SRC may decide to evaluate a higher dose cohort ([redacted] mg/kg), additional subjects within a dose cohort, intermediate dose cohorts, smaller dose increments, alternate dosing schedules, and/or declare the RP2D based on their review of available clinical and laboratory safety data, efficacy, PK profiles, and PD findings. For a dose level to be selected by the SRC for dose expansion (Parts B, C, and D), [redacted] should be evaluated for DLT in Part A to declare a tolerable dose level.

In the event that an alternate dosing schedule is evaluated, [redacted]

Dose reduction and temporary delay of CC-95251 and combination agents due to toxicity is allowed, [redacted]

7.2.3 Definition of a Subject Evaluable for DLT

All subjects who receive at least one dose of CC-95251 and/or combination drug(s) will be evaluable for safety. After the first dose is administered in any cohort of subjects during dose escalation, subjects in each cohort are observed [redacted]

A subject evaluable for a DLT is defined as one who:

[redacted]

In the absence of persistent AML blasts in the bone marrow, [redacted]

7.2.4 Definition of [redacted]

The [redacted] is defined [redacted]. An intermediate dose level of CC-95251 or a variable dose schedule [redacted] may be evaluated to accurately determine the RP2D at the recommendation of the SRC. The investigation of any other alternate dosing schedule beyond those stipulated in the current protocol version will be submitted in a protocol amendment.

7.2.5 Definition of Dose-Limiting Toxicity (DLT)

Toxicity severity will be graded according to NCI CTCAE Version 5 except for CRS and TLS, which will be graded according to the revised CRS grading system (Lee, 2014) and Cairo-Bishop TLS grading system (Cairo, 2004), respectively. DLTs during dose escalation will be based on adverse events that occur during the DLT observation period. [redacted] and subjects will be evaluated at the completion of each cohort at a given dose level. [redacted]

[redacted]

[redacted]

Any reduced dose level of CC-95251 will be jointly defined by the Investigator and the Sponsor's Medical Monitor. The dose may be increased thereafter upon joint determination of the Investigator and the Sponsor's Medical Monitor (see Section 7.2.7.5). All decisions regarding continued dosing for individual subjects with DLT will be medically managed by the Investigator, and per discussion with the Sponsor's Medical Monitor, as appropriate.

[redacted]

7.2.6 Criteria for Dose Escalation in the Next Cohort of Subjects

Subjects considered evaluable for dose escalation decisions are outlined in Section 7.2.3. Dose escalation decisions will be made by the SRC. Decisions will be based on a synthesis of all relevant data available from all dose levels evaluated in the ongoing study [redacted]

PK data from subjects will be made available on an on-going basis throughout the study and dosing will be adapted accordingly. [redacted]

[redacted]. For a dose level to be selected by the SRC for dose expansion (Part B, C, and D), at least [redacted] should be evaluated for DLT in Part A to declare a tolerable dose level.

The number of dose levels depends on incidence of DLT. A subject may experience more than one DLT. Dose escalation decisions are based on the number of subjects experiencing DLT events.

7.2.7 Definition of Stopping Criteria

7.2.7.1 Criteria for Stopping a Dose Cohort

During dose escalation (Part A), dose escalation stops when the preliminary RP2D is declared by the SRC, based on the number of subjects experiencing DLT events during the DLT evaluation period or when CC-95251 escalates to the highest planned dose of [redacted] mg/kg. The preliminary RP2D is declared by the SRC based on a cumulative review of the available safety, tolerability, PK, PD, and preliminary efficacy data. [redacted]

During the dose expansion (Parts B, C, and D), a non-binding [redacted] safety monitoring method will be utilized to continuously monitor for excessive toxicities defined [redacted]. In Parts B, C, and D, after a

minimum [redacted] have enrolled, the non-binding [redacted] stopping criterion [redacted]

[redacted]

The [redacted] decision will be made by the SRC upon reviewing all available safety, PK, PD, and any efficacy results in dose expansion phase, including considerations on adjustment of the RP2D dose. Otherwise, the cohort will be expanded to up to approximately [redacted] evaluable subjects in Part B, approximately [redacted] evaluable subjects in Part C, and approximately [redacted] evaluable subjects in Part D (Section 9.9.2).

7.2.7.2 Criteria for Pausing or Stopping the study

Further enrollment and treatment in the study will be paused pending review and recommendations of the SRC and immediate notification to all Investigators and appropriate regulatory authorities

[redacted]

Adverse events and SAEs are expected to occur frequently in this study based on the subject population being accrued and on the nature of the advanced hematologic malignancy under study. Regular systematic review of SAEs will serve as the basis for pausing or prematurely stopping the study. Unexpected SAEs that are related to study treatment will be the primary criteria for pausing or stopping the study. Review of these SAEs, and any decision to pause enrollment or terminate the study, will be determined by the SRC. Decisions to pause enrollment or terminate the study will be communicated promptly to Investigators, to the Institutional Review Boards (IRBs)/Ethics Committees (ECs), Institutional Biosafety Committees (IBCs) (if applicable), and to the appropriate regulatory authorities.

7.2.7.3 Permitted Study Drug Adjustments

Dose reductions of CC-95251 are permitted in any cycle, including Cycle 1. [redacted]

When a dose reduction of CC-95251 is indicated, [redacted] Dose omission and reduction are allowed after consultation with the Sponsor's Medical Monitor. [redacted]

Modifications to the administration of azacitidine and venetoclax are allowed per local prescribing information and institutional standard of care. (eg, United States Prescribing Information [USPI] or Summary of Product Characteristics [SmPC]).

7.2.7.4 Criteria for Dose Reduction

Any study drug AE meeting the definition of DLT (refer to Section 7.2.5) will require dose interruption and/or reduction.

[redacted]

Dose reductions of azacitidine for management of toxicities are allowed per local prescribing information and institutional standard of care. (eg, United States Prescribing Information [USPI] or Summary of Product Characteristics [SmPC]). Recommended dosing adjustments to venetoclax due to toxicity are summarized below (Section 7.2.7.7).

7.2.7.5 Criteria for Dose Increase

In Part A, intra-subject dose escalation beyond the dose initially assigned to a subject is [redacted]. However, [redacted] In expansion phases, no dose escalation beyond the RP2D is allowed.

7.2.7.6 Treatment Interruption for Adverse Events

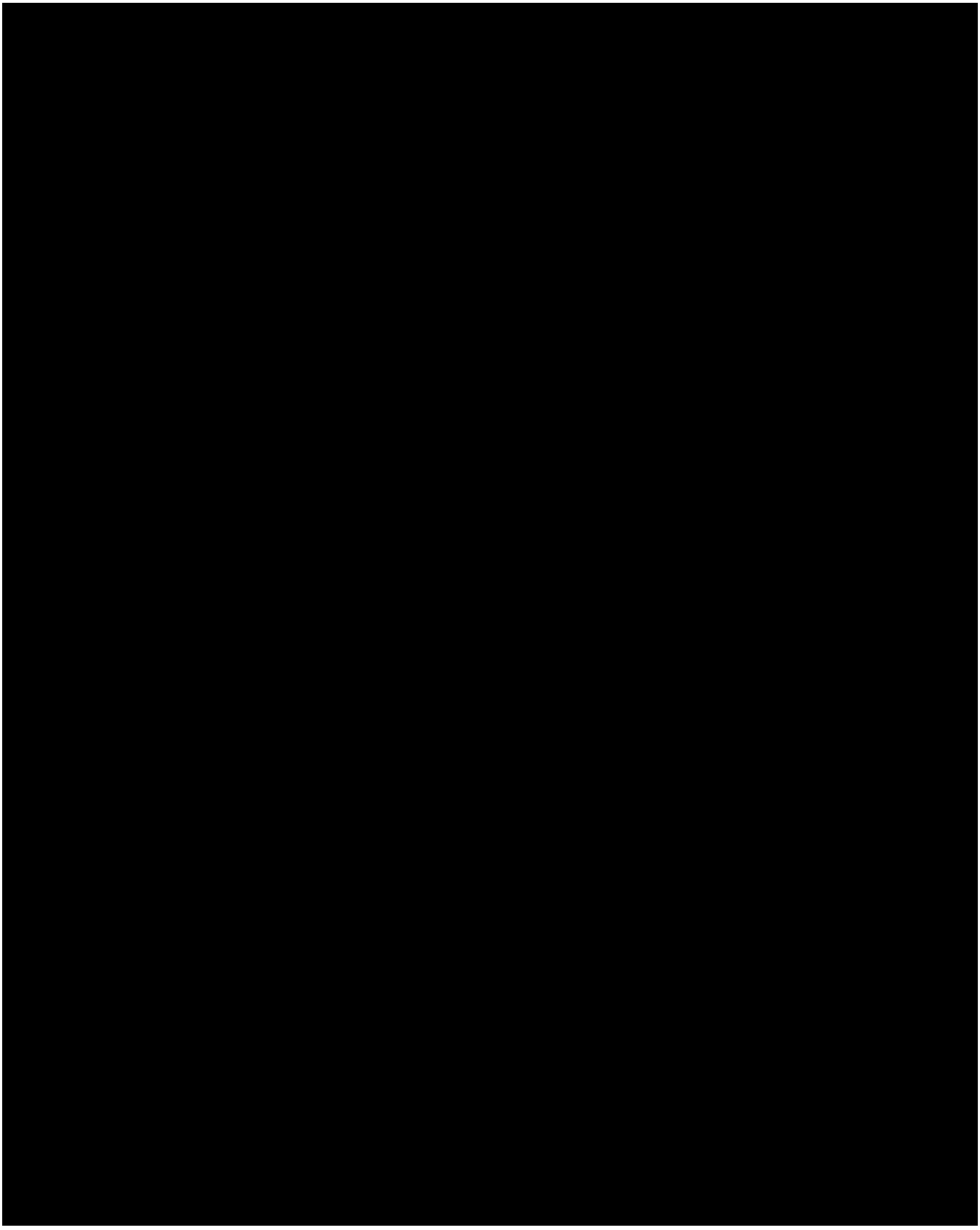
Treatment may be interrupted [redacted]. CC-95251 should also be delayed if subject has confirmed SARS-CoV-2 infection (see Section 7.2.7.8.5).

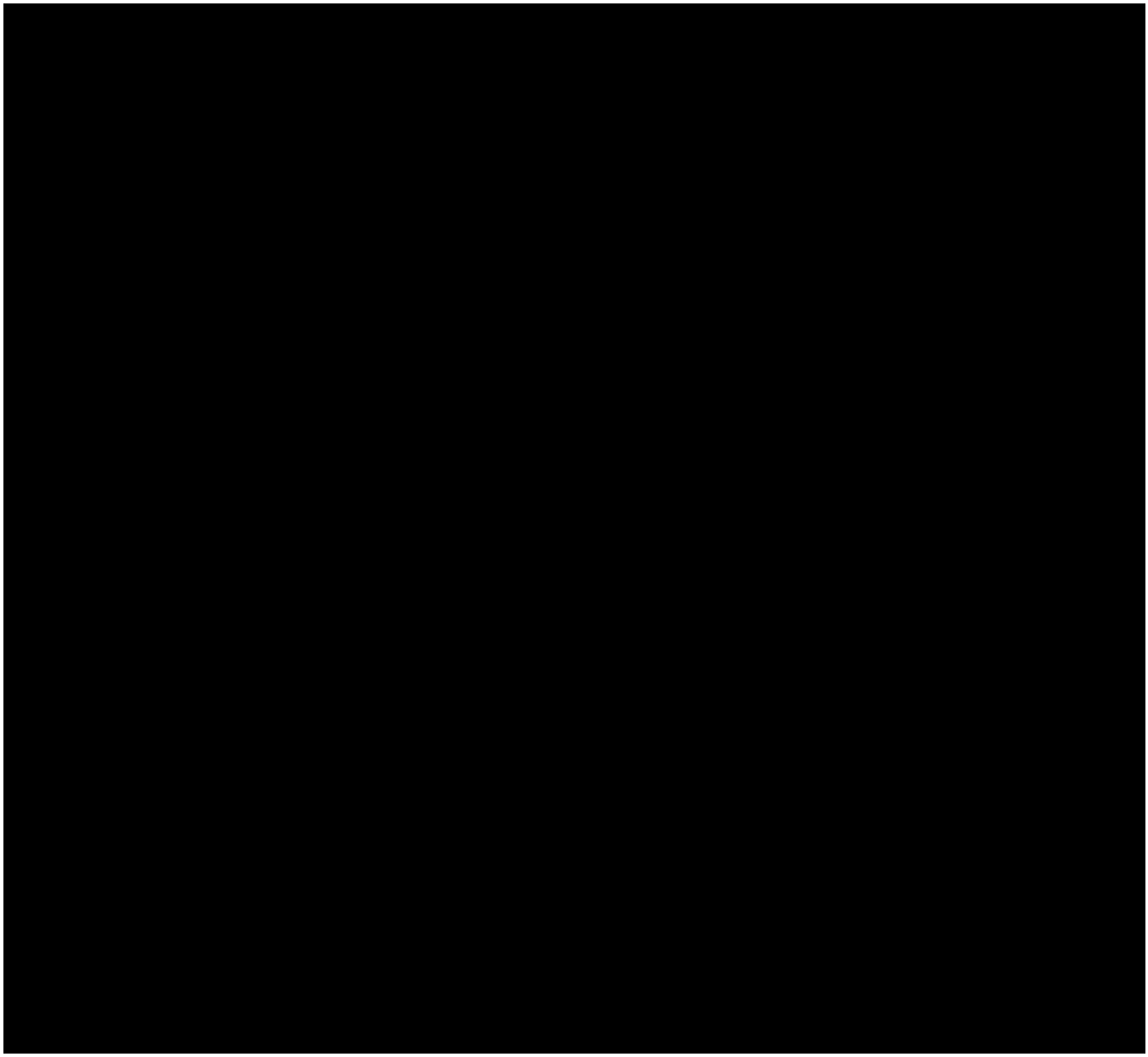
If treatment is interrupted and not given in the visit window [redacted] treatment may restart at the next scheduled visit for CC-95251 administration. Treatment may restart either at the same, or a reduced dose, at the Investigator's discretion or as described in Section 7.2.7.3. In Part A during Cycle 1, [redacted] Treatment interruption of azacitidine for adverse events are allowed per local prescribing information and institutional standard of care. Refer to [redacted] for dose modification guidance for venetoclax and azacitidine-related toxicities.

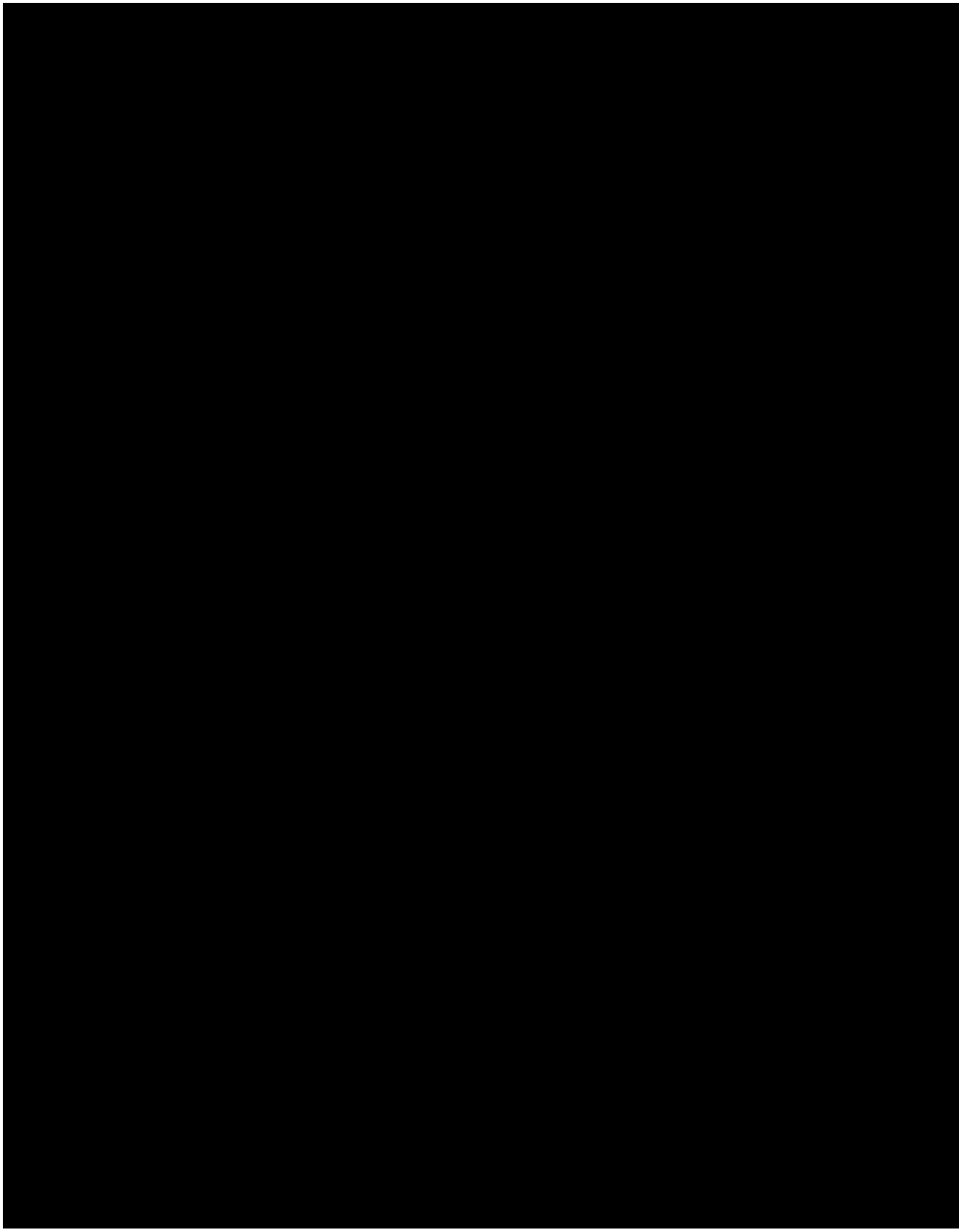
7.2.7.7 Dose Modification Guidelines

The criteria for dose modifications are presented in [redacted]

[redacted]







[redacted]

7.2.7.8 Management of Select Adverse Events

7.2.7.8.1 Prophylaxis, Monitoring, and Management of Infusion Reactions

Infusion of a biologic product may cause severe and life-threatening infusion reactions. [redacted] Symptoms may include hypotension, tachycardia, dyspnea and respiratory symptoms (eg, bronchospasm, throat irritation, wheezing, laryngeal edema). Other possible symptoms include nausea, vomiting, diarrhea, hypertension, flushing, skin rash, headache, fever and chills. Full emergency resuscitation facilities should be immediately available, and subjects should be under close supervision of the Investigator or appropriately trained staff at all times.

[redacted]

Medical management of infusion reactions should be instituted according to standard medical practice using glucocorticoids, epinephrine, oxygen, IV fluids and other medications as medically indicated. [redacted]

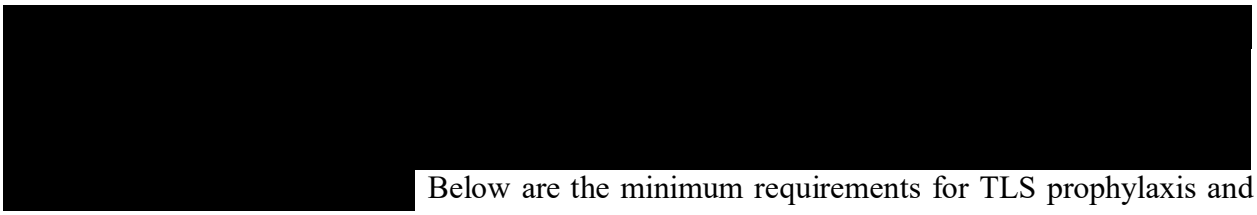
[redacted]

The Sponsor's Medical Monitor should be notified of any Grade 4 or recurrent Grade 3 infusion reactions within 24 hours of the event.

7.2.7.8.2 Prophylaxis and Management of Tumor Lysis Syndrome

Treatment with cytolytic cancer therapies in the setting of high tumor burden may cause rapid tumor lysis and associated electrolyte and renal disturbance with risk of cardiac arrhythmia and sudden death.

TLS is manifested by rapid release of large amounts of potassium, phosphate and nucleic acids into the circulation with associated hyperkalemia, hyperphosphatemia, hyperuricemia, and hypocalcemia. Precipitation of uric acid and calcium phosphate crystals in the renal tubules can result in acute kidney injury and electrolyte disturbances can trigger cardiac arrhythmias, seizures and sudden death.



Below are the minimum requirements for TLS prophylaxis and management. All other prophylaxis and monitoring procedures will be done as per institutional/regional standards:

[redacted]

- As part of serum chemistry laboratory tests, subjects will be monitored for TLS during the study [redacted]
  - Investigators are to exercise clinical judgment as to whether more frequent serum chemistry monitoring may be appropriate at their discretion. Subjects with laboratory abnormalities suspicious for clinically significant TLS should be managed as inpatients.
- Abnormal chemistry tests should be corrected promptly.
- Medications to treat TLS are permitted. [redacted]

- If a subject experiences blood chemistry changes or symptoms suggestive of TLS, maintaining the same ramp-up dose for longer duration or withholding subsequent dose of venetoclax may be required.
- For subjects who had a dose delay or interruption, monitor for evidence of TLS during the restart of treatment and manage abnormalities of serum creatinine, uric acid, and electrolytes promptly. Dose ramp-up of venetoclax is permissible on restart.

7.2.7.8.3 Monitoring and Management of Cytokine Release Syndrome and Macrophage Activation Syndrome/Hemophagocytic Lymphohistiocytosis

[redacted] As such, the CC-95251 clinical study will follow the management of CRS based on the revised CRS grading system (Lee, 2014).

The clinical signs and symptoms of CRS include, but are not limited to: fever, nausea, vomiting, headache, rash, hypotension, tachycardia, tachypnea, elevated D-dimer, hypofibrinogenemia, bleeding, acute renal failure, hyperbilirubinemia, transaminitis, headache, mental status changes, and seizures. Cytokine release syndrome is associated with elevated levels of serum cytokines including interleukin (IL)-6 and interferon γ (IFN γ). Clinical experience with managing this syndrome has supported that treatment with tocilizumab, an anti-IL-6 receptor antibody, with or without corticosteroids, can reverse the syndrome.

[redacted]

[redacted]

The SRC will review the incidence and grade of CRS during the trial and will make recommendations on [redacted] The Sponsor's Medical Monitor should be notified of any episode of Grade ≥ 2 CRS within 24 hours of the event.

[redacted] The diagnosis of MAS/HLH (according to HLH-2004 consensus criteria, further revised in 2014 for HLH associated with malignancies) (Lehmberg, 2015) can be established if either of the 2 criteria below is fulfilled:

1. A molecular diagnosis consistent with MAS/HLH
2. Diagnostic criteria for MAS/HLH fulfilled (five out of the eight criteria below):
   - High persistent fever (≥ 38.5°C)
   - Splenomegaly
   - Cytopenias (affecting 2 of 3 lineages in the peripheral blood): Hemoglobin < 9.0 g/dL, platelets < 100 × 10^9/L, neutrophils < 1.0 x 10^9/L
   - Triglycerides ≥ 3.0 mmol/L (ie, 265 mg/dL) or fibrinogen ≤ 1.5 g/L
   - Hemophagocytosis in bone marrow, spleen, and/or lymph nodes
   - Low or absent natural killer -cell activity (according to local laboratory reference)
   - Ferritin ≥ 500 ng/mL
   - Soluble CD25 (ie, soluble IL-2 receptor) ≥ 2400 U/mL

Effective treatment of MAS/HLH requires multiple simultaneous approaches (Ramos-Casals, 2014; Lehmberg, 2015).

1) Supportive care is essential because of frequent life-threatening severe manifestations at presentation.
2) The elimination of triggers (particularly infection) is crucial to remove the stimuli that initiate the abnormal immune system activation. Appropriate broad-spectrum antiviral, antibacterial, antifungal prophylaxis and treatment must be initiated.
3) Suppression of the inflammatory response and cell proliferation by immunosuppressive and cytotoxic drugs, respectively, is necessary. [redacted]
4) Newer emerging treatments include emapalumab (anti IFN-gamma antibody), which has been approved by the FDA for the treatment of primary refractory or recurrent MAS/HLH (Benedetti, 2019).

7.2.7.8.4 Hematological Toxicity

Hematopoietic growth factors or other hematologic support, such as erythropoietin, darbepoetin, [redacted], red blood cell- or platelet- transfusions are allowed in the study with therapeutic intent. [redacted]

Baseline neutrophil counts worsened in 97% to 100% subjects treated with venetoclax in combination with azacitidine. Neutropenia can recur with subsequent cycles of venetoclax plus

azacitidine therapy. [redacted]

In subjects with elevated WBC, [redacted]

Dose reductions of azacitidine are generally not recommended. If a dose reduction in azacitidine is believed to be necessary, a discussion with the Sponsor Medical Monitor is required.

7.2.7.8.5 Infection

Vigilance for the signs and symptoms of infection should be practiced and managed according to institutional standard medical practice. Routine infectious disease [redacted] recommended during the study according to institutional standard medical practice.

7.2.7.8.5.1 SARS-CoV-2 Infection

Subjects with confirmed SARS-CoV-2 infection following the start of study treatment should have treatment interrupted.

For confirmed SARS-CoV-2 infection, treatment may be resumed after:

- [redacted]) have passed since symptoms first appeared, positive RT-PCR test result, or positive viral antigen test result,
- resolution of acute symptoms [redacted]
- evaluation by the Investigator with confirmation that there are no sequelae that would place the subject at a higher risk of receiving investigational treatment, and
- consultation by the Sponsor's Medical Monitor.
- For suspected cases, treatment may also resume if SARS-CoV-2 infection is ruled-out and other criteria to resume treatment are met. Prior to re-initiating on-study treatment in a subject with a dosing delay lasting [redacted] due to SARS-CoV-2 infection, the Sponsor's Medical Monitor/designee must be consulted.

7.2.7.8.6 Pain

Tumor pain or treatment-induced pain can be controlled with opioid and opioid-related analgesics, such as codeine, meperidine, propoxyphene or morphine, administered at the clinician's discretion, and as dictated by medical need. The risk of bleeding, especially in the setting of

thrombocytopenia, should be considered prior to use of non-steroidal anti-inflammatory drugs and aspirin.

7.2.7.8.7 Gastrointestinal Disorders

Appropriate monitoring and timely management of gastrointestinal disorders is critical in avoiding malnourishment and dehydration. At the discretion of the Investigator, prophylactic and/or therapeutic use of medications (eg, antiemetics for nausea and vomiting, antidiarrheals for diarrhea, laxatives and/or stool softeners for constipation) may be appropriate. Subjects experiencing diarrhea associated with study drugs may be managed according to the guidelines provided in Appendix M. Dose modifications of study drugs may be considered based on the severity of treatment-related gastrointestinal complications ([redacted]).

7.2.7.9 Retreatment or Increased Dose Intensity of CC-95251

Retreatment with CC-95251 may be considered, at the Investigator's discretion and after discussion with the Sponsor's Medical Monitor, if all of the following criteria are met:

[redacted]

Subjects who are retreated will follow the Table of Events (Section 5) [redacted]

7.2.7.10 Definition of Overdose

Overdose, as defined for this protocol, refers to CC-95251, azacitidine, and venetoclax.

On a per dose basis, an overdose is defined as the following amount over the protocol-specified dose of CC-95251 or azacitidine or venetoclax assigned to a given subject, regardless of any associated AEs or sequelae:

[redacted]

Complete data about drug administration, including any overdose, regardless of whether the overdose was accidental or intentional, should be reported in the case report form. Refer to Section 10.1 for the reporting of adverse events associated with overdose.

7.3 Method of Treatment Assignment

Subjects will begin treatment upon confirmation of eligibility.

The subject must start treatment within [redacted] of signing the ICF and can be rescreened if the Screening window lapses. An IRT system will be used to track subject assignments to the dose levels in dose escalation (Part A) and cohorts in dose expansion (Parts B, C, and D).

Subjects will be enrolled sequentially in Part A with no more than one subject enrolled per day into dose escalation cohorts. Enrollment in dose expansion will be stratified by Parts B, C, and D, as applicable. Enrollment in Part C may proceed concurrently with enrollment in the Part B expansion cohorts. Similarly, enrollment in Part D may proceed concurrently with enrollment in the Part B and Part C expansion cohorts.

7.4 Packaging and Labeling

The label(s) for IP will include Sponsor name, address and telephone number, the protocol number, IP name, dosage form and strength (where applicable), amount of IP per container, lot number, expiry date (where applicable), medication identification/kit number, dosing instructions, storage conditions, and required caution statements and/or regulatory statements as applicable. Additional information may be included on the label as applicable per local regulations.

7.5 Investigational Product Accountability and Disposal

Accountability for study drug that is administrated during the course of the study is the responsibility of the Investigator or designee. Investigational clinical supplies must be received by a designated person at the clinical site and kept in a secure and temperature-controlled location. For CC-95251, azacitidine, and venetoclax, the investigational site must maintain accurate records demonstrating dates and amounts of study drug received or obtained from the pharmacy, to whom it was administered (subject-by-subject accounting), and accounts of any vials accidentally or deliberately damaged and/or returned to the Sponsor.

The Sponsor (or designee) will review with the Investigator and relevant site personnel the process for documenting receipt of IP, as well as procedures for accounting, reconciling IP, and documenting this process.

The Sponsor (or designee) will review with the Investigator and relevant site personnel the process for IP return, disposal, and/or destruction including responsibilities for the site versus the Sponsor (or designee).

7.6 Investigational Product Compliance

Only the pharmacist or Investigator's designee will dispense CC-95251 and azacitidine. A record of the total dose (and number of vials used) of CC-95251 and azacitidine administered to each subject must be maintained.

The pharmacist or Investigator's designee will document the doses dispensed/administered in the appropriate study records and the appropriate eCRF. Study intervention compliance will be periodically monitored by drug accountability, including the review of dosing diary cards. Drug accountability should be reviewed by the study site staff at each visit to confirm treatment compliance. Study sites should discuss discrepancies with the subject at each on-treatment study visit.

- When subjects are dosed at the site, they will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the electronic case report form (eCRF). The dose of study intervention and study subject identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.
- When subjects self-administer venetoclax at home, compliance with study intervention will be assessed at each visit. Compliance will be assessed by direct questioning, and counting returned tablets during the site visits, and documented in the source documents and relevant form. Deviation(s) from the prescribed dosage regimen should be recorded in the eCRF.
- Accountability records of study interventions in respective sub-protocols dispensed and administered to each subject must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for intervention delays and/or dose reductions, will also be recorded in the eCRF.

8 CONCOMITANT MEDICATIONS AND PROCEDURES

All medications (excluding prior cancer therapy for the tumor under evaluation) taken beginning when the subject signs the ICF and all concomitant therapy during the study [redacted]

All prior chemotherapy (biologic, immunologic, or radiation therapy) and anticancer surgery prior to the administration of either study drug, will be recorded in the appropriate section of the eCRF.

Packed red cell and platelet transfusion history [redacted]

The Investigator will instruct subjects to notify the study staff about any new medications taken after signing the ICF. All medications and significant non-drug therapies (herbal medicines, physical therapy, etc.) and any changes in dosing with existing medications will be documented on the eCRFs.

8.1 Permitted Concomitant Medications and Procedures

Subject to the precautions described in Section 8.2, the use of any concomitant medication or therapies deemed necessary for the care of the subject should be used. Repeat PK evaluations may be conducted if changes are made to concomitant medications suspected of affecting drug absorption or metabolism.

[redacted]

Prophylactic and/or therapeutic use of medications (eg, antiemetics for nausea and vomiting, antidiarrheals for diarrhea, laxatives and/or stool softeners for constipation) for gastrointestinal disorders are permitted.

Parenteral flu vaccination is permitted.

Routine infectious disease [redacted]

Subjects may receive authorized or approved COVID-19 vaccines while continuing on study treatment at the discretion of the Investigator. COVID-19 vaccines that are NOT live are allowed and should be handled in the same manner as other vaccines. Administration may occur during the study, including during the administration of the BMS study treatment and after the last administration of the BMS study treatment.

Treatment of active SARS-CoV-2 infections or high risk exposures, including use of investigational therapies, is allowed and should be discussed with the Sponsor's medical monitor.

8.2 Prohibited Concomitant Medications and Procedures

Other investigational therapies must not be used while the subject is on the study.

Anticancer therapy (chemotherapy, biologic or investigational therapy, and surgery) other than the study treatments must not be given to subjects while the subject is on the study. If such treatment is required, the subject must be discontinued from the study. [redacted]

[redacted]

[redacted] Temporary use of corticosteroids for concurrent illnesses (eg, food allergies, pneumonitis, etc.) are acceptable upon discussion with the Sponsor's Medical Monitor.

The administration of investigational COVID-19 vaccines is not allowed during the study. Live COVID-19 vaccines should not be administered to a subject during the study, including during the treatment, safety follow-up period and [redacted] following the last dose of study drug. In addition, the administration of a live COVID-19 vaccine is prohibited [redacted] prior to initiation of study treatment.

[redacted]

[redacted]

Table 12: Management of Potential Venetoclax Interactions with CYP3A and P-gp Inhibitors

Cycle Day	Moderate CYP3A or P-gp Inhibitor[a]	Strong CYP3A Inhibitors (Other than Posaconazole)[b]	Posaconazole[c]
Day 1	50 mg	10 mg	10 mg
Day 2	100 mg	20 mg	20 mg
Day 3	200 mg	50 mg	50 mg
Day 4 and beyond	200 mg	100 mg	70 mg

Abbreviations: CYP = cytochrome P450; P-gp = P-glycoprotein.

[a] Following discontinuation of the CYP3A or P-gp inhibitor: 2 to 3 days after the inhibitor is discontinued, resume the venetoclax dose that was used prior to initiating the CYP3A or P-gp inhibitor.

[b] For subjects who have completed dose escalation and are on a steady daily venetoclax dose, reduce the venetoclax dose to 100 mg once daily when a strong CYP3A inhibitor (other than posaconazole) must be used concurrently.

[c] For subjects who have completed dose escalation and are on a steady daily venetoclax dose, reduce the venetoclax dose to 70 mg once daily when posaconazole must be used concurrently.

- Based on in vitro data, azacitidine metabolism does not appear to be mediated by CYPs; therefore, CYP inhibitors and inducers are unlikely to have any impact on the metabolism of azacitidine. Clinically relevant inhibitory or inductive effects of azacitidine on the metabolism of CYP substrates are unlikely.

[redacted]

[redacted]

9 STATISTICAL CONSIDERATIONS

9.1 Overview

Study CA059-001 is a multi-center, open-label, three-part, Phase 1, dose finding study to determine the safety, tolerability, PK, and PD of CC-95251 both alone and in combination with antineoplastic agents in subjects with R/R AML and R/R or treatment-naïve MDS or TN AML. The study will consist of dose escalation (Part A) and dose expansion (Parts B, C, and D). [redacted] to determine the preliminary RP2D of CC-95251 both alone and in combination with azacitidine in R/R AML and R/R (IPSS-R [redacted] MDS subjects , and CC-99251 in combination with axacitidine and venetoclax in RR AML. Part B further evaluates the safety and efficacy of CC-95251 alone and in combination with azacitidine in R/R AML and R/R (IPSS-R [redacted] MDS subjects. Part C evaluates the safety and efficacy of CC-95251 in combination with azacitidine in treatment-naïve MDS (IPSS-R [redacted] subjects. Part D consists of a dose expansion in combination with injectable azacitidine and venetoclax (triple combination) in subjects with TN AML ineligible for intensive chemotherapy. One or more dosing regimens from Part A may be selected for cohort expansion in Parts B, C, and D [redacted].

Data from all sites will be combined for the final analysis. Results will be presented using descriptive statistics. Statistical analyses will be performed by drug combination and dose level (Part A) and by cohort (Parts B, C, and D) as needed or applicable. In the dose escalation (Part A) of the trial, summaries will be prepared by dose level and overall. [redacted] In the treatment-naïve MDS (IPSS-R [redacted] dose expansion (Part C) and treatment-naive AML dose expansion (Part D) of the trial, summaries will be prepared by cohort and overall.

All analyses will be descriptive in nature. Summary tables for continuous variables will contain the following statistics: n (the corresponding sample size), mean, median, standard deviation (SD), minimum (min), and maximum (max). Summary tables for categorical variables will include n, percentage, and [redacted] confidence intervals on the percentage as appropriate. Unless otherwise indicated, [redacted] confidence intervals for [redacted]

9.2 Study Population Definitions

Table 13: Definition of study population

Population	Description
Enrolled	[redacted]
Safety (all treated)	
Efficacy Evaluable (EE)	
Pharmacokinetic (PK) population	
Biomarker evaluable (BE) population	

Abbreviations: BE = biomarker evaluable; EE = efficacy evaluable; PK = pharmacokinetic.

9.3 Sample Size and Power Considerations

During Part A of the study (dose escalation), [redacted] evaluable subjects are treated at a dose level [redacted]

The proposed dose levels for testing the CC-95251 monotherapy include a [redacted] 20 mg/kg, [redacted] 30 mg/kg [redacted] 10 mg/kg, [redacted], and the total estimated subjects will be [redacted] for CC-95251 monotherapy [redacted] An intermediate dose may be investigated if [redacted] is not tolerated while [redacted] is tolerated. In the event the [redacted] is not tolerated in the CC-95251 monotherapy cohort, [redacted] may be recommended by the SRC.

The proposed dose levels for CC-95251 in combination with azacitidine include a [redacted] 10 mg/kg, [redacted] 20 mg/kg, [redacted] 30 mg/kg, [redacted] 3 mg/kg, [redacted], and the total estimated subjects will be [redacted] for CC-95251 in combination with azacitidine [redacted] In the event the DL1a is not tolerated in the CC-95251 plus azacitidine cohort, DL1a may be recommended by the SRC.

The proposed dose levels for CC-95251 in combination with azacitidine and venetoclax include a [redacted] 20 mg/kg [redacted] 30 mg/kg QW; and [redacted] 10 mg/kg, [redacted]; and the total estimated subjects will be [redacted] for CC-95251 in combination with azacitidine and venetoclax. In the event that DL1b is not tolerated in the CC-95251 plus azacitidine and venetoclax cohort, DL1b may be recommended by the SRC.

In Part B, approximately [redacted] subjects per cohort will be enrolled to further evaluate the safety and assess the efficacy of CC-95251 alone and in combination with azacitidine in R/R AML and R/R MDS (IPSS-R [redacted] at the preliminary RP2D established in dose escalation, or at an alternative tolerable dose and schedule based on review of available safety, PK, PD, and preliminary efficacy data from Part A. [redacted]

Enrollment in Part C may start only after [redacted] (cumulatively between Parts A and B) with relapsed/refractory MDS have been treated at the proposed Part C expansion dose and schedule of CC-95251 plus azacitidine. The SRC will review the safety data from this group of subjects utilizing [redacted] prior to the opening of the Part C expansion. The dose of CC-95251 selected for Part C may occur at the preliminary RP2D established in dose escalation, or at an alternative tolerable dose based on review of available safety, PK, PD, and preliminary efficacy data.

The Part C expansion will initially evaluate [redacted] with treatment-naïve MDS treated [redacted] The SRC will review the available safety utilizing [redacted], PK, PD and preliminary efficacy data in the [redacted] to determine if the dose and schedule is tolerated prior to escalating the CC-95251 dose to the proposed Part C expansion dose and schedule. A lower dose of CC-95251 plus azacitidine may be selected for continued enrollment in the expansion based on SRC review of the available data from [redacted]. Thereafter, a total of approximately [redacted] additional subjects with treatment-naïve MDS may be enrolled in Part [redacted] During enrollment in Part C the SRC will review available safety data from [redacted]

Approximately [redacted] subjects with treatment-naïve MDS will be enrolled in the Part C expansion. The preliminary efficacy data for dose cohorts in Part C may be combined for analysis.

In the Part D expansion, [redacted] will be enrolled at the preliminary RP2D established in dose escalation, or at an alternative tolerable dose and schedule based on review of available safety, PK, PD, and preliminary efficacy data from Part A. Thereafter, an additional approximately [redacted] subjects will be enrolled for the sample size of an initial [redacted] response-evaluable subjects dosed at the proposed expansion dose to further evaluate the safety and estimate the preliminary efficacy of triple combination.

During enrollment in Part D the SRC will review available safety data from [redacted] If the efficacy assessment on the [redacted] response-evaluable subjects provides an initial evidence for preliminary efficacy, [redacted] will be enrolled to further evaluate safety and efficacy, Therefore, approximately [redacted] response-evaluable subjects with treatment-naïve AML will be enrolled in the Part D expansion. [redacted]

9.4 Background and Demographic Characteristics

In Part A, the baseline characteristics of subjects will be summarized by drug combination and dose level for the enrolled population. In Parts B, C, and D the baseline characteristics of subjects will be summarized by cohort. Subject's age, height, weight, and baseline characteristics will be summarized using descriptive statistics, while sex, race and other categorical variables will be provided using frequency tabulations. Medical history data will be summarized using frequency tabulations by MedDRA system organ class and preferred term.

9.5 Subject Disposition

Subject disposition (analysis population allocation, ongoing, discontinued, along with primary reason) from treatment and study will be summarized using frequency and percent. A summary of subjects enrolled by site will be provided. Protocol deviations will be summarized using frequency tabulations. Supportive corresponding subject listings will also be provided.

9.6 Efficacy Analysis

The key efficacy variables are CRR (defined as CR + CRi + CRh for AML; CR for MDS) and ORR (all responses of CR [ie, CR_{MRD-}, morphologic CR, CRh, CRi] + MLFS + PR for AML and CR + CRh + marrow CR + PR for MDS) by disease -appropriate response criteria. For dose expansion, efficacy variables to be analyzed include CRR and ORR, duration of remission, duration of response, stable disease rate (MDS only), relapse-free survival, event-free survival, progression-free survival, time to remission/response, transfusion independence, time to AML transformation for MDS subjects, and OS rates at 6 and 12 months. Point estimates and 2-sided 90% exact Clopper-Pearson confidence intervals of CRR and ORR will be reported. For time to event endpoints, Kaplan-Meier survival analyses will be performed. The PFS and overall survival rate will be measured and reported at pre-specified time points (ie, 6 months, 12 months).

Exploration of PK, PD, safety and activity relationships may be assessed.

9.7 Safety Analysis

The primary objective of this study is to define the RP2D of CC-95251 alone and in combination with azacitidine in eligible subjects with AML or MDS and in combination with azacitidine and venetoclax in eligible subjects with AML. [redacted] The final determination of RP2D will be decided by the SRC.

Statistical analyses will be performed by dose level or dose schedule and a combination product as needed or applicable. Study data will be summarized for disposition, demographic and baseline characteristics, exposure, efficacy, safety, PK, and PD per respective analysis population defined in Section 9 as applicable. All analyses will be descriptive in nature.

Adverse events, including treatment-emergent adverse events, will be graded by NCI CTCAE version 5 grades, except for CRS and TLS, which will be graded according to the revised CRS grading system ([Lee, 2014] and Cairo-Bishop TLS grading system [Cairo, 2004], respectively). The frequency of AEs will be tabulated by Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term. Grade 3 or higher AEs, AEs leading to discontinuation of study treatment or to death, study intervention-related AEs, and SAEs will be tabulated separately. Changes from baseline in selected laboratory analytes for example transfusion dependence (platelet count or red blood cell [RBC] transfusion units), vital signs, and [redacted] will be summarized.

[redacted].

9.9 Other Topics

9.9.1 Statistical Method for Dose Escalation

Dose-escalation/de-escalation decisions [redacted]

In [redacted] the columns indicate numbers of evaluable subjects treated at each dose level, and [redacted] Dose escalation may be halted once a dose level with acceptable safety and satisfactory antitumor activity has been selected for evaluation in the dose expansion part.

Dose escalation (Part A) may be stopped for the following reasons:

[redacted]

[redacted] The final determination of RP2D will be decided by the SRC. Each dose level may enroll [redacted] with the potential to expand to approximately [redacted] in order to further inform selection of dose and schedule for dose expansion. Enrollment to the highest open dose level will be prioritized if multiple dose levels are open for enrollment.

[redacted]

9.9.2 Stopping Rules Regarding Toxicity in Dose Expansion

During the dose expansion (Parts B, C, and D), a non-binding [redacted] safety monitoring method will be utilized to continuously monitor for excessive toxicities defined as the occurrence of AEs [redacted]. The SRC will also utilize this method to monitor for excessive toxicities in subjects with relapsed/refractory MDS [redacted] prior to the opening of Part C and D expansion. [redacted]

After a [redacted] have enrolled and completed at least one cycle of study treatment, the following non-binding [redacted] stopping criterion to pause the trial based on the posterior distribution of excessive toxicity will be calculated.

[redacted]

[redacted]

Regular systematic review of SAEs will serve as the basis for pausing enrollment or prematurely stopping the study. Review of these SAEs, and any decision to pause enrollment or terminate the study, will be determined by the SRC. Decisions to pause enrollment or terminate the study will be communicated promptly to Investigators, to the IRBs and to the appropriate regulatory authorities.

[redacted]

9.9.3 Assessment of Pharmacokinetics

Plasma PK parameters such as C_{max}, C_{min}, AUC, t_{max}, and CLT of CC-95251 where feasible will be calculated by the noncompartmental analysis (NCA) method from the plasma concentration-time profiles of CC-95251. Other PK parameters may be calculated as appropriate. In addition to the NCA analysis, compartmental analysis may be conducted to estimate PK parameters based on all cycle data for each subject and/or the cohorts.

Summary statistics including number of subjects (N), mean, SD, coefficient of variation (CV%), geometric mean, geometric CV%, median, minimum, and maximum will be provided for CC-95251 concentration by nominal time point, study day, and dose cohort. Mean and individual plots of plasma concentrations will be presented in both original and semi-logarithmic scales. Summary statistics will also be provided for CC-95251 PK parameters by study day and dose cohort and be presented in tabular form.

9.9.4 Assessment of Immunogenicity

The incidence of ADAs will be summarized for the Safety Population. In addition, subjects who are positive for ADAs will also be listed. Potential relationships between ADA and safety and efficacy will be assessed.

9.9.5 Assessment of Pharmacodynamics and Exploratory Biomarkers

Descriptive statistics (N, mean, SD, median, min, and max) will be provided for baseline, post-baseline values, and changes from baseline or percent change from baseline for biomarkers including receptor occupancy and cytokines by dose cohort (Part A) and visit. Subjects' biomarker results over time will be plotted. Comparison of biomarker levels before and during treatment will be performed by Wilcoxon signed rank test. If sufficient and valid results from biomarker assays can be obtained, the relationship between percent changes in biomarker levels and clinical endpoints including ORR may be explored.

9.9.6 Assessment of Other Exploratory Endpoints

Proportion of subjects achieving MRD negativity at any time on/after treatment with CC-95251 alone, in combination with azacitidine and in combination with azacitidine and venetoclax will be summarized for the Safety and Efficacy Evaluable Populations. Point estimates and 2-sided 95% confidence intervals of CRMRD- rates will be reported.

9.10 Safety Review Committee

The SRC membership will be comprised of Investigators (and/or designated representatives), the Sponsor's Medical Monitor, safety physician, clinical scientist, and the study manager. Ad hoc attendees may include the study PK scientist, biostatistician, and translational research scientist. Other internal and external experts may be consulted by the SRC, as necessary.

The SRC will recommend dose escalation/de-escalation decisions in Part A. The decision to evaluate additional subjects within a dose cohort, smaller dose increments, alternate dosing schedules, or make a recommendation of the preliminary dose and schedule of CC-95251 to test in the expansion cohorts (Parts B and C) will also be at the discretion of the SRC, based on their review of available safety, tolerability, PK, PD, and preliminary efficacy. During dose expansion phase, the SRC will continue to review safety data regularly throughout the study and make recommendations about study continuation, dose modification and establishment of a RP2D as appropriate.

All decisions made by the SRC at the dose escalation meetings will be formally documented (via meeting minutes and memos) and circulated to all sites in writing. No dose escalation, de-

escalation, change of dosing schedule, or expansion of existing dose cohorts will commence prior to written notification having been sent to participating sites of the respective SRC decision(s).

The meeting frequency will depend on enrollment rate and when dosing decision milestones are reached in the dose escalation part and when a meaningful amount, as decided by the SRC, of safety/efficacy data are available after dose escalation.

[redacted]

The Sponsor has implemented a comprehensive safety process that is appropriate in managing subject safety at this stage of development: a multi-layered process to ensure safety monitoring through close collaboration of study site investigators, the BMS study team, and the Worldwide Patient Safety-led SMT. To support safety oversight, the Sponsor has established processes for collection, ongoing review, analysis, and submission of individual AE reports and their aggregate analyses. Because this is an open-label study, the BMS safety physicians, Medical Monitors, and the investigators will have access to all data necessary for real-time safety evaluation.

10 ADVERSE EVENTS

10.1 Monitoring, Recording and Reporting of Adverse Events

An AE is any noxious, unintended, or untoward medical occurrence that may appear or worsen in a subject during the course of a study. It may be a new intercurrent illness, a worsening concomitant illness, an injury, or any concomitant impairment of the subject's health, including laboratory test values (as specified by the criteria in Section 10.3), regardless of etiology. Any worsening (ie, any clinically significant adverse change in the frequency or intensity of a pre-existing condition) should be considered an AE. A diagnosis or syndrome should be recorded on the AE page of the CRF rather than the individual signs or symptoms of the diagnosis or syndrome.

Abuse, withdrawal, sensitivity, or toxicity to an investigational product should be reported as an AE. Overdose, accidental or intentional, whether or not it is associated with an AE should be reported on the overdose CRF. (See Section 7.2.7.10 for the definition of overdose). Any sequela of an accidental or intentional overdose of an investigational product (IP) which meets the definition of an adverse event, should be reported as an AE on the CRF. If the sequela of an overdose meets serious criteria, then it must be marked as serious on the CRF. The overdose itself should not be reported as an AE.

In the event of overdose, the subject should be monitored as appropriate and should receive supportive measures as necessary. There is no known specific antidote for CC-95251 overdose. Actual treatment should depend on the severity of the clinical situation and the judgment and experience of the treating physician.

All subjects will be monitored for AEs during the study. Assessments may include monitoring of any or all of the following parameters: the subject's clinical symptoms, laboratory, pathological, radiological or surgical findings, physical examination findings, or findings from other tests and/or procedures.

All AEs will be recorded by the Investigator from the time the subject signs informed consent until [redacted] after the last dose of study drug. In addition, SAEs made known to the Investigator at any time thereafter that are suspected of being related to IP will be reported until such SAEs have recovered (returned to baseline), recovered with sequelae, or death (due to the SAE). All adverse events (serious/non-serious) will be recorded on the CRF and in the subject's source documents. Refer to Section 10.5 for instructions on how to report SAEs to Drug Safety.

Subjects will be followed for all SAEs, and AEs (SAEs and non-serious AEs) associated with confirmed or suspected SARS-CoV-2 infection until resolution, the condition stabilizes, the event is otherwise explained, the event is deemed irreversible, the subject is lost to follow-up, or for suspected cases, until SARS-CoV-2 infection is ruled out.

10.2 Evaluation of Adverse Events

A qualified Investigator will evaluate all adverse events as to:

10.2.1 Seriousness

An SAE is any AE occurring at any dose that:

- Results in death;
- Is life-threatening (ie, in the opinion of the Investigator, the subject is at immediate risk of death from the AE);
- Requires inpatient hospitalization or prolongation of existing hospitalization (hospitalization is defined as an inpatient admission, regardless of length of stay);
- Results in persistent or significant disability/incapacity (a substantial disruption of the subject's ability to conduct normal life functions);
- Is a congenital anomaly/birth defect;
- Constitutes an important medical event.

Important medical events are defined as those occurrences that may not be immediately life-threatening or result in death, hospitalization, or disability, but may jeopardize the subject or require medical or surgical intervention to prevent one of the other outcomes listed above. Medical and scientific judgment should be exercised in deciding whether such an AE should be considered serious.

Events **not considered** to be SAEs are hospitalizations for:

- a standard procedure for protocol therapy administration. However, hospitalization or prolonged hospitalization for a complication of therapy administration will be reported as an SAE.
- routine treatment or monitoring of the studied indication not associated with any deterioration in condition.
- the administration of blood or platelet transfusion as routine treatment of studied indication. However, hospitalization or prolonged hospitalization for a complication of such transfusion remains a reportable SAE.

- a procedure for protocol/disease-related investigations (eg, surgery, scans, endoscopy, sampling for laboratory tests, bone marrow sampling). However, hospitalization or prolonged hospitalization for a complication of such procedures remains a reportable SAE.
- hospitalization or prolongation of hospitalization for technical, practical, or social reasons, in absence of an AE.
- a procedure that is planned (ie, planned prior to start of treatment on study); must be documented in the source document and the CRF. Hospitalization or prolonged hospitalization for a complication remains a reportable SAE.
- an elective treatment of or an elective procedure for a pre-existing condition, unrelated to the studied indication, that has not worsened from baseline.
- emergency outpatient treatment or observation that does not result in admission, unless fulfilling other seriousness criteria above.

For each AE, the Investigator will provide information on severity, start and stop dates, relationship to the IP, action taken regarding the IP, and outcome.

10.2.2 Severity/Intensity

For each AE, the Investigator must assess the severity/ intensity of the event.

The severity/intensity of AEs will be graded based upon the subject's symptoms according to the current active minor version of the Common Terminology Criteria for Adverse Events (CTCAE, Version 5.0);

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

AEs that are not defined in the CTCAE should be evaluated for severity/intensity according to the following scale:

- Grade 1 = Mild – transient or mild discomfort; no limitation in activity; no medical intervention/therapy required
- Grade 2 = Moderate – mild to moderate limitation in activity, some assistance may be needed; no or minimal medical intervention/therapy required
- Grade 3 = Severe – marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalization is possible
- Grade 4 = Life-threatening – extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable
- Grade 5 = Death – the event results in death

The term "severe" is often used to describe the intensity of a specific event (as in mild, moderate or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This criterion is *not* the same as "serious" which is based on subject/event *outcome* or *action* criteria associated with events that pose a threat to a subject's life or functioning.

Seriousness, not severity, serves as a guide for defining regulatory obligations.

10.2.3 Causality

The Investigator must determine the relationship between the administration of the IP and the occurrence of an AE as Not Suspected or Suspected as defined below:

Not suspected:	a causal relationship of the adverse event to IP administration is **unlikely or remote**, or other medications, therapeutic interventions, or underlying conditions provide a sufficient explanation for the observed event.
Suspected:	there is a **reasonable possibility** that the administration of IP caused the adverse event. 'Reasonable possibility' means there is evidence to suggest a causal relationship between the IP and the adverse event.

Causality should be assessed and provided for each AE based on currently available information. Causality is to be reassessed and provided as additional information becomes available.

If an event is assessed as suspected of being related to a comparator, ancillary or additional IP that has not been manufactured or provided by the Sponsor, please provide the name of the manufacturer when reporting the event.

10.2.4 Duration

For each AE, the Investigator will provide a record of the start and stop dates of the event.

10.2.5 Action Taken

The Investigator will report the action taken with IP as a result of each AE, as applicable (eg, discontinuation, interruption, or dose reduction of IP, as appropriate) and report if concomitant and/or additional treatments were given for the event.

10.2.6 Outcome

The Investigator will report the outcome of the event for each AE.

All SAEs that have not resolved upon discontinuation of the subject's participation in the study must be followed until recovered (returned to baseline), recovered with sequelae, or death (due to the SAE).

10.3 Abnormal Laboratory Values

An abnormal laboratory value is considered to be an AE if the abnormality:

- results in discontinuation from the study;
- requires treatment, modification/ interruption of IP dose, or any other therapeutic intervention; or
- is judged to be of significant clinical importance, eg, one that indicates a new disease process and/or organ toxicity, or is an exacerbation or worsening of an existing condition.

Regardless of severity grade, only laboratory abnormalities that fulfill a seriousness criterion need to be documented as a serious adverse event.

If a laboratory abnormality is one component of a diagnosis or syndrome, then only the diagnosis or syndrome should be recorded as the AE. If the abnormality was not a part of a diagnosis or syndrome, then the laboratory abnormality should be recorded as the AE. If possible, the laboratory abnormality should be recorded as a medical term and not simply as an abnormal laboratory result (eg, record thrombocytopenia rather than decreased platelets).

10.4 Pregnancy

All pregnancies or suspected pregnancies occurring in either a SCBP or partner of childbearing potential of a subject are immediately reportable events.

The exposure of any pregnant individual (eg, caregiver, pharmacist, study coordinator, or monitor) to IP is also an immediately reportable event.

10.4.1 Subjects of Childbearing Potential

Pregnancies and suspected pregnancies (including elevated βhCG or positive pregnancy test in a SCBP regardless of disease state) occurring while the subject is on IP, or within [redacted] of the subject's last dose of CC-95251 or 6 months of the subject's last dose of azacitidine (or longer if required by local regulations), are considered immediately reportable events. Investigational product is to be discontinued immediately. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to the Sponsor's Drug Safety immediately by email, phone or facsimile, or other appropriate method, using the Pregnancy Initial Report Form, or approved equivalent form.

The SCBP may be referred to an obstetrician-gynecologist or another appropriate healthcare professional for further evaluation.

The Investigator will follow the SCBP until completion of the pregnancy and must notify the Sponsor's Drug Safety immediately about the outcome of the pregnancy (either normal or abnormal outcome) using the Pregnancy Follow-up Report Form, or approved equivalent form.

If the outcome of the pregnancy was abnormal (eg, spontaneous abortion), the Investigator should report the abnormal outcome as an AE. If the abnormal outcome meets any of the serious criteria, it must be reported as an SAE to the Sponsor's Drug Safety within 24 hours of the Investigator's knowledge of the event.

All neonatal deaths that occur within 28 days of birth should be reported, without regard to causality, as an SAE. In addition, any infant death after 28 days that the Investigator suspects is related to the in utero exposure to the IP should also be reported as an SAE to the Sponsor's Drug Safety within 24 hours of the Investigator's knowledge of the event.

10.4.2 Subjects Who Are Able to Impregnate Their Partner

If a partner of childbearing potential of a subject taking IP becomes pregnant, the subject taking IP should notify the Investigator, and the pregnant partner should be advised to call their healthcare provider immediately.

10.5 Reporting of Serious Adverse Events

Any AE that meets any serious criterion requires reporting as an SAE within 24 hours of the Investigator's knowledge of the event. This instruction pertains to initial SAE reports as well as any follow-up reports.

This requirement applies to all SAEs (regardless of relationship to IP) that occur during the study (from the time the subject signs informed consent until [redacted] after the last dose of IP) or any SAE made known to the Investigator at any time thereafter that are suspected of being related to IP. Serious adverse events occurring prior to treatment (after signing the ICF) are to be recorded within the CRF, but do not require reporting to the Sponsor's Drug Safety.

Where required by local legislation, the Investigator is responsible for informing the Institutional Review Board/Ethics Committee (IRB/EC) of the SAE and providing them with all relevant initial and follow-up information about the event. The Investigator must keep copies of all SAE information on file including correspondence with the Sponsor and the IRB/EC.

The SAE is recorded within the CRF, and the data is transmitted electronically to the Sponsor's Drug Safety. In the event electronic transmission is not available, a paper SAE Report Form will be completed and sent directly to the Sponsor's Drug Safety, ensuring the event is recorded on the CRF as well.

10.6 Expedited Reporting of Adverse Events

For the purpose of regulatory reporting, the Sponsor's Drug Safety will determine the expectedness of events suspected of being related to CC-95251 based on the Investigator Brochure and azacitidine based on SmPC.

In the United States, expedited reports sent to the FDA by the sponsor based on the reasonable possibility threshold are known as 'IND safety reports' and will be reported in accordance with 21 CFR 312.32.

For reporting to the FDA, events that are not suspected to be causally related to CC-95251 and azacitidine by the sponsor will not be considered adverse reactions.

For countries within the European Economic Area (EEA), the Sponsor or its authorized representative will report in an expedited manner to Regulatory Authorities and Ethics Committees concerned, suspected unexpected serious adverse reactions (SUSARs) in accordance with Directive 2001/20/EC and the Detailed Guidance on collection, verification and presentation of adverse reaction reports arising from clinical trials on investigational products for human use (ENTR/CT3) and also in accordance with country-specific requirements.

The Sponsor or its authorized representative shall notify the Investigator of the following information:

- Any AE suspected of being related to the use of IP in this study or in other studies that is both serious and unexpected (ie, SUSAR);
- Any finding from tests in laboratory animals that suggests a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity.

Where required by local legislation, the Investigator shall notify his/her IRB/EC promptly of these new serious and unexpected AE(s) or significant risks to subjects.

The Investigator must keep copies of all pertinent safety information on file including correspondence with the IRB/EC. (See Section 13.3 for record retention information).

The Sponsor's Drug Safety Contact Information:

For the Sponsor's Drug Safety contact information, please refer to the Serious Adverse Event Report Form Completion Guidelines or to the Pregnancy Report Form Completion Guidelines.

11 DISCONTINUATIONS

11.1 Treatment Discontinuation

The following events are considered sufficient reasons for discontinuing a subject from the investigational product(s):

- Adverse Event
- Withdrawal by subject
- Completed
- Progressive disease
- Treatment failure
- Pregnancy
- Death
- Lost to follow-up
- Physician decision
- Other (to be specified on the CRF)

The reason for discontinuation of treatment should be recorded in the CRF and in the source documents.

The decision to discontinue a subject from treatment remains the responsibility of the treating physician, which will not be delayed or refused by the Sponsor. However, prior to discontinuing a subject, the Investigator may contact the Sponsor's Medical Monitor and forward appropriate supporting documents for review and discussion.

11.2 Study Discontinuation

The following events are considered sufficient reasons for discontinuing a subject from the study:

- Screen failure
- Withdrawal by subject
- Completed
- Death
- Lost to follow-up

- Other (to be specified on the CRF)

The reason for study discontinuation should be recorded in the CRF and in the source documents.

11.3 Emergency Contact

In emergency situations, the Investigator should contact the responsible Clinical Research Physician/Medical Monitor or designee by telephone at the number(s) listed on the Emergency Contact Information page of the protocol (after title page).

In the unlikely event that the Clinical Research Physician/Medical Monitor or designee cannot be reached, please contact the global Emergency Call Center by telephone at the number listed on the Emergency Contact Information page of the protocol (after title page). This global Emergency Call Center is available 24 hours a day and 7 days a week. The representatives are responsible for obtaining your call-back information and contacting the on-call Sponsor/contract research organization Medical Monitor, who will then contact you promptly.

Note: The back-up 24-hour global emergency contact call center should only be used if you are not able to reach the Sponsor's Research Physician(s) or Medical Monitor or designee for emergency calls.

11.4 Emergency Identification of Investigational Products

This is an open-label study; therefore, IP will be identified on the package labeling.

12 REGULATORY CONSIDERATIONS

12.1 Good Clinical Practice

The procedures set out in this study protocol pertaining to the conduct, evaluation, and documentation of this study are designed to ensure that the Sponsor, its authorized representative, and Investigator abide by Good Clinical Practice (GCP), as described in International Conference on Harmonisation (ICH) Guideline E6 and in accordance with the general ethical principles outlined in the Declaration of Helsinki. The study will receive approval from an IRB/EC prior to commencement. The Investigator will conduct all aspects of this study in accordance with applicable national, state, and local laws of the pertinent regulatory authorities.

12.2 Investigator Responsibilities

Investigator responsibilities are set out in the ICH Guideline for Good Clinical Practice and in the local regulations. The Sponsor's staff or an authorized representative will evaluate and approve all Investigators who in turn will select their staff.

The Investigator should ensure that all persons assisting with the study are adequately informed about the protocol, amendments, study treatments, as well as study-related duties and functions, including obligations of confidentiality of the Sponsor's information. The Investigator should maintain a list of Sub-investigators and other appropriately qualified persons to whom he or she has delegated significant study-related duties.

The Investigator is responsible for keeping a record of all subjects who sign an ICF and are screened for entry into the study. Subjects who fail screening must have the reason(s) recorded in the subject's source documents.

The Investigator, or a designated member of the Investigator's staff, must be available during monitoring visits to review data, resolve queries and allow direct access to subject records (eg, medical records, office charts, hospital charts, and study-related charts) for source data verification. The Investigator must ensure timely and accurate completion of CRFs and queries.

The information contained in the protocol and amendments (with the exception of the information provided by the Sponsor on public registry websites) is considered the Sponsor's confidential information. Only information that is previously disclosed by the Sponsor on a public registry website may be freely disclosed by the Investigator or its institution, or as outlined in the Clinical Trial Agreement. The Sponsor's protocol, amendment and IB information is not to be made publicly available (for example on the Investigator's or their institution's website) without express written approval from the Sponsor. Information proposed for posting on the Investigator's or their institution's website must be submitted to the Sponsor for review and approval, providing at least 5 business days for review.

At the time results of this study are made available to the public, the Sponsor will provide Investigators with a summary of the results that is written for the lay person. The Investigator is responsible for sharing these results with the subject and/or their caregiver as agreed by the subject.

12.3 Subject Information and Informed Consent

The Investigator must obtain informed consent of a subject and/or a subject's legal representative prior to any study related procedures.

Documentation that informed consent occurred prior to the study subject's entry into the study and of the informed consent process should be recorded in the study subject's source documents including the date. The original ICF signed and dated by the study subject and by the person consenting the study subject prior to the study subject's entry into the study, must be maintained in the Investigator's study files and a copy given to the study subject. In addition, if a protocol is amended and it impacts on the content of the informed consent, the ICF must be revised. Study subjects participating in the study when the amended protocol is implemented must be re-consented with the revised version of the ICF. The revised ICF signed and dated by the study subject and by the person consenting the study subject must be maintained in the Investigator's study files and a copy given to the study subject.

12.4 Confidentiality

The Sponsor affirms the subject's right to protection against invasion of privacy and to be in compliance with ICH and other local regulations (whichever is most stringent). The Sponsor requires the Investigator to permit the Sponsor's representatives and, when necessary, representatives from regulatory authorities, to review and/or copy any medical records relevant to the study in accordance with local laws.

Should direct access to medical records require a waiver or authorization separate from the subject's signed ICF, it is the responsibility of the Investigator to obtain such permission in writing from the appropriate individual.

12.5 Protocol Amendments

Any amendment to this protocol must be approved by the Sponsor's Clinical Research Physician/Medical Monitor. Amendments will be submitted to the IRB/EC for written approval. Written approval must be obtained before implementation of the amended version occurs. The written signed approval from the IRB/EC should specifically reference the Investigator name, protocol number, study title and amendment number(s) that is applicable. Amendments that are administrative in nature do not require IRB/IEC approval but will be submitted to the IRB/IEC for information purposes.

12.6 Institutional Review Board/Independent Ethics Committee Review and Approval

Before the start of the study, the study protocol, ICF, and any other appropriate documents will be submitted to the IRB/EC with a cover letter or a form listing the documents submitted, their dates of issue, and the site (or region or area of jurisdiction, as applicable) for which approval is sought. If applicable, the documents will also be submitted to the authorities in accordance with local legal requirements.

IP can only be supplied to an Investigator by the Sponsor or its authorized representative after documentation on all ethical and legal requirements for starting the study has been received by the Sponsor or its authorized representative. This documentation must also include a list of the members of the IRB/EC and their occupation and qualifications. If the IRB/EC will not disclose the names, occupations and qualifications of the committee members, it should be asked to issue a statement confirming that the composition of the committee is in accordance with GCP. For example, the IRB General Assurance Number may be accepted as a substitute for this list. Formal approval by the IRB/EC should mention the protocol title, number, amendment number (if applicable), study site (or region or area of jurisdiction, as applicable), and any other documents reviewed. It must mention the date on which the decision was made and must be officially signed by a committee member. Before the first subject is enrolled in the study, all ethical and legal requirements must be met.

The IRB/EC and, if applicable, the authorities, must be informed of all subsequent protocol amendments in accordance with local legal requirements. Amendments must be evaluated to determine whether formal approval must be sought and whether the ICF should also be revised.

The Investigator must keep a record of all communication with the IRB/EC and, if applicable, between a Coordinating Investigator and the IRB/EC. This statement also applies to any communication between the Investigator (or Coordinating Investigator, if applicable) and regulatory authorities.

Any advertisements used to recruit subjects for the study must be reviewed by the Sponsor and the IRB/EC prior to use.

12.7 Ongoing Information for Institutional Review Board/ Ethics Committee

If required by legislation or the IRB/EC, the Investigator must submit to the IRB/EC:

- Information on serious or unexpected adverse events as soon as possible;
- Periodic reports on the progress of the study;
- Deviations from the protocol or anything that may involve added risk to subjects.

12.8 Termination of the Study

The Sponsor reserves the right to terminate this study prematurely at any time for reasonable medical or administrative reasons. Any premature discontinuation will be appropriately documented according to local requirements (eg, IRB/EC, regulatory authorities, etc).

In addition, the Investigator or the Sponsor has the right to discontinue a single site at any time during the study for medical or administrative reasons such as:

[redacted]

13 DATA HANDLING AND RECORDKEEPING

13.1 Data/Documents

The Investigator must ensure that the records and documents pertaining to the conduct of the study and the distribution of the investigational product are complete, accurate, filed and retained. Examples of source documents include hospital records; clinic and office charts; laboratory notes; memoranda; subject's diaries or evaluation checklists; dispensing records; recorded data from automated instruments; copies or transcriptions certified after verification as being accurate copies; microfiche; x-ray film and reports; and records kept at the pharmacy, and the laboratories, as well as copies of CRFs or CD-ROM.

13.2 Data Management

Data will be collected via CRF and entered into the clinical database per the Sponsor's SOPs. This data will be electronically verified through use of programmed edit checks specified by the clinical team. Discrepancies in the data will be brought to the attention of the clinical team, and investigational site personnel, if necessary. Resolutions to these issues will be reflected in the database. An audit trail within the system will track all changes made to the data.

13.3 Record Retention

Essential documents must be retained by the Investigator according to the period of time outlined in the clinical trial agreement. The Investigator must retain these documents for the time period

described above or according to local laws or requirements, whichever is longer. Essential documents include, but are not limited to, the following:

- Signed ICFs for all subjects;
- Subject identification code list, screening log (if applicable), and enrollment log;
- Record of all communications between the Investigator and the IRB/EC;
- Composition of the IRB/EC;
- Record of all communications between the Investigator, the Sponsor, and their authorized representative(s);
- List of Sub-investigators and other appropriately qualified persons to whom the Investigator has delegated significant study-related duties, together with their roles in the study, curriculum vitae, and their signatures;
- Copies of CRFs (if paper) and of documentation of corrections for all subjects;
- IP accountability records;
- Record of any body fluids or tissue samples retained;
- All other source documents (subject records, hospital records, laboratory records, etc.);
- All other documents as listed in Section 8 of the ICH consolidated guideline on GCP (Essential Documents for the Conduct of a Clinical Trial).

The Investigator must notify the Sponsor if he/she wishes to assign the essential documents to someone else, remove them to another location or is unable to retain them for a specified period. The Investigator must obtain approval in writing from the Sponsor prior to destruction of any records. If the Investigator is unable to meet this obligation, the Investigator must ask the Sponsor for permission to make alternative arrangements. Details of these arrangements should be documented.

All study documents should be made available if required by relevant health authorities. Investigator or institution should take measures to prevent accidental or premature destruction of these documents.

14 QUALITY CONTROL AND QUALITY ASSURANCE

All aspects of the study will be carefully monitored by the Sponsor or its authorized representative for compliance with applicable government regulations with respect to current GCP and SOPs.

14.1 Study Monitoring and Source Data Verification

The Sponsor ensures that appropriate monitoring procedures are performed before, during and after the study. All aspects of the study are reviewed with the Investigator and the staff at a study initiation visit and/or at an Investigators' Meeting. Prior to enrolling subjects into the study, a Sponsor representative will review the protocol, CRFs, procedures for obtaining informed consent, record keeping, and reporting of AEs/SAEs with the Investigator.

Monitoring details describing strategy, including definition of study critical data items and processes (eg, risk-based initiatives in operations and quality such as risk management and

mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the monitoring plan.

Accuracy will be checked by performing source data verification that is a direct comparison of the entries made onto the CRFs against the appropriate source documentation. Any resulting discrepancies will be reviewed with the Investigator and/or his/her staff. Any necessary corrections will be made directly to the CRFs or via queries by the Investigator and/or his/her staff. Monitoring procedures require that informed consents, adherence to inclusion/exclusion criteria and documentation of SAEs and their proper recording be verified. Additional monitoring activities may be outlined in a study-specific monitoring plan.

14.2 Audits and Inspections

In addition to the routine monitoring procedures, a Good Clinical Practice Quality Assurance unit exists within the Sponsor. Representatives of this unit will conduct audits of clinical research activities in accordance with the Sponsor's standard operating procedures (SOPs) to evaluate compliance with Good Clinical Practice guidelines and regulations.

The Investigator is required to permit direct access to the facilities where the study took place, source documents, CRFs and applicable supporting records of study subject participation for audits and inspections by IRB/ECs, regulatory authorities (eg, FDA, EMA, Health Canada) and company authorized representatives. The Investigator should make every effort to be available for the audits and/or inspections. If the Investigator is contacted by any regulatory authority regarding an inspection, he/she should contact the Sponsor immediately.

14.3 Investigational Medicinal Product Quality Issues

Issues that call into question IP safety, purity, potency, quality and identity (eg, evidence of suspected tampering of product) must be reported as soon as possible to the study Clinical Trial Monitor and/or Clinical Trial Manager or designee. Report an issue or concern with all sponsor supplied IP suspected to have occurred before the product was transferred to the responsibility of the investigational site (eg, during manufacturing, packaging and labeling, storage, and/or distribution).

This includes suspected quality issues of components co-packaged with the drug, labelling, and IP device/drug combination products, and medical devices.

In the event of a suspected product quality issue, the immediate action to be taken by site is to quarantine the affected product. Do not dispose of the product unless retention presents a risk to personnel (eg, cytotoxic, risk of injury from broken glass or sharps).

When reporting, provide as much product information as possible. Suspected IP quality issues will be investigated and a response will be provided back to the investigational site.

15 PUBLICATIONS

As described in Section 12.2, all protocol- and amendment-related information, with the exception of the information provided by the Sponsor on public registry websites, is considered the Sponsor's

confidential information and is not to be used in any publications. The Sponsor's protocol-related information proposed for use in a publication must be submitted to the Sponsor for review and approval and should not be utilized in a publication without express written approval from the Sponsor, or as described in the Clinical Trial Agreement.

The Sponsor will ensure Sponsor-sponsored studies are considered for publication in the scientific literature in a peer-reviewed journal, irrespective of the results. At a minimum, this applies to results from all Phase 3 clinical studies, and any other study results of significant medical importance. This also includes results relating to investigational medicines whose development programs have been discontinued.

Study results may also be presented at one or more medical congresses and may be used for scientific exchange and teaching purposes. Additionally, this study and its results may be submitted for inclusion in all appropriate health authority study registries, as well as publication on health authority study registry websites, as required by local health authority regulations.

Eligibility for external authorship, as well as selection of first authorship, will be based on several considerations, including, but not limited to, contribution to protocol development, study recruitment, data quality, participation in data analysis, participation in study steering committee (when applicable) and contribution to abstract, presentation and/or publication development.

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APPENDIX A TABLE OF ABBREVIATIONS

Table 17: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
ADA	Anti-drug antibody
[redacted]	[redacted]
ADCP	Antibody-dependent cellular phagocytosis
ADL	Activity of daily life
AE	Adverse event
ALT	Alanine aminotransferase (SGPT)
AML	Acute myeloid leukemia
ANC	Absolute neutrophil count
Anri-CD20	Anti-cluster of differentiation 20
Anti-EGFR	Anti-epidermal growth factor receptor
APL	Acute promyelocytic leukemia
[redacted]	[redacted]
AST	Aspartate aminotransferase (SGOT)
AUC	Area under the serum concentration time-curve
Aza	Azacitidine
β-hCG	β-subunit of human chorionic gonadotropin
BCL-2	B-cell lymphoma-2
BE	Biomarker evaluable
BLRM	Bayesian logistic regression model
BM	Bone marrow
BMA	Bone marrow aspirate
BMB	Bone marrow biopsy
BSA	Body surface area
BUN	Blood urea nitrogen
C	Cycle
C1q	Complement component 1q
CBC	Complete blood count
CCR	Conventional care regimen
cCRR	Combined rate of CRs
CD4	Cluster of differentiation 4
CD47	Cluster of differentiation 47

Table 17: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
CD8	Cluster of differentiation 8
[redacted]	[redacted]
CI	Confidence interval
CLT	Total body clearance
C_{max}	Maximum plasma concentration of drug
C_{min}	Minimum serum concentration
CMMoL	Chronic myelomonocytic leukemia
CNS	Central nervous system
CO2	Carbon dioxide
COVID-19	Coronavirus disease 2019
CR	Complete remission
CRA	Cytokine release assay
CRh	Morphologic complete remission with partial hematologic recovery
CRi	Morphologic complete remission with incomplete blood recovery
CR_{MRD-}	Morphologic complete remission without minimal residual disease
CRO	Contract research organization
CRF	Case report form
[redacted]	[redacted]
CRR	Complete remission rate
CRS	Cytokine release syndrome
CS	Clinical scientist
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
D	Day
DCR	Disease control rate
DIC	Disseminated intravascular coagulation
DL	Dose level
DLT	Dose-limiting toxicity
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic acid
DOR	Duration of response
EC	Ethics Committee

Table 17: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
ECG	Electrocardiogram
ECL	Electrochemiluminescence
[redacted]	[redacted]
ECOG	Eastern Cooperative Oncology Group
ECOG PS	Eastern Cooperative Oncology Group Performance Status
eCRF	Electronic case report form
EE	Efficacy evaluable
EEA	European Economic Area
[redacted]	[redacted]
ELN	European Leukemia Net
EMD	Extramedullary disease
EOI	End of infusion
EOT	End of treatment
[redacted]	[redacted]
FAB	French-American-British
[redacted]	[redacted]
FDA	Food and Drug Administration
FIH	First-in-human
FLT3-ITD	fms-like tyrosine kinase 3 internal tandem duplication
[redacted]	[redacted]
GCP	Good Clinical Practice
[redacted]	[redacted]
GI	Gastrointestinal
[redacted]	[redacted]
[redacted]	[redacted]
Hgb	Hemoglobin
HI	Hematologic improvement
[redacted]	[redacted]

Table 17: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
HMA	Hypomethylating agent
HR	Hazard ratio
HR-MDS	Higher-risk myelodysplastic syndromes
[redacted]	[redacted]
IB	Investigator's Brochure
IC	Intensive Chemotherapy
ICF	Informed consent form
ICH	International Council on Harmonisation
IDH	Isocitrate dehydrogenase
IFNγ	Interferon γ
IE	Ineligible
Ig	Immunoglobulin
IgG(1)	Immunoglobulin G(1)
[redacted]	[redacted]
IHC	Immunohistochemistry
IL	Interleukin
IND	Investigational New Drug
[redacted]	[redacted]
int-2	Intermediate-2
IP	Investigational product
IPSS	International Prognostic Scoring System score
IPSS-R	Revised International Prognostic Scoring System score
IRB	Institutional Review Board
[redacted]	[redacted]
IRT	Integrated Response Technology
IV	Intravenous
IWG	International Working Group
LDAC	low-dose cytarabine
LDH	Lactate dehydrogenase
[redacted]	[redacted]
LVEF	Left ventricular ejection fraction
MAS	Macrophage Activation Syndrome

Table 17: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
MDS	Myelodysplastic syndromes
MedDRA	Medical Dictionary for Regulatory Activities
MLFS	Morphologic leukemia-free state
MM	Medical monitor
mOS	Median overall survival
MRD	Minimal residual disease
MRI	Magnetic resonance imaging
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
NA	Not applicable
NCI	National Cancer Institute
ND	Newly diagnosed
NGS	Next generation sequencing
NHL	Non-Hodgkins Lymphoma
NOAEL	No observed adverse effect level
NOS	Not otherwise specified
ORR	Overall response rate
OS	Overall survival
P-gp	P-glycoprotein
PB	Peripheral blood
PBMC	Peripheral blood mononuclear cell
PBS	Peripheral blood smear
PFS	Progression-free survival
PD	Pharmacodynamics
PDX	Subject-derived xenograft
PFS	Progression free survival
PK	Pharmacokinetics
PO	Orally
[redacted]	[redacted]
PR	Partial remission

Table 17: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
[redacted]	[redacted]
[redacted]	[redacted]
Q	Every
[redacted]	[redacted]
QD	Once daily
[redacted]	[redacted]
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 count
RECIST	Response Evaluation Criteria in Solid Tumors
RO	Receptor occupancy
RP2D	Recommended Phase 2 dose
RSV	Respiratory syncytial virus
R/R	Relapsed or refractory
RT-PCR	Reverse transcription-polymerase chain reaction
SAE	Serious adverse event
SAP	Statistical analysis plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SC	Subcutaneous
SCBP	Subject of childbearing potential
SCCHN	Squamous cell carcinoma of the head and neck
SCT	Stem cell transplantation
SD	Stable disease/standard deviation (based on context)
SEER	Surveillance, Epidemiology, and End Results
SIRPα	Signal regulatory protein alpha
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SIRPα	Signal regulatory protein alpha
SmPC	Summary of Product Characteristics
SOP	Standard operating procedure

Table 17: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
SRC	Safety Review Committee
SUSAR	Suspected unexpected serious adverse reaction
TAM	Transient abnormal myelopoiesis
TEAE	Treatment-emergent adverse events
TLS	Tumor lysis syndrome
t_{max}	Time to peak (maximum) serum concentration
TMDD	Target mediated drug disposition
TN	Treatment-naïve
[redacted]	[redacted]
ULN	Upper limit of normal
[redacted]	[redacted]
US	United States
USP	United States Pharmacopeia
USPI	United States Prescribing Information
VAS	Visual analog scale
WBC	White blood cell count
WHO	World Health Organization

APPENDIX B THE WORLD HEALTH ORGANIZATION (WHO) CLASSIFICATION OF ACUTE MYELOID LEUKEMIA (AML)

Table 18: WHO classification of AML

AML with recurrent genetic abnormalities
AML with t(8;21)(q22;q22.1);RUNX1-RUNX1T1
AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22);CBFB-MYH11
APL with PML-RARA
AML with t(9;11)(p21.3;q23.3);MLLT3-KMT2A
AML with t(6;9)(p23;q34.1);DEK-NUP214
AML with inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); GATA2, MECOM
AML (megakaryoblastic) with t(1;22)(p13.3;q13.3);RBM15-MKL1
Provisional entity: AML with BCR-ABL1
AML with mutated NPM1
AML with biallelic mutations of CEBPA
Provisional entity: AML with mutated RUNX1
AML with myelodysplasia-related changes
Therapy-related myeloid neoplasms
AML, NOS
AML with minimal differentiation
AML without maturation
AML with maturation
Acute myelomonocytic leukemia
Acute monoblastic/monocytic leukemia
Pure erythroid leukemia
Acute megakaryoblastic leukemia
Acute basophilic leukemia
Acute panmyelosis with myelofibrosis
Myeloid sarcoma
Myeloid proliferations related to Down Syndrome
Transient abnormal myelopoiesis (TAM)
Myeloid leukemia associated with Down Syndrome

Abbreviations: AML = acute myelogenous leukemia; NOS = not otherwise specified; TAM = transient abnormal myelopoiesis.

Source: Arber, 2016.

APPENDIX C RESPONSE CRITERIA FOR ACUTE MYELOID LEUKEMIA (AML)

The revised recommendations of the European Leukemia Net (ELN) for diagnosis, standardization of response criteria, treatment outcomes, and reporting standards for therapeutic trials in acute myeloid leukemia modified for this protocol.

Table 19: Hematologic/Molecular Response According to ELN Criteria for AML

Response Criterion	Time of Assessment	Absolute Neutrophils (µL)	Platelets (µL)	BM Blasts (%)	Other
Early Treatment assessment	7-10 days after therapy	NA	NA	< 5	
Morphologic Leukemia-free State (MLFS)	Varies by protocol	NA	NA	< 5	Flow cytometry EMD-
Morphologic CR	Varies by protocol	≥ 1,000	≥100,000	< 5	Transfusion EMD-
CR without minimal residual disease (CR_{MRD-})	Varies by protocol	≥ 1,000	≥100,000	< 5	Molecular/genetic marker - negative, EMD-
Morphologic CR with incomplete blood recovery (CRi)	Varies by protocol	Fulfill all criteria for CR except for residual neutropenia (< 1,000/µL) or thrombocytopenia (< 100,000/µL).			
Morphologic CR with partial hematologic recovery (CRh)	Per protocol	>500	>50,000	< 5	Absence of peripheral leukemic blasts, EMD-
Partial Remission (PR)	Varies by protocol	≥ 1,000	≥100,000	Decrease ≥ 50 resulting in 5 to 25	Blasts ≤ 5% if Auer rod positive
Hematologic Response (HR)	Varies by protocol	≥ 500	Improvement in hematologic parameters that do not meet criteria for PR, ie, transfusion independence*.		
Stable Disease	Varies by protocol	Absence of CR_{MRD-}, CR, CRi, CRh, PR, MLFS; and criteria for PD not met			
Hematologic relapse after CR_{MRD-}, CR, CRi, CRh	Varies by protocol	Reappearance of leukemic blasts in the peripheral blood or ≥ 5% blasts in the bone marrow not attributable to any other cause (eg, bone marrow regeneration after consolidation therapy) or EMD+.			
Molecular relapse after CR_{MRD-}	Varies by protocol	Reoccurrence of MRD as assessed by RT-qPCR or by MFC			

Abbreviations: AML = acute myeloid leukemia; BM = bone marrow; CR = complete remission; CRh = morphologic CR with partial hematologic recovery; CRi = morphologic CR with incomplete blood recovery; CR_{MRD-} = CR without minimal residual disease; ELN = European Leukemia Net; EMD = extramedullary disease; EMD- = extramedullary disease negative; EMD+ = extramedullary disease positive; HR = hematologic response; MFC = multiparameter flow cytometry; MLFS = morphologic leukemia-free state; MRD = minimal residual disease; NA = not applicable; PD = progressive disease; PR = partial remission; RT-qPCR = quantitative reverse transcription polymerase chain reaction.

* Transfusion independence for hematologic response is defined as the absence of any red blood cell or platelet transfusion during any consecutive [redacted] during the treatment period (Silverman, 2009). Packed red cell and platelet transfusion history for up to [redacted] before beginning study treatment will be collected.

Source: Bloomfield, 2018; Dohner, 2017.

APPENDIX D THE WORLD HEALTH ORGANIZATION (WHO) CLASSIFICATION OF THE MYELODYSPLASTIC SYNDROMES (MDS)

Table 20: WHO classifications for MDS

WHO myeloid neoplasm and acute leukemia classification	Dysplastic findings	Cytopenias[a]	PB and BM findings and cytogenetics
MDS with single lineage dysplasia (MDS-SLD)	1	1 or 2	BM < 5%, PB < 1%, no Auer Rods Any cytogenetics, unless fulfills all criteria for MDS with isolated del(5q)
MDS with multilineage dysplasia (MDS-MLD)	2 or 3	1-3	BM < 5%, PB < 1%, no Auer Rods Any cytogenetics, unless fulfills all criteria for MDS with isolated del(5q)
MDS with ring sideroblasts (MDS-RS)[b] MDS-RS and single lineage dysplasia (MDS-RS-SLD) MDS-RS and multilineage dysplasia (MDS-RS-MLD)	 1 2 or 3	 1 or 2 1-3	BM < 5%, PB < 1%, no Auer Rods Any cytogenetics, unless fulfills all criteria for MDS with isolated del(5q)
MDS with isolated del(5q)	1-3	1-2	BM < 5%, PB < 1%, no Auer Rods del(5q) alone or with 1 additional abnormality except -7 or del(7q)
MDS with excess blasts (MDS-EB)			
MDS-EB-1	0-3	1-3	BM 5-9% or PB 2-4%, no Auer Rods Any cytogenetics
MDS-EB-2	0-3	1-3	BM 10-19% or PB 5-19% or Auer Rods Any cytogenetics
MDS, unclassifiable (MDS-U)			
MDS-U with 1% blood blasts	1-3	1-3	BM < 5%, PB =1%[c], no Auer Rods Any cytogenetics
MDS-U with SLD and pancytopenia	1	3	BM < 5%, PB <1%, no Auer Rods Any cytogenetics
MDS-U based on defining cytogenetic abnormality	0	1-3	BM < 5%, PB <1%, no Auer Rods MDS-defining abnormality[d]

Abbreviations: BM = bone marrow; del = deletion; FISH = fluorescence in situ hybridization; MDS = myelodysplastic syndromes; MDS-EB = MDS with excess blasts; MDS-EB-1 = MDS with excess blasts-1; MDS-EB-2 = MDS with excess blasts-2; MDS-MLD = MDS with multilineage dysplasia; MDS-RS = MDS with ring sideroblasts; MDS-RS-MLD = MDS-RS and multilineage dysplasia; MDS-RS-SLD = MDS-RS and single lineage dysplasia; MDS-SLD = MDS with single lineage dysplasia; MDS-U = MDS, unclassifiable; PB = peripheral blood; WHO = World Health Organization.

[a] Cytopenias defined as : hemoglobin, <10 g/dL, platelet count, <100 x 10^9/L; and absolute neutrophil count, <1.8 x 10^9/L. Rarely, MDS may present with mild anemia or thrombocytopenia above these levels. Peripheral blood monocytes must be < 1 x 10^9/L.

[b] Cases with ≥ 15% ring sideroblasts by definition have significant erythroid dysplasia, and are classified as MDS-RS-SLD.

[c] One percent PB blasts must be recorded on at least 2 separate occasions.

[d] Abnormality must be demonstrated by conventional karyotyping, not by FISH or sequencing. The presence of +8, -Y, of del(20q) is not considered to be MDS-defining in the absence of diagnostic morphologic features of MDS. Sources: Arber, 2016 and Vardiman, 2009.

APPENDIX E RESPONSE CRITERIA FOR MYELODYSPLASTIC SYNDROMES (MDS)

The revised recommendations of the International Working Group (IWG) for diagnosis, standardization of response criteria, treatment outcomes, and reporting standards for therapeutic trials in myelodysplastic syndromes (MDS) modified for this protocol.

Table 21: Modified IWG Response Criteria for MDS

Category	Response criteria (responses must last at least 4 weeks)
Complete remission (CR)	Bone marrow: ≤ 5% myeloblasts with normal maturation of all cell lines[a] Persistent dysplasia will be noted[a,b] Peripheral blood[c] - Hemoglobin ≥ 11 g/dL - Platelets ≥ 100×10^9/L - Neutrophils ≥ 1.0×10^9/L[b] - Blasts 0%
Morphologic CR with partial hematologic recovery (CRh)	Bone marrow: ≤ 5% myeloblasts with normal maturation of all cell lines[a] Persistent dysplasia will be noted[a,b] Peripheral blood[c] - Hemoglobin ≥ 11 g/dL - Platelets > 50×10^9/L - Neutrophils > 0.5×10^9/L[b] - Blasts 0%
Partial remission (PR)	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[b] ± Hematologic Improvement (HI)	Bone marrow: ≤ 5% myeloblasts and decrease by ≥ 50% over pretreatment[b] Note: Blasts at baseline must be ≥ 5% in order for subject to be evaluable for Marrow CR[d] Peripheral blood: if HI responses, they will be noted in addition to marrow CR[b]
Stable disease (SD)	Failure to achieve at least PR, but no evidence of progression for > [redacted]
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 of 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 (PD)	For subjects with: • Less than 5% blasts: ≥ 50% increase in blasts to > 5% blasts • 5% - 10% blasts: ≥ 50% increase in blasts to > 10% blasts • 10% - 20% blasts: ≥ 50% increase in blasts to > 20% blasts Any of the following: • At least 50% decrement from maximum remission/response levels in granulocytes or platelets • Reduction in Hgb concentration by ≥ 2 g/dL • Transfusion dependence

Table 21: Modified IWG Response Criteria for MDS

Category	Response criteria (responses must last at least 4 weeks)
Disease transformation	Transformation to AML (20% or more BM or PB blasts)[d]
Hematologic Improvement (HI)	
Erythroid response (HI-E) (Pretreatment < 11 g/dL)	Hgb increase by ≥ 1.5 g/dL Relevant reduction of units of RBC transfusions by an absolute number of at least 4 RBC transfusions/[redacted] compared with the pretreatment transfusion number in the previous [redacted]. Only RBC transfusions given for a Hgb of ≤ 9.0 g/dL pretreatment will count in the RBC transfusion evaluation
Platelet response (HI-P) (Pretreatment < 100 × 10^9/L)	Absolute increase of ≥ 30 × 10^9/L for subjects starting with > 20 × 10^9/L Increase from < 20 × 10^9/L to > 20 × 10^9/L and by at least 100%
Neutrophil response (HI-N) (Pretreatment < 1.0 × 10^9/L)	At least 100% increase and an absolute increase of > 0.5 × 10^9/L
Progression/relapse after HI	At least one of the following: • At least 50% decrement from maximum response levels in granulocytes or platelets • Reduction in Hgb by ≥ 1.5 g/dL • Transfusion dependence

Abbreviations: AML = acute myeloid leukemia; BM = bone marrow; CR = complete remission; FAB = French-American-British; Hgb = hemoglobin; HI = hematologic improvement; HI-E = HI - erythroid response; HI-P = HI - platelet response; HI-N = HI - neutrophil response; IWG = International Working Group; MDS = myelodysplastic syndromes; PB = peripheral blood; PD = Disease Progression; PR = partial remission; RBC = red blood cell; SD = stable disease.

[a] Dysplastic changes should consider the normal range of dysplastic changes (modification).

[b] Modification to IWG response criteria.

[c] In some circumstances, protocol therapy may require the initiation of further treatment (eg, consolidation, maintenance) before the 4-week period. Such subjects can be included in the response category into which they fit at the time the therapy is started. Transient cytopenias during repeated chemotherapy courses should not be considered as interrupting durability of response, as long as they recover to the improved counts of the previous course.

[d] Sponsor modification of IWG criteria.

Sources: Bloomfield, 2018; Cheson, 2006; Vardiman, 2009.

APPENDIX F RISK STATUS BASED ON CYTOGENETICS FOR ACUTE MYELOID LEUKEMIA

Table 22: Risk Stratification by Genetics in Non-APL AML

Risk Category*	Genetic Abnormality
Favorable	t(8;21)(q22;q22.1); RUNX1-RUNX1T1 inv(16)(p13.1q22) or t(16;16)(p13.1;q22); CBFB-MYH11 Biallelic mutated CEBPA Mutated NPM1 without FLT3-ITD or with FLT3-ITD^{low}†
Intermediate	Mutated NPM1 and FLT3-ITD^{high}† Wild-type NPM1 without FLT3-ITD or with FLT3-ITD^{low}† (without adverse-risk genetic lesions) t(9;11)(p21.3;q23.3); MLLT3-KMT2A‡ Cytogenetic abnormalities not classified as favorable or adverse
Poor/Adverse	t(6;9)(p23;q34.1); DEK-NUP214 t(v;11q23.3); KMT2A rearranged t(9;22)(q34.1;q11.2); BCR-ABL1 inv(3)(q21.3q26.32) or t(3;3)(q21.3;q26.2); GATA2,MECOM(EVl1) -5 or del(5q); -7; -17/abn(17p) Complex karyotype§, monosomal karyotype‖ Wild-type NPM1 and FLT3-ITD^{high}† Mutated RUNX1¶ Mutated ASXL1¶ Mutated TP53#

Abbreviations: ABL1 = ABL proto-oncogene 1; abn = arm band number; ASXL1 = ASXL transcriptional regulator 1; BCR = breakpoint cluster region protein; CBFB = core-binding factor subunit β; CEBPA = CCAAT/enhancer binding protein α; DEK = DEK proto-oncogene; del = deletion; FLT3-ITD = FLT3 internal tandem duplication; GATA2 = GATA binding protein 2; KMT2A = lysine methyltransferase 2A; inv = inversion; MECOM(EVl1) = MDS1 and EVl1 complex locus protein (ecotropic virus integration site 1 protein homolog) ; MLLT3 = myeloid/lymphoid or mixed-lineage leukemia (trithorax homolog, Drosophila), translocated to, 3 ; MYH11 = myosin heavy chain 11; NPM1 = nucleophosmin 1; NUP214 = nucleoporin 214; p = short arm of a chromosome; q = long arm of a chromosome; RUNX1 = runt-related transcription factor 1; RUNX1T1 = RUNX1 partner transcriptional co-repressor 1; t = translocation; TP53 = tumor protein 53.

* Prognostic impact of a marker is treatment-dependent and may change with new therapies.

† Low, low allelic ratio (<0.5); high, high allelic ratio (≥0.5); semiquantitative assessment of FLT3-ITD allelic ratio (using DNA fragment analysis) is determined as ratio of the area under the curve "FLT3-ITD" divided by area under the curve "FLT3-wild type"; recent studies indicate that AML with NPM1 mutation and FLT3-ITD low allelic ratio may also have a more favorable prognosis and patients should not routinely be assigned to allogeneic HCT. FLT3 allelic ratio is not yet pervasively used, and IF not available, the presence of an FLT3 mutation should be considered high-risk unless it occurs concurrently with an NPM1 mutation, in which case it is intermediate risk. As data emerge, this measure will evolve.

‡ The presence of t(9;11)(p21.3;q23.3) takes precedence over rare, concurrent adverse-risk gene mutations.

§ Three or more unrelated chromosome abnormalities in the absence of 1 of the WHO-designated recurring translocations or inversions, that is, t(8;21), inv(16) or t(16;16), t(9;11), t(v;11)(v;q23.3), t(6;9), inv(3) or t(3;3); AML with BCR-ABL1.

‖ Defined by the presence of 1 single monosomy (excluding loss of X or Y) in association with at least 1 additional monosomy or structural chromosome abnormality (excluding core-binding factor AML).

¶ These markers should not be used as an adverse prognostic marker if they co-occur with favorable-risk AML subtypes.

TP53 mutations are significantly associated with AML with complex and monosomal karyotype.

Source: NCCN, 2021a.

APPENDIX G REVISED INTERNATIONAL PROGNOSTIC SCORING SYSTEM FOR MDS

Table 23: IPSS-R Cytogenetic Risk Groups

Cytogenetic Prognostic Subgroups	Cytogenetic Abnormalities
Very good	-Y, del(11q)
Good	Normal, del(5q), del(12p), del(20q), double including del(5q)
Intermediate	del(7q), +8, +19, i(17q), any other single or double independent clones
Poor	-7, inv(3)/t(3q)/del(3q), double including -7/del(7q), Complex: 3 abnormalities
Very poor	Complex: > 3 abnormalities

Abbreviations: del = deletion; inv = inversion; IPSS-R = Revised International Prognostic Scoring System score; p = short arm of a chromosome; q = long arm of a chromosome; t = translocation.
Source: Greenberg, 2012.

Table 24: IPSS-R Prognostic Score Values

Prognostic variable	0	0.5	1	1.5	2	3	4
Cytogenetics	Very Good	-	Good	-	Inter-mediate	Poor	Very Poor
Bone Marrow Blast (%)	≤ 2	-	> 2 - < 5	-	5 - 10	> 10	-
Hemoglobin (g/dL)	≥10	-	8 - < 10	<8	-	-	-
Platelets ($\times 10^9$/L)	≥100	50 - < 100	< 50	-	-	-	-
ANC ($\times 10^9$/L)	≥0.8	< 0.8	-	-	-	-	-

Abbreviations: ANC = absolute neutrophil count; IPSS-R = Revised International Prognostic Scoring System score.
Source: Greenberg, 2012.

The total IPSS-R score is calculated as the sum of the cytogenetics, bone marrow blast percentage, hemoglobin, platelets, and ANC individual scores.

Table 25: IPSS-R Prognostic Risk Categories/Scores

Risk Category	Risk Score
Very Low	≤ 1.5
Low	> 1.5 – 3
Intermediate	> 3 – 4.5
High	> 4.5 – 6
Very High	> 6

Abbreviations: IPSS-R = Revised International Prognostic Scoring System score.
Source: Greenberg, 2012.

Table 26: IPSS-R: Prognostic Risk Category Clinical Outcomes

Prognostic variable	No. pts	Very Low	Low	Intermediate	High	Very High
Subjects, %	7012	19%	38%	20%	13%	10%
Median Overall Survival (years)	-	8.8	5.3	3.0	1.6	0.8
Median time to 25% AML evolution	-	Not reached	10.8	3.2	1.4	0.73

Abbreviations: AML = acute myeloid leukemia; IPSS-R = Revised International Prognostic Scoring System score.
Source: Greenberg, 2012.

APPENDIX H PERFORMANCE STATUS CRITERIA

Table 27: Eastern Cooperative Oncology Group (ECOG) Performance Status (PS)

Score	Description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light housework, office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Abbreviations: ECOG = Eastern Cooperative Oncology Group; PS = performance status.
Source: Oken, 1982.

APPENDIX I TUMOR LYSIS SYNDROME PROPHYLAXIS RECOMMENDATIONS

Table 28: Tumor Lysis Syndrome (TLS) Prophylaxis Recommendations Based on TLS Risk

Low risk disease (LRD)	Intermediate risk disease (IRD)	High risk disease (HRD)
ST*	N/A	N/A
MM	N/A	N/A
CML	N/A	N/A
Indolent NHL	N/A	N/A
HL	N/A	N/A
CLL†	N/A	N/A
AML and WBC <25 × 10^9/l and LDH <2 × ULN	AML with WBC 25–100 × 10^9/l AML and WBC <25 × 10^9/l and LDH ≥2 × ULN	AML and WBC ≥100 × 10^9/l
Adult Intermediate grade NHL and LDH <2 × ULN	Adult intermediate grade NHL and LDH ≥2 × ULN	N/A
Adult ALCL	Childhood ALCL stage III/IV	N/A
N/A	Childhood intermediate grade NHL stage III/IV with LDH <2 × ULN	N/A
N/A	ALL and WBC <100 × 10^9/l and LDH <2 × ULN	ALL and WBC ≥100 × 10^9/l and/or LDH ≥2 × ULN
N/A	BL and LDH <2 × ULN	BL stage III/IV and/or LDH ≥2 × ULN
N/A	LL stage I/II and LDH <2 × ULN	LL stage III/IV and/or LDH ≥2 × ULN
N/A	N/A	IRD with renal dysfunction and/or renal involvement IRD with uric acid, potassium and/or phosphate >ULN
Prophylaxis recommendations		
Monitoring Hydration ±Allopurinol	Monitoring Hydration Allopurinol	Monitoring Hydration Rasburicase‡

ST, solid tumours; MM, multiple myeloma; CML, chronic myeloid leukaemia; NHL, non-Hodgkin lymphoma; HL, Hodgkin lymphoma; CLL, chronic lymphoid leukaemia; AML, acute myeloid leukaemia; WBC, white blood cell count; LDH, lactate dehydrogenase; ULN, upper limit of normal; ALCL, anaplastic large cell lymphoma; N/A, not applicable; ALL, acute lymphoblastic leukaemia; BL, Burkitt lymphoma/leukaemia; LL, lymphoblastic lymphoma.
*Rare solid tumours, such as neuroblastoma, germ cell tumours and small cell lung cancer or others with bulky or advanced stage disease, may be classified as IRD.
†CLL treated with fludarabine, rituximab and/or those with high WBC (≥50 × 10^9/l), should be classified as IRD.
‡Contraindicated in patients with a history consistent with glucose-6 phosphate dehydrogenase. In these patients, rasburicase should be substituted with allopurinol.

Abbreviations: ALCL = anaplastic large cell lymphoma; ALL = acute lymphoblastic leukemia; AML = acute myeloid leukemia; BL = Burkitt lymphoma/leukemia; CLL = chronic lymphoid leukemia; CML = chronic myeloid leukemia; HL = Hodgkin lymphoma; LDH = lactate dehydrogenase; LL = lymphoblastic lymphoma; MM = multiple myeloma; N/A = not applicable; NH: = non-Hodgkin lymphoma; ST = solid tumor; TLS = tumor lysis syndrome; ULN = upper limit of normal; WBC = white blood cell count.

Source: Cairo, 2004 and Cairo, 2010.

Table 29: Cairo-Bishop Definition of Laboratory Tumor Lysis Syndrome

Uric Acid	≥ 476 µmol/l (≥ 8.0 mg/dl) or 25% increase from baseline
Potassium	≥ 6.0 mmol/l (≥ 6.0 mEq/l) or 25% increase from baseline
Phosphorous	≥ 1.45 mmol/l (≥ 4.5 mg/dl) or 25% increase from baseline
Calcium	≤ 1.75 mmol/l (≤ 7.0 mg/dl) or 25% decrease from baseline

Notes: Laboratory tumor lysis syndrome (LTLS) is defined as either a 25% change or level above or below normal, as defined above, for any 2 or more serum values of uric acid, potassium, phosphate, and calcium within 3 days before or 7 days after the initiation of chemotherapy. This assessment assumes that a subject has or will receive adequate hydration (± alkalinization) and a hypouricemic agent(s).

Source: Cairo, 2004 and Cairo, 2010.

The Cairo-Bishop Definition of Clinical Tumor Lysis Syndrome

The Presence of Laboratory TLS and One or More of the Following Criteria:

- Creatinine: ≥ 1.5 upper limit of normal ([ULN] age > 12 years or age-adjusted)
- Cardiac arrhythmia / sudden death
- Seizure not directly attributable to a therapeutic agent

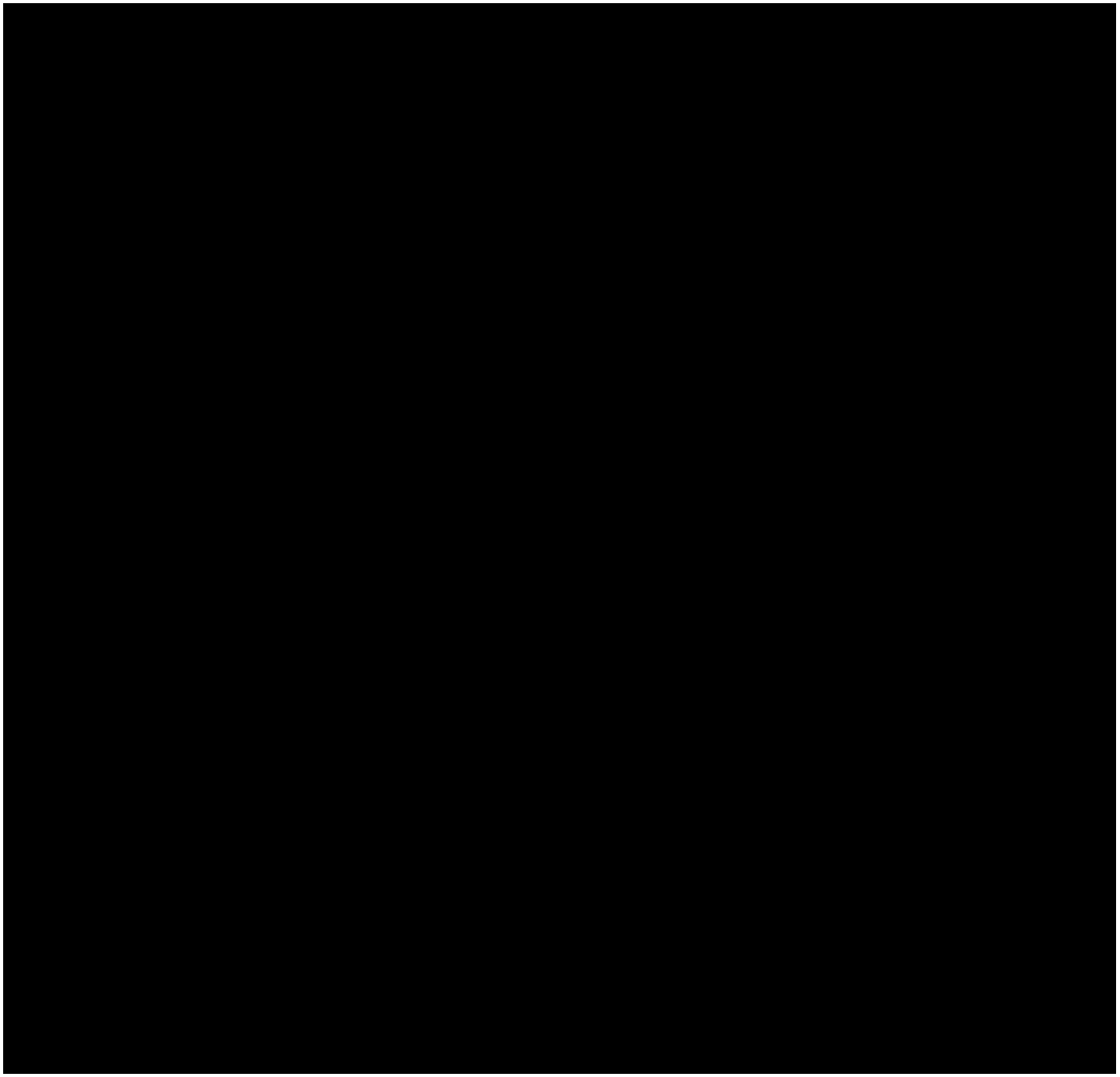
Table 30: Cairo-Bishop Grading System for Tumor Lysis Syndrome

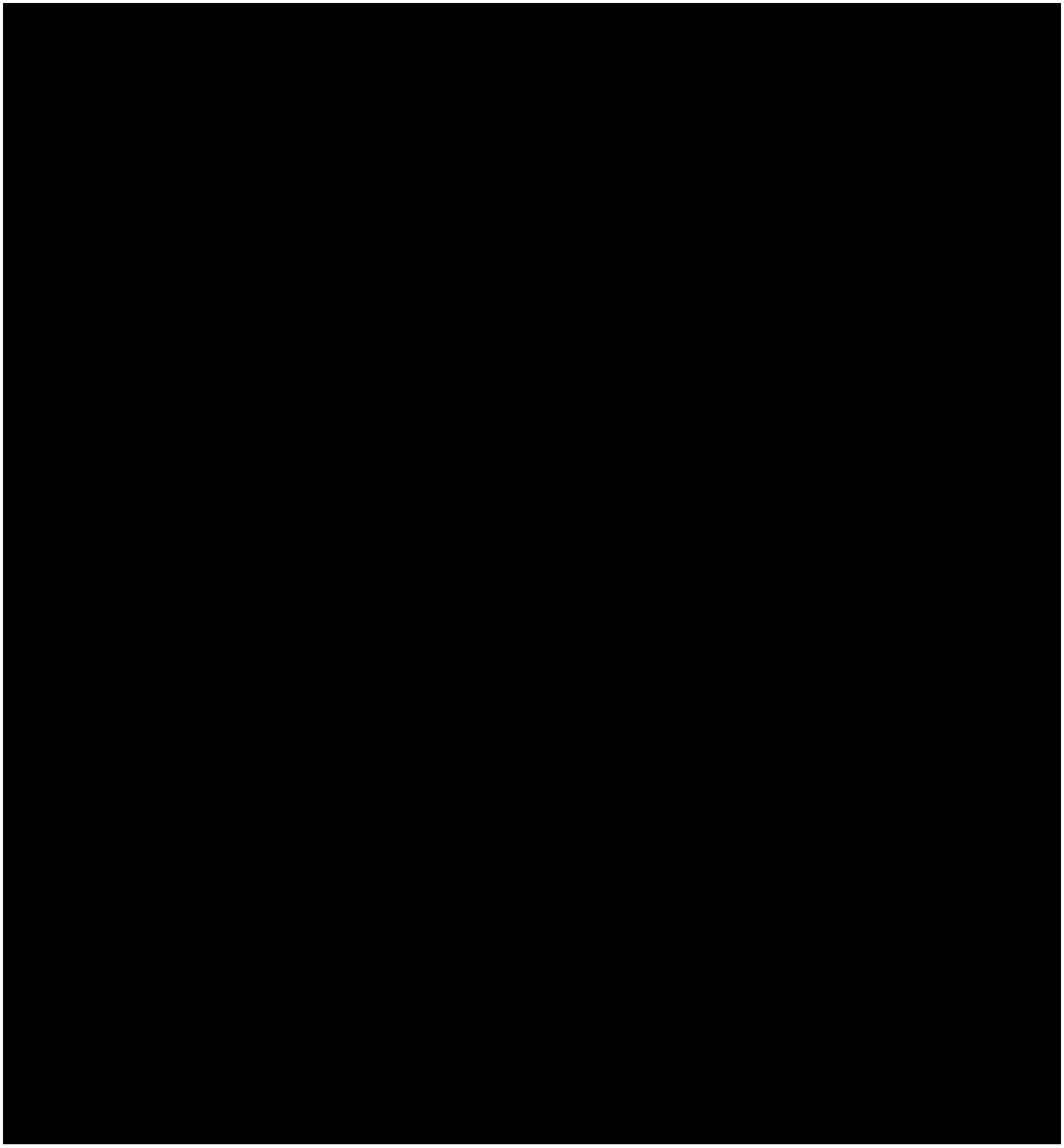
Grade	LTLS	Creatinine	Cardiac Arrhythmia	Seizure
0	-	≤ 1.5 x ULN	None	None
1	+	1.5 x ULN	Intervention not indicated	None
2	+	> 1.5 – 3.0 x ULN	Non-urgent medical intervention indicated	One brief generalized seizure; seizure(s) well controlled by anti-convulsants or infrequent focal motor seizures not interfering with ADL
3	+	> 3.0 – 6.0 x ULN	Symptomatic and incompletely controlled medically or controlled with device	Seizure in which consciousness is altered; poorly controlled seizure disorder; breakthrough generalized seizures despite medical intervention
4	+	> 6.0 x ULN	Life-Threatening	Seizures of any kind that are prolonged, repetitive, or difficult to control
5	+	Death[a]	Death	Death

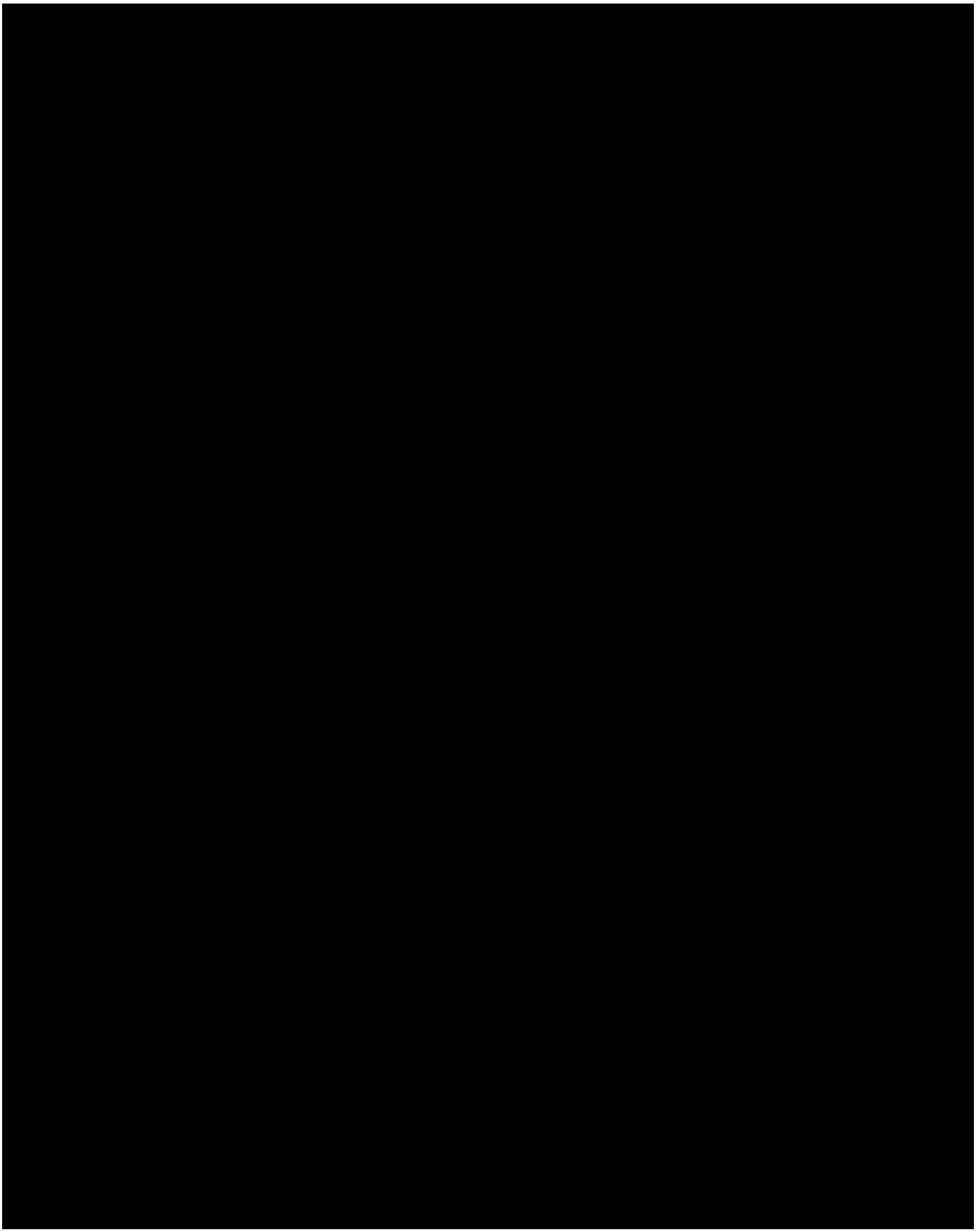
Abbreviations: ADL = Activities of Daily Living; LTLS = Laboratory Tumor Lysis Syndrome; ULN = Upper Limit of Normal.

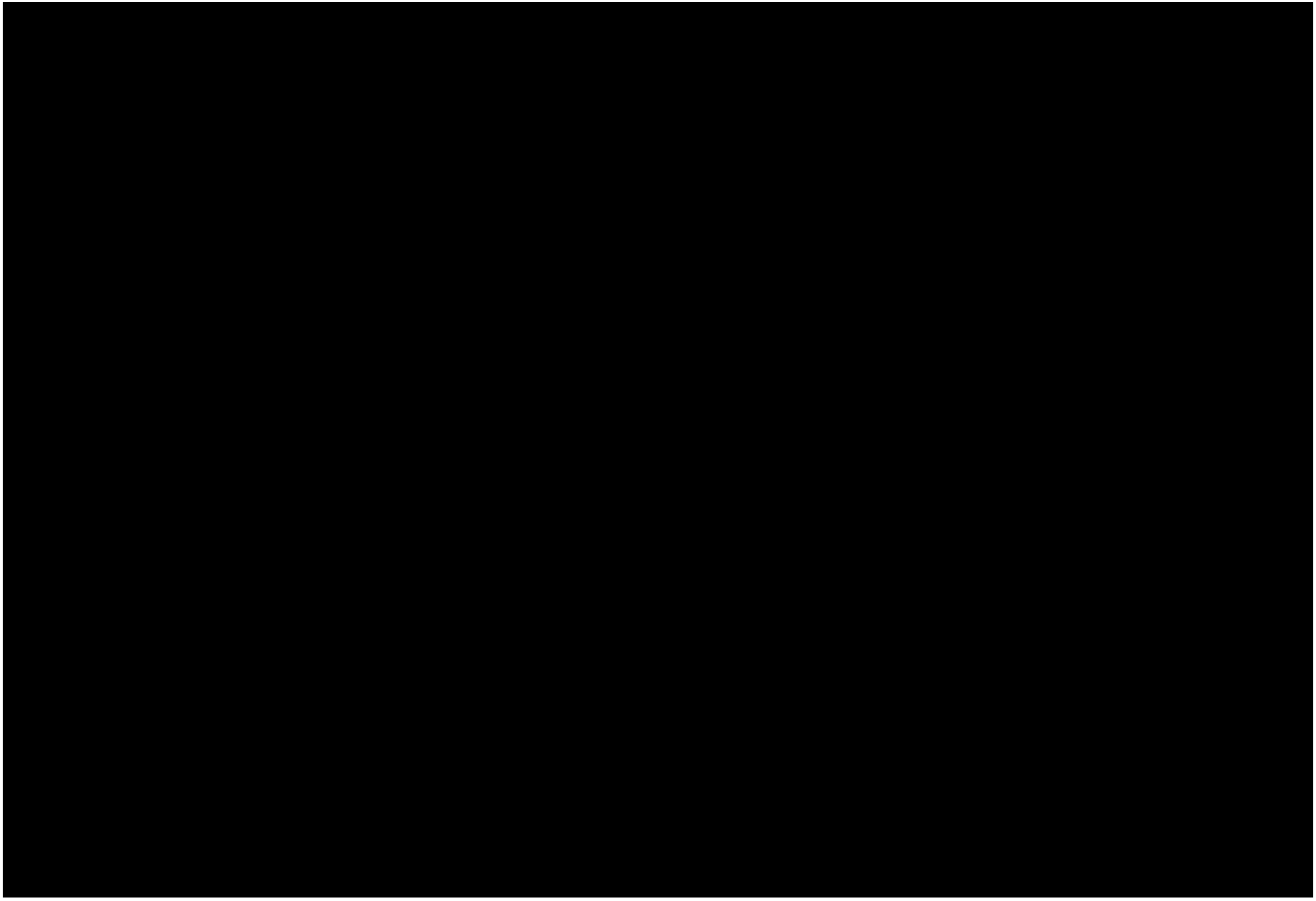
[a] Probably or definitely attributable to clinical TLS.

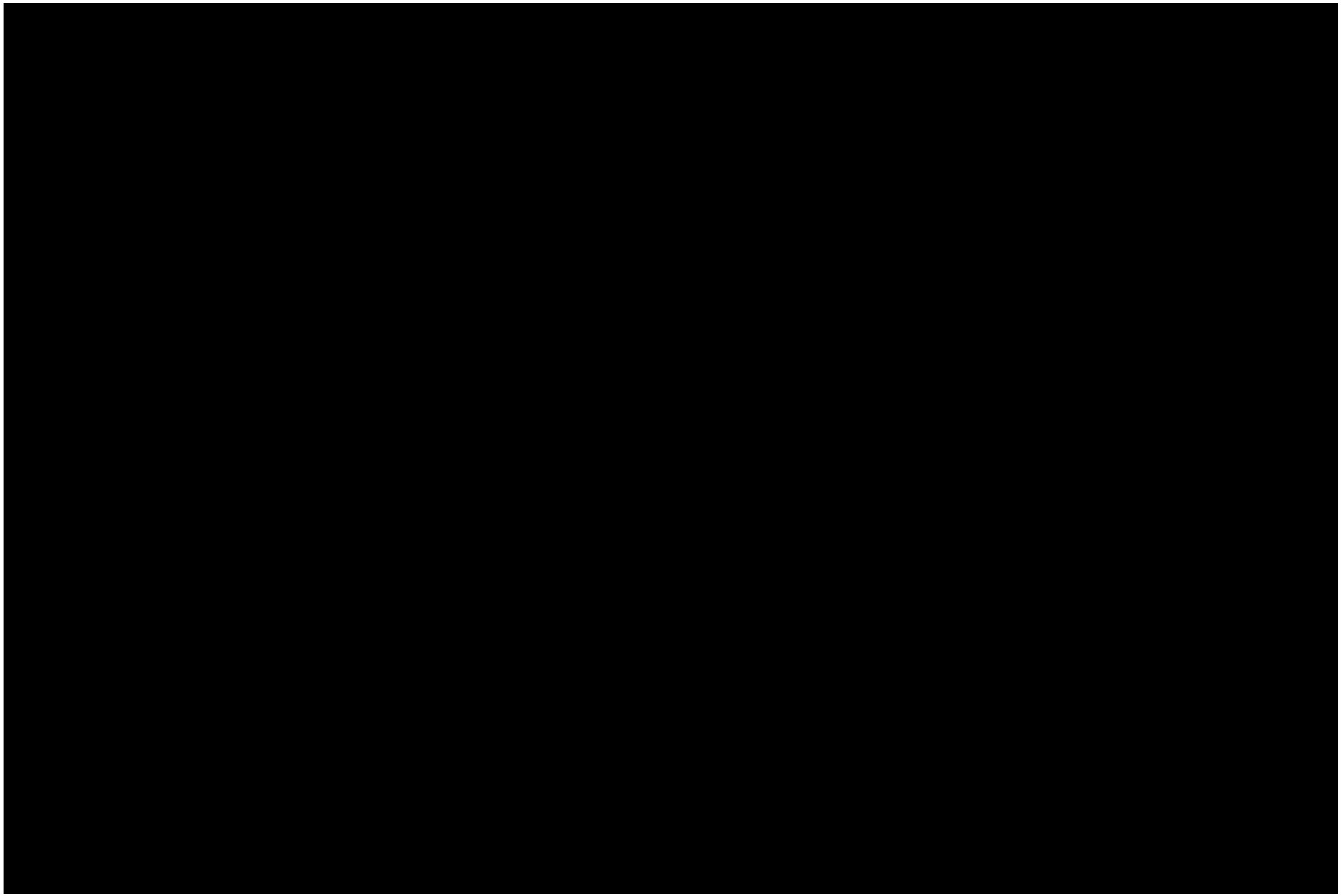
Source: Cairo, 2004.

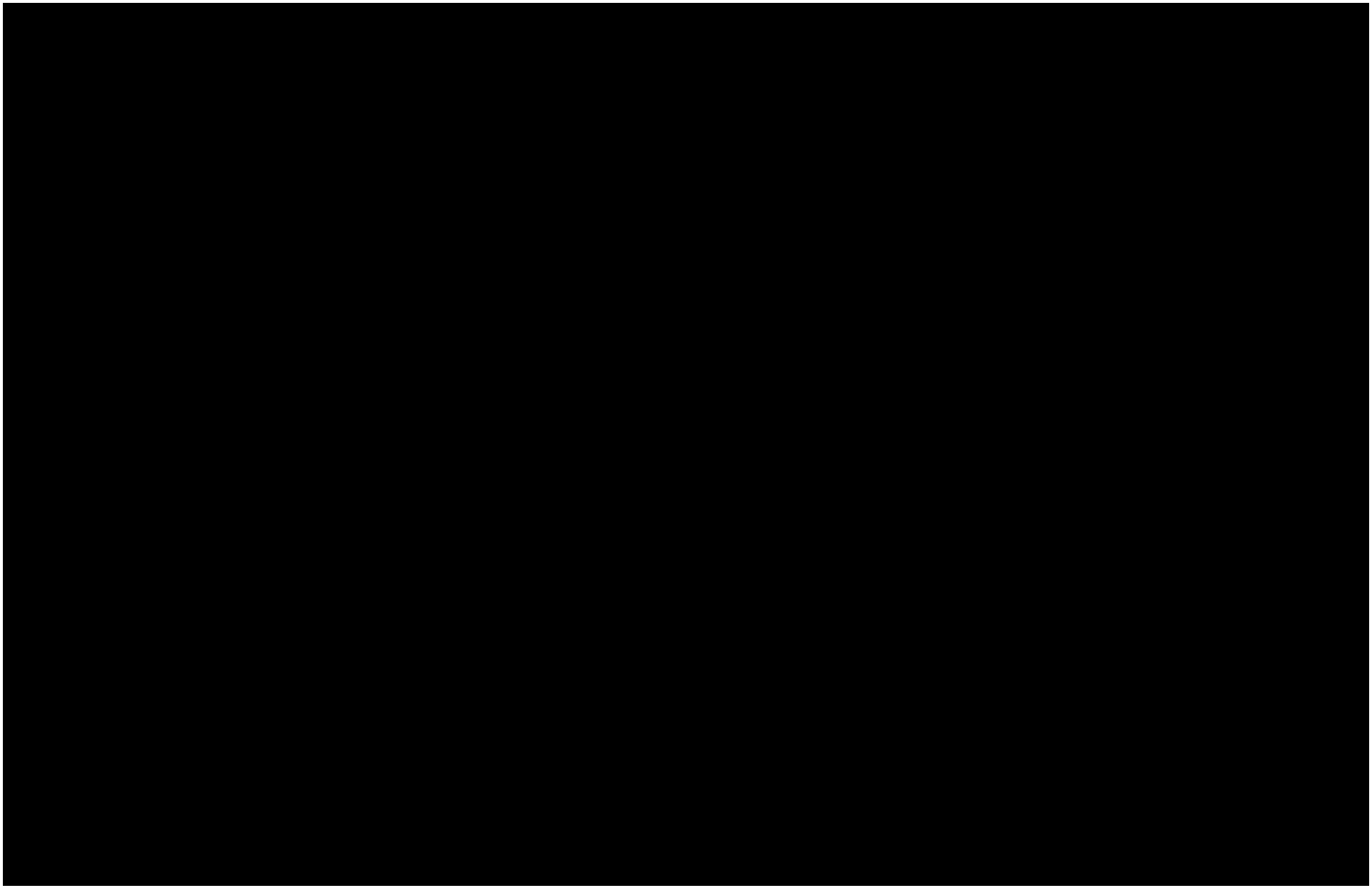


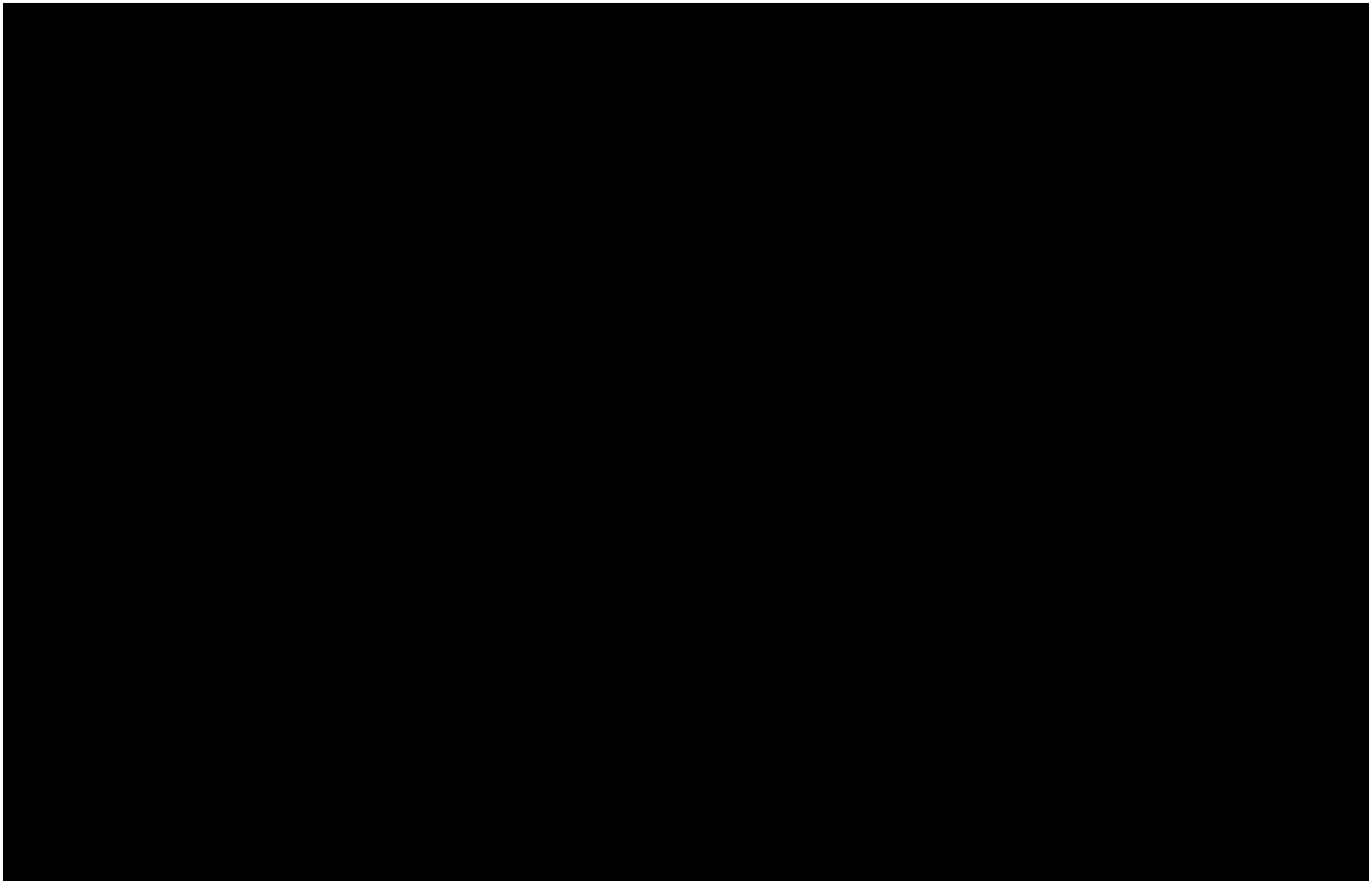


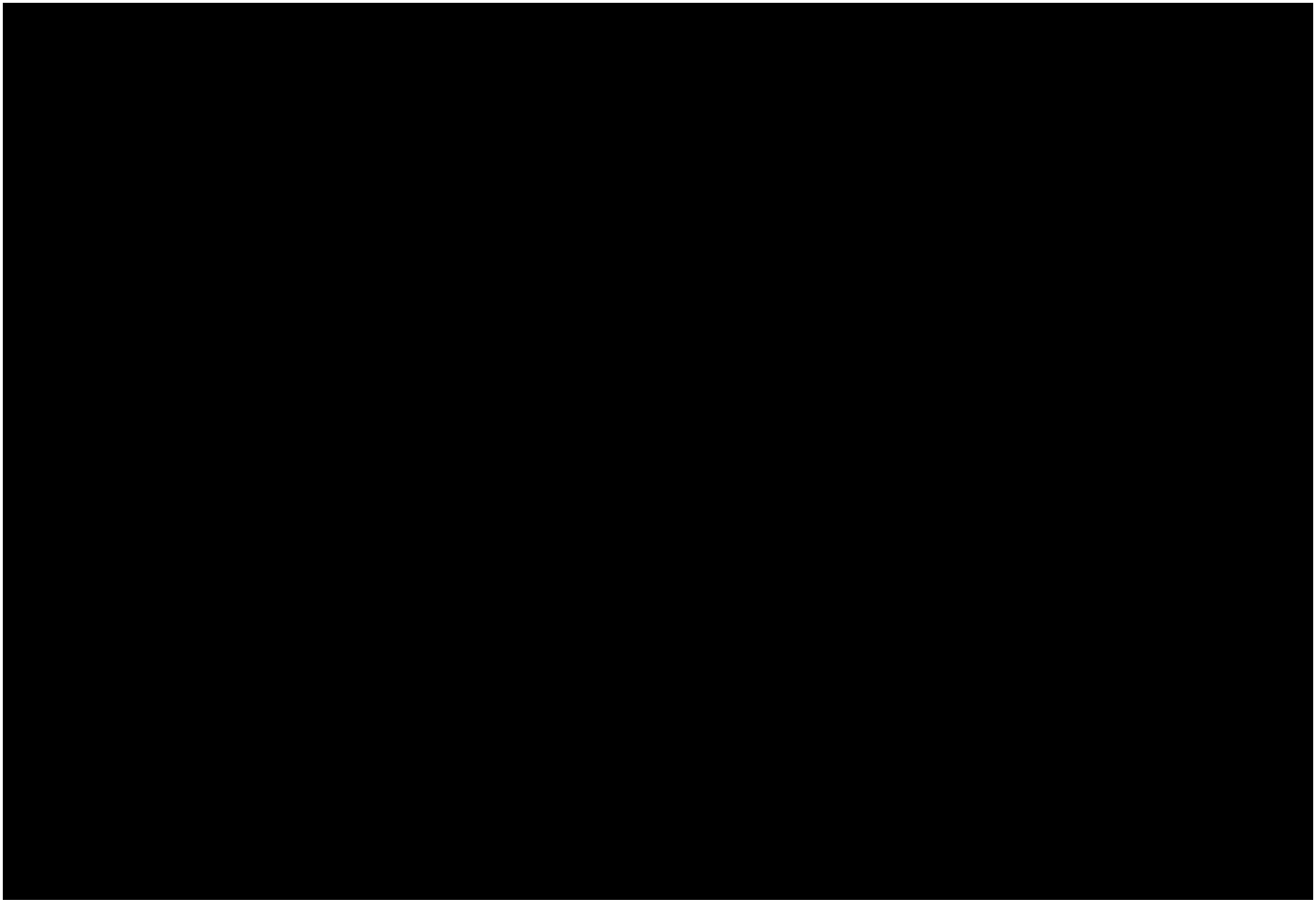


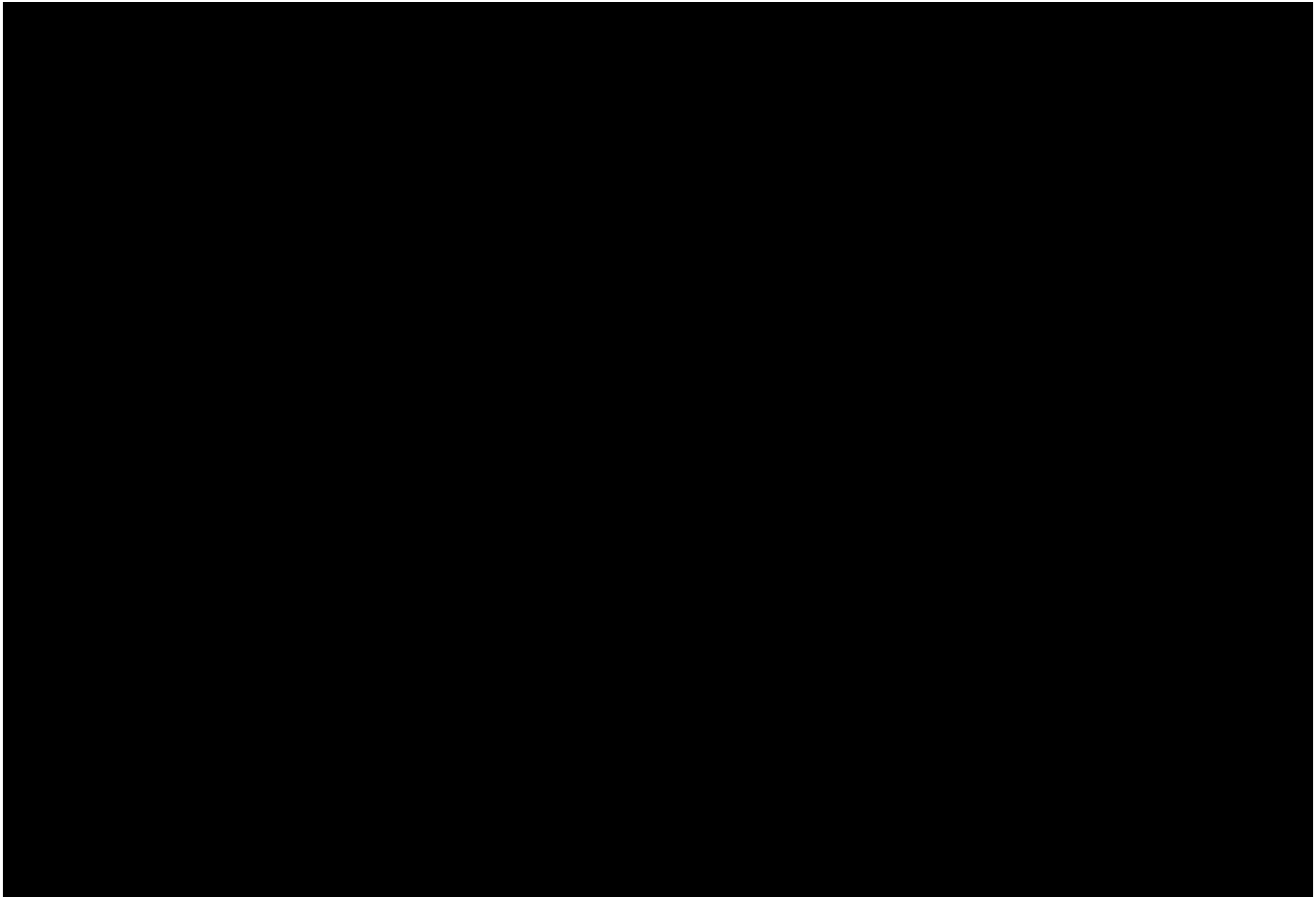


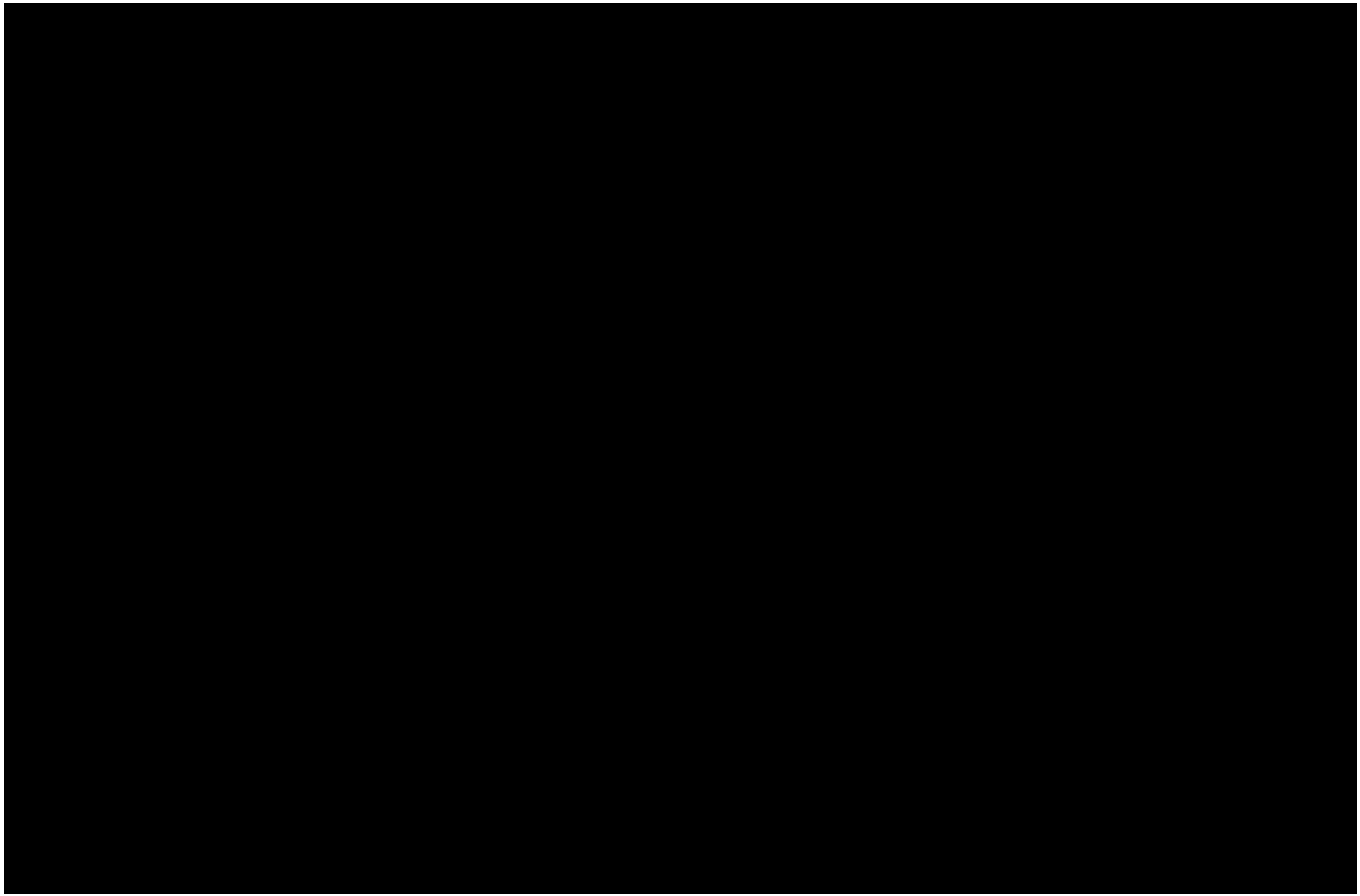


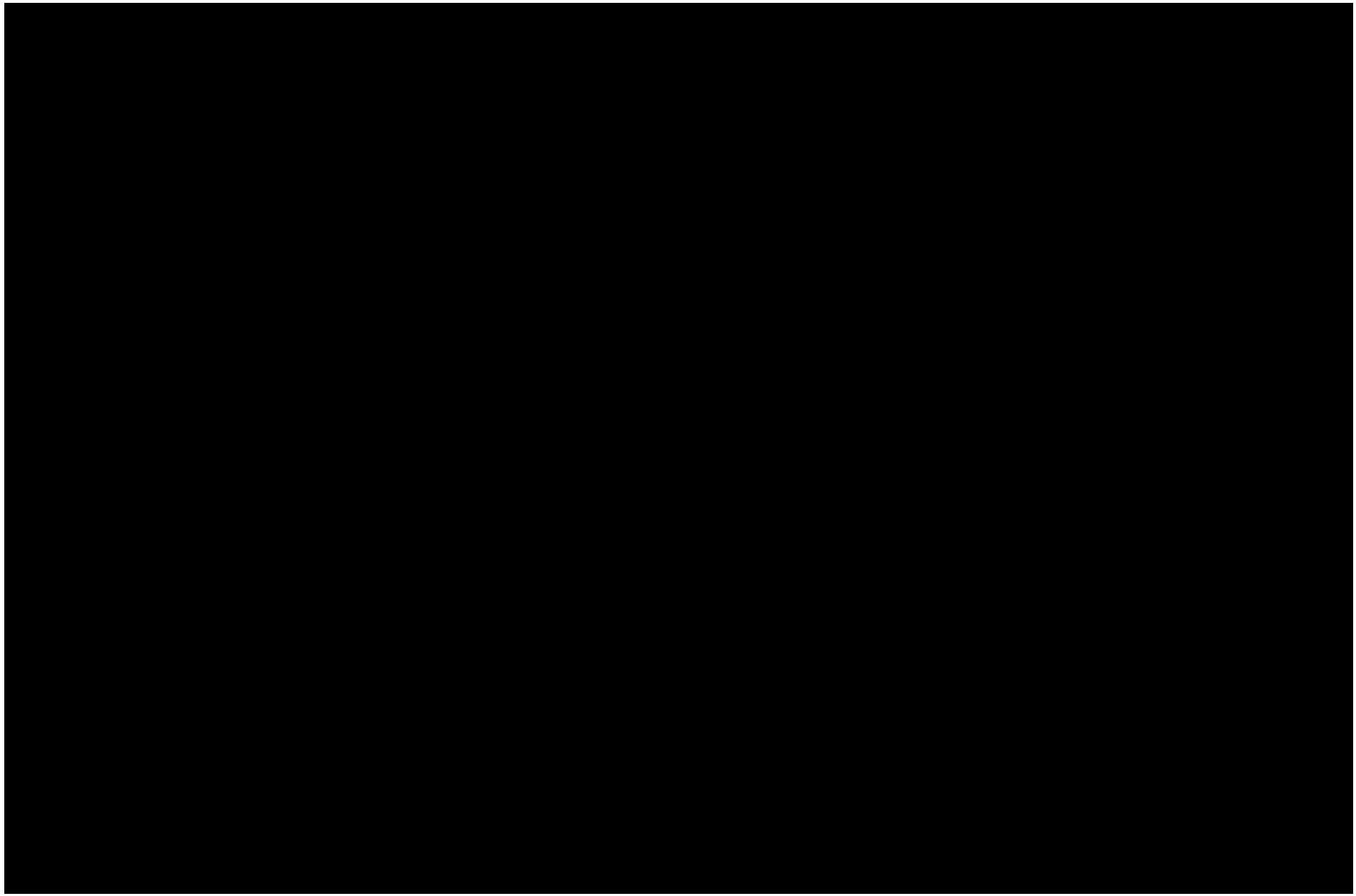


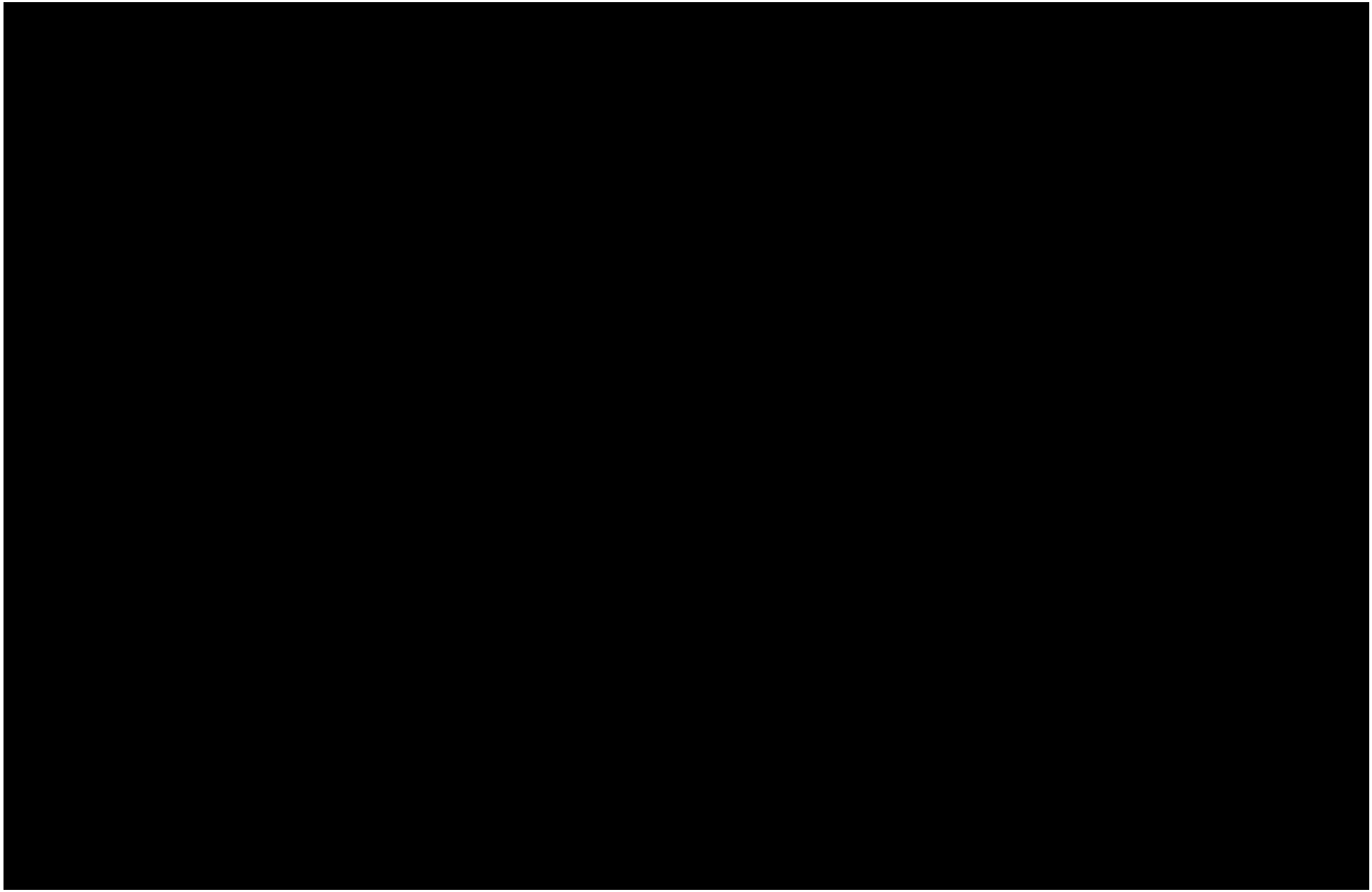


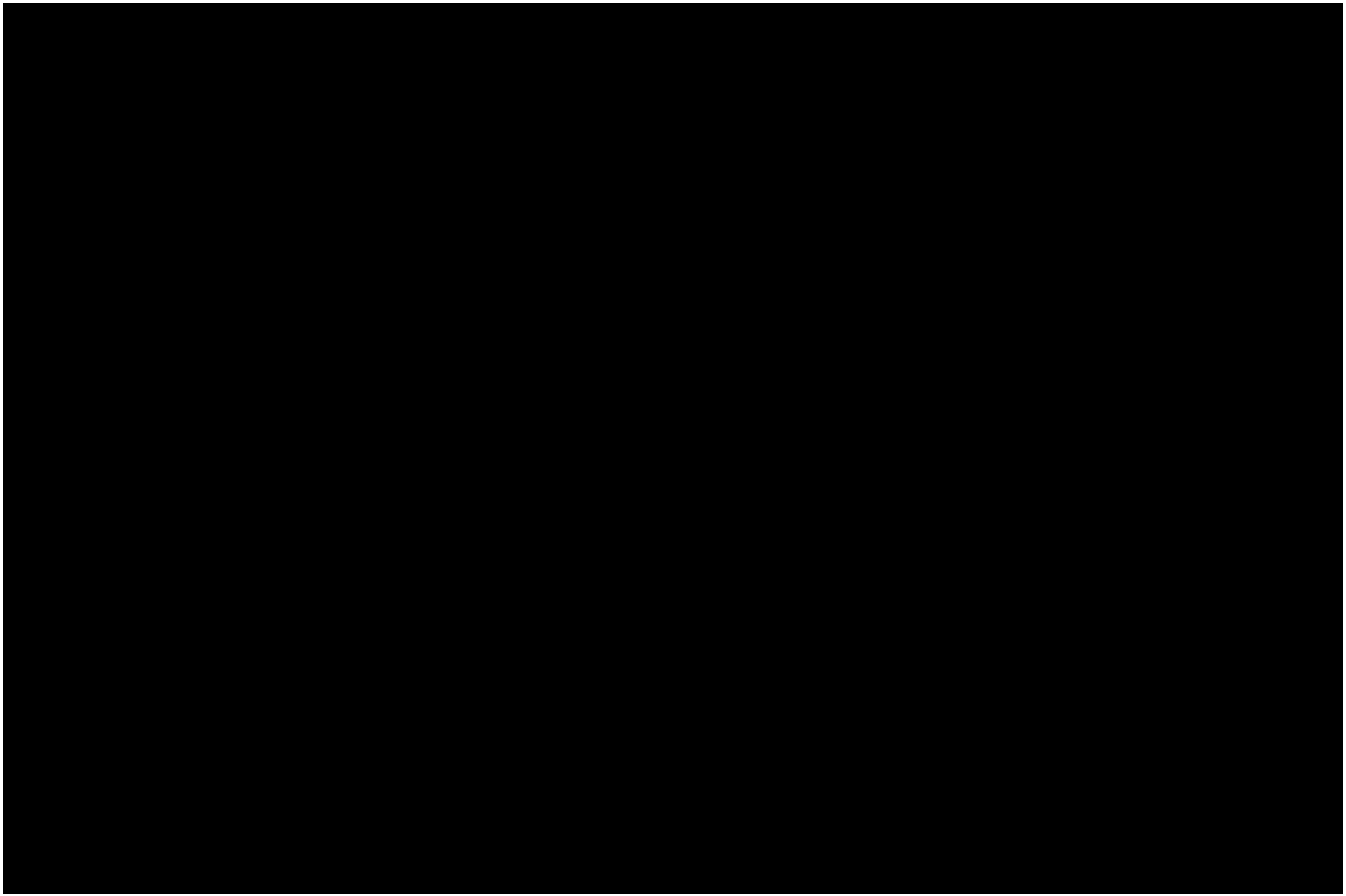


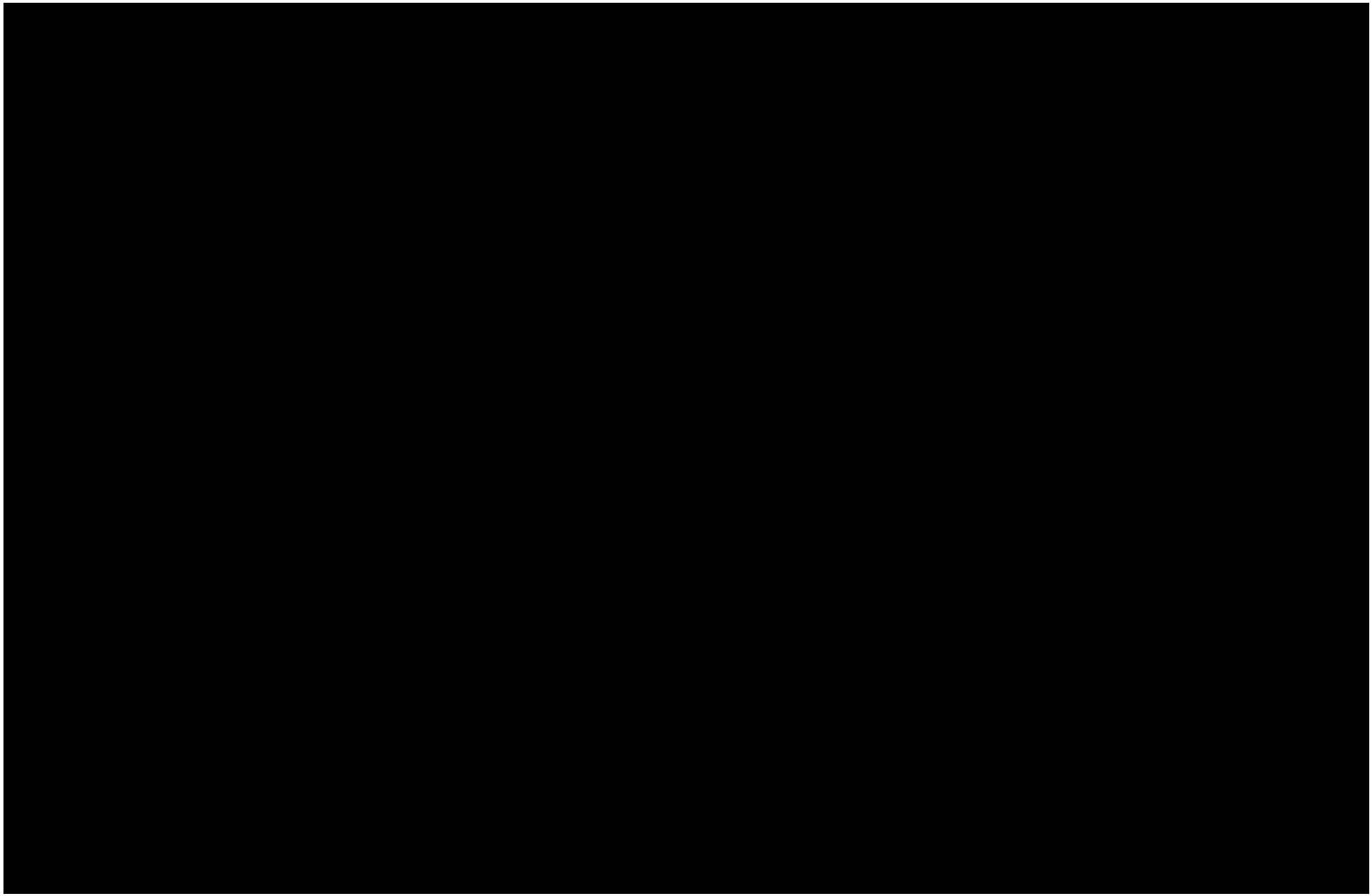


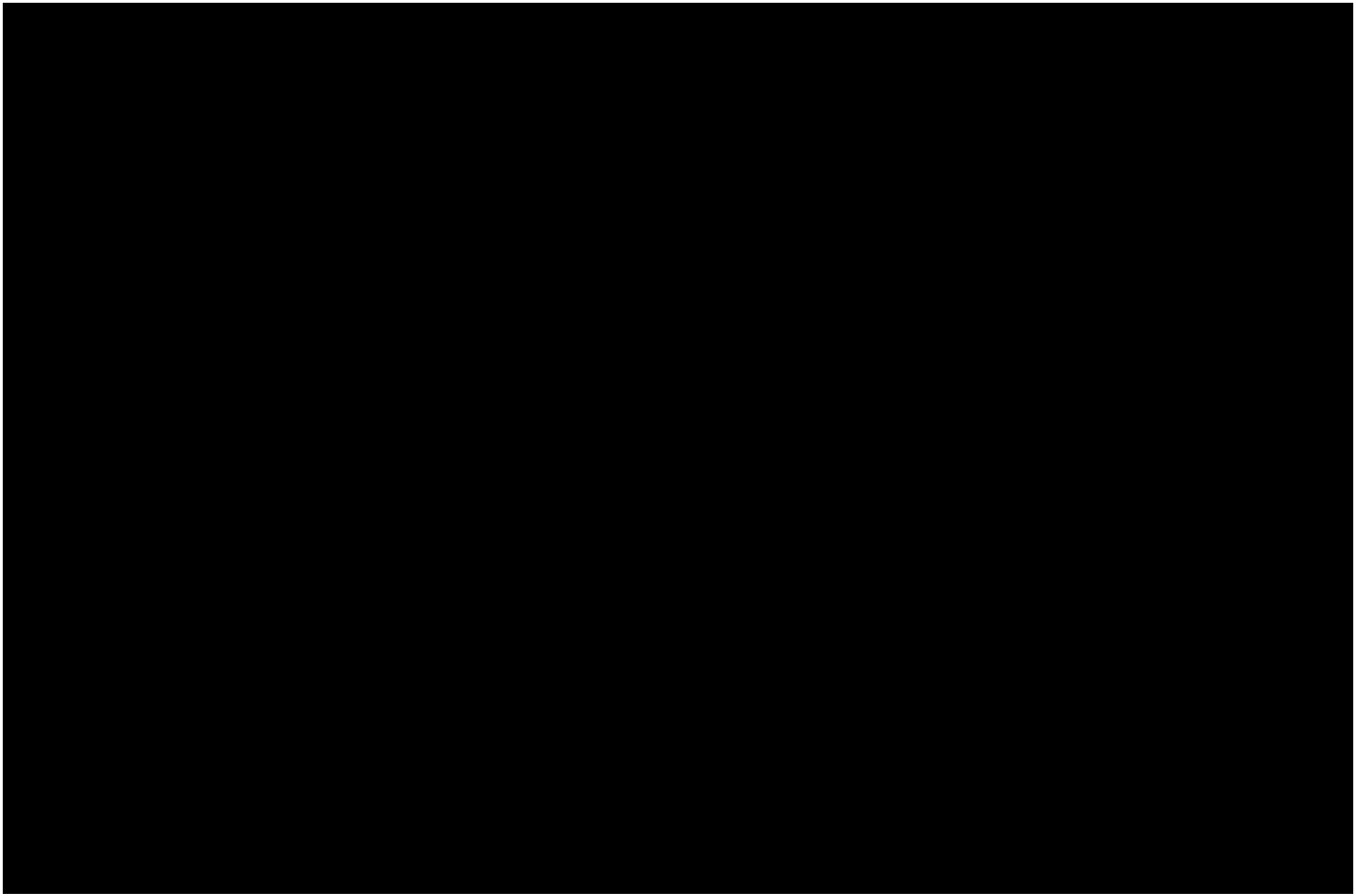


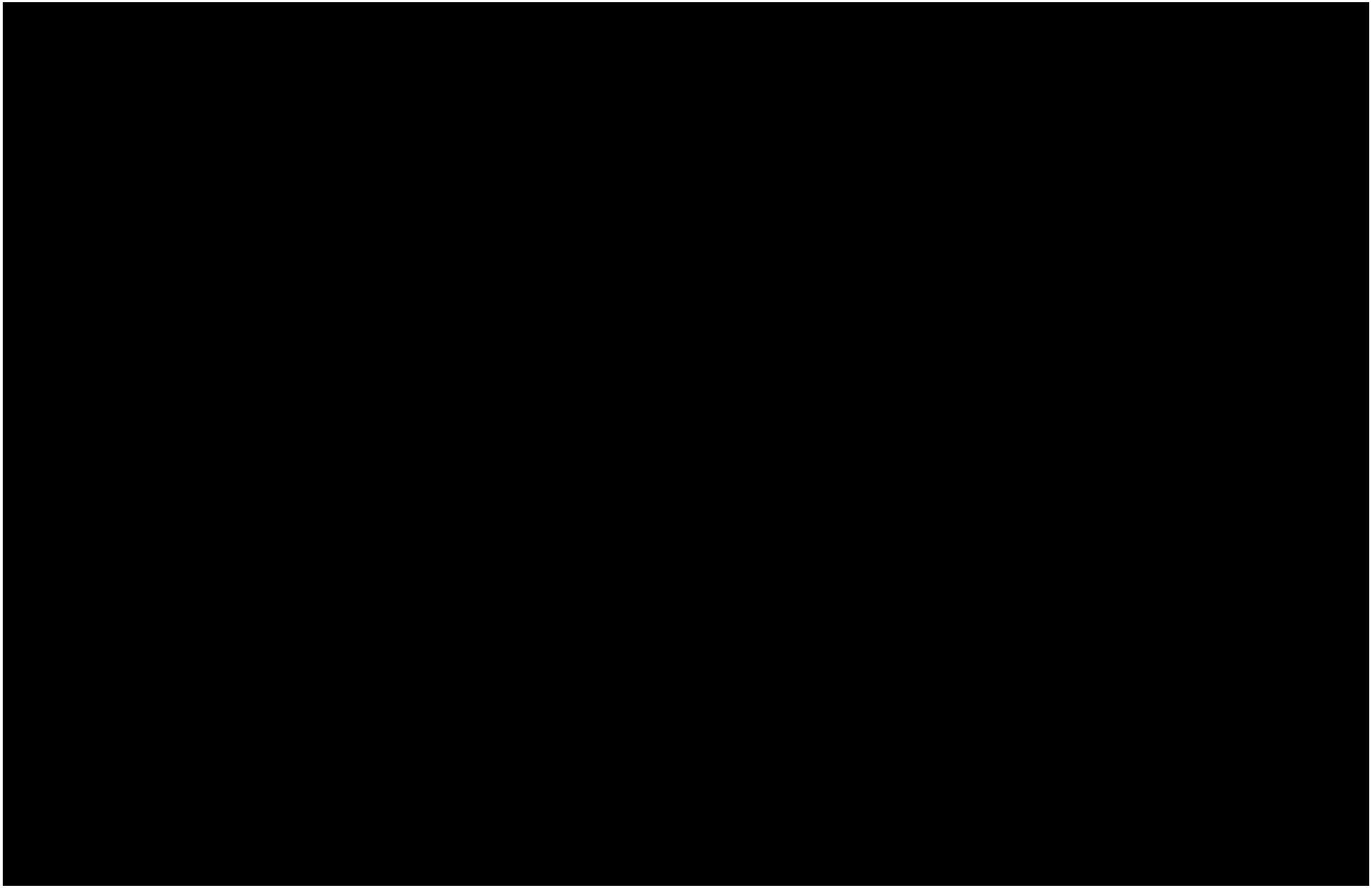


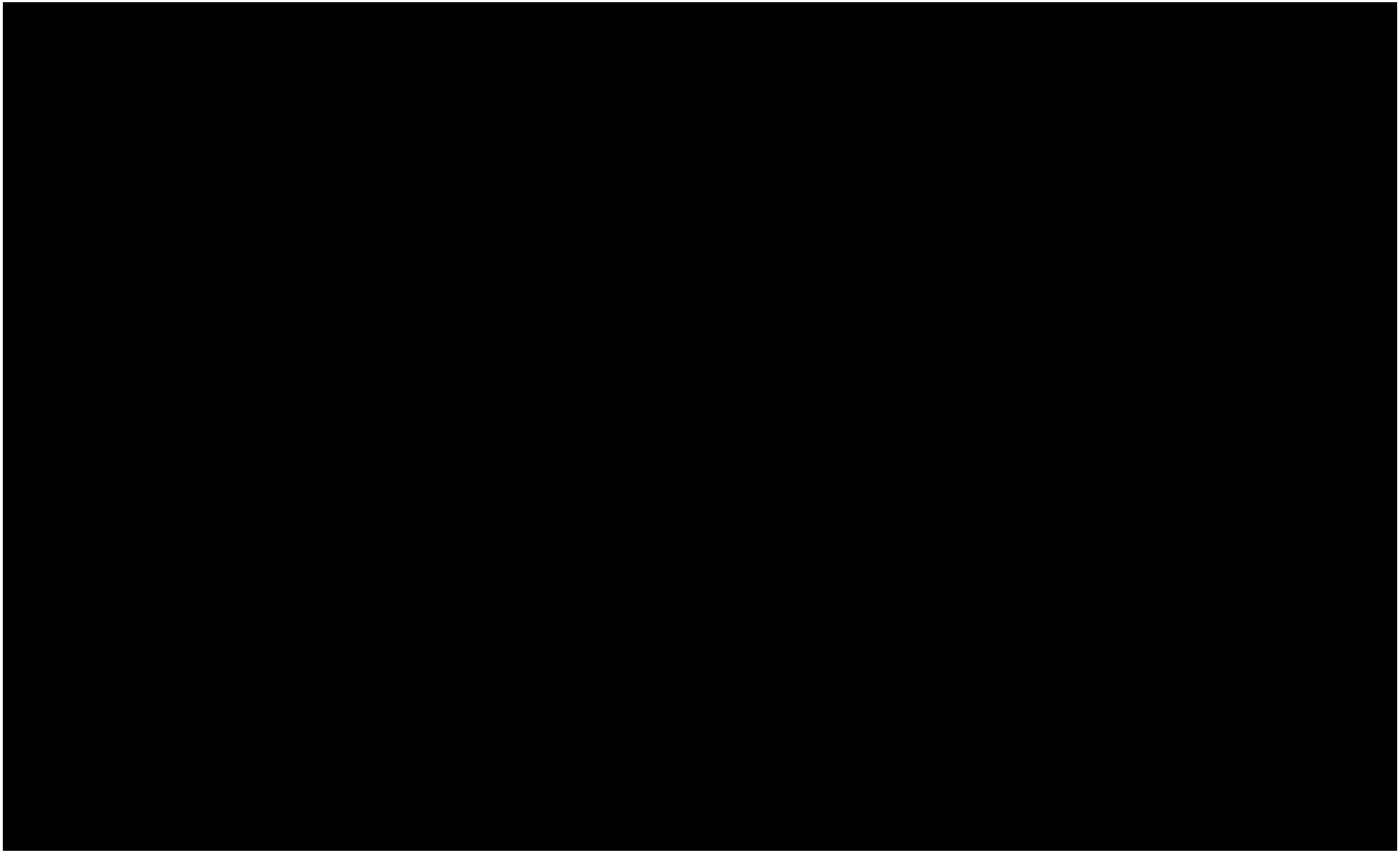


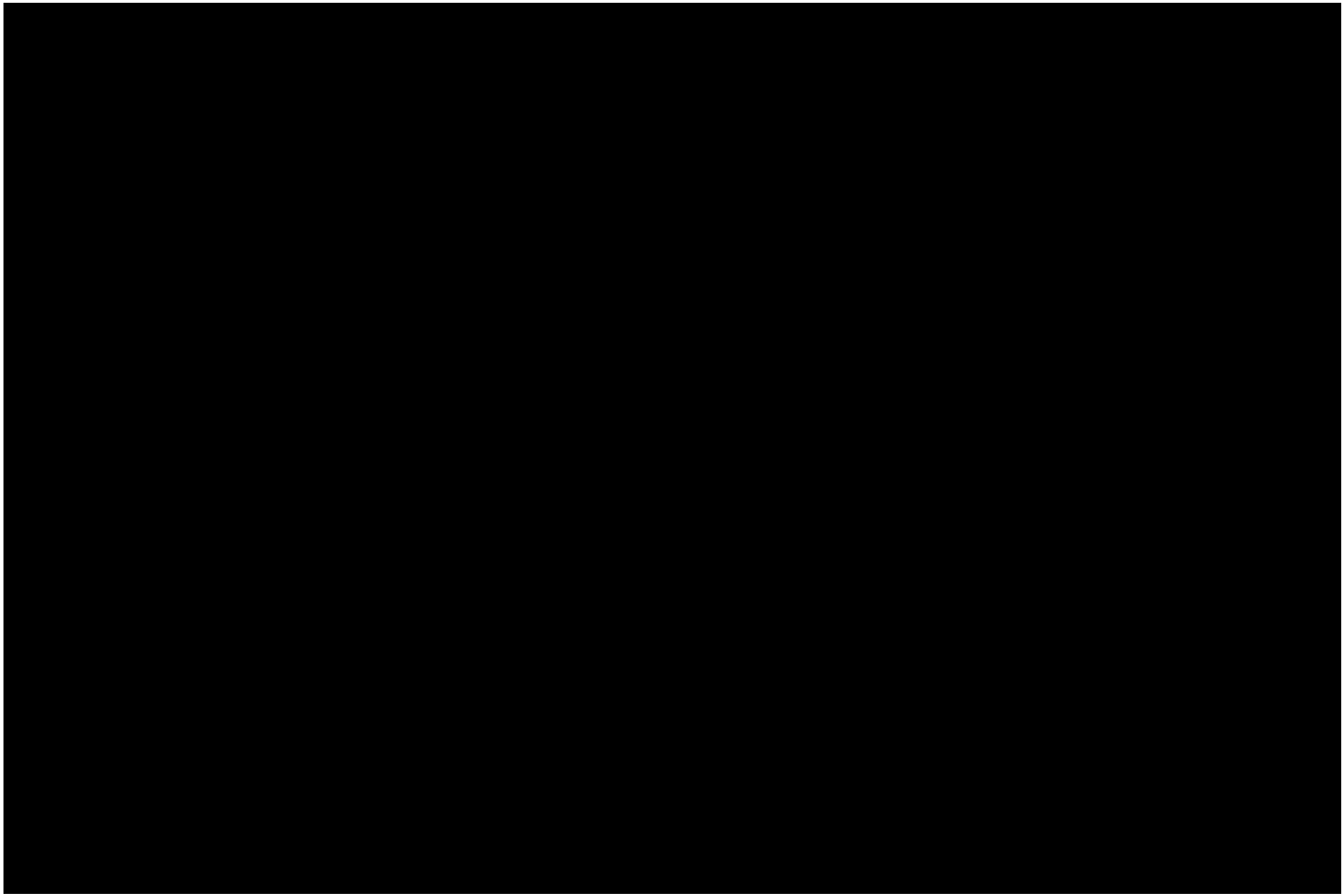


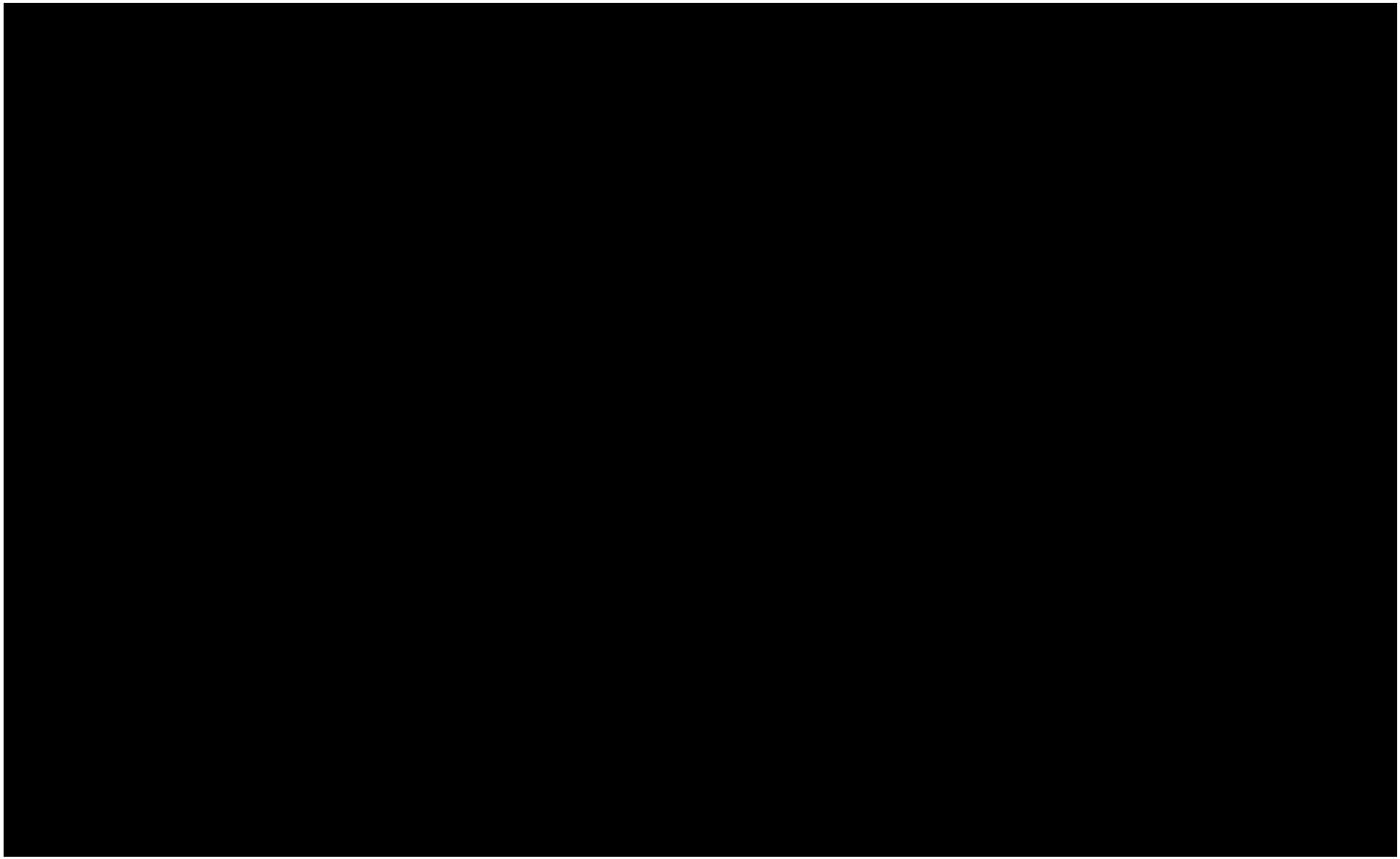






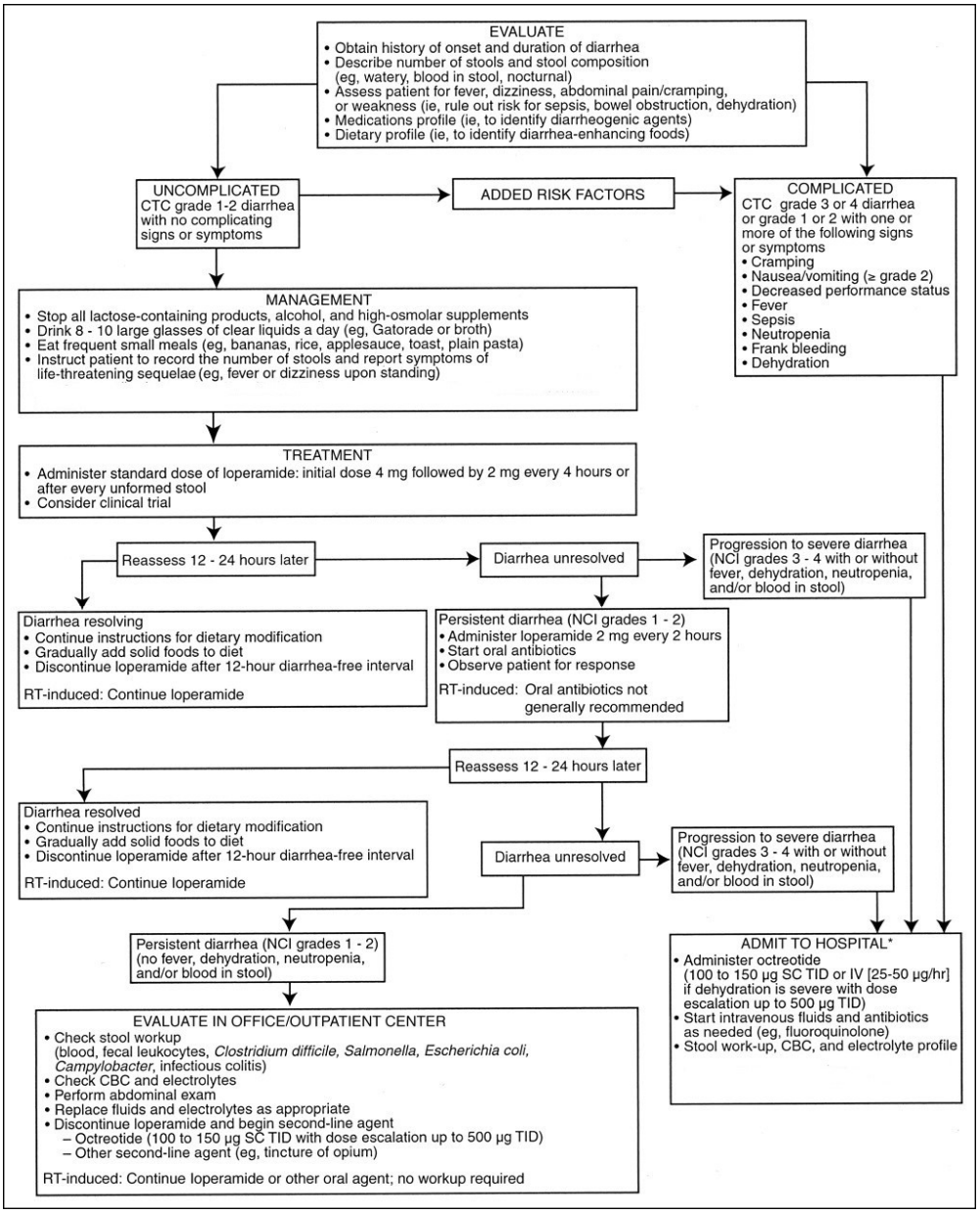






APPENDIX M RECOMMENDATIONS FOR THE MANAGEMENT OF TREATMENT-INDUCED DIARRHEA

The following published guidelines (Benson, 2004) were modified in order to be consistent with the study protocol.



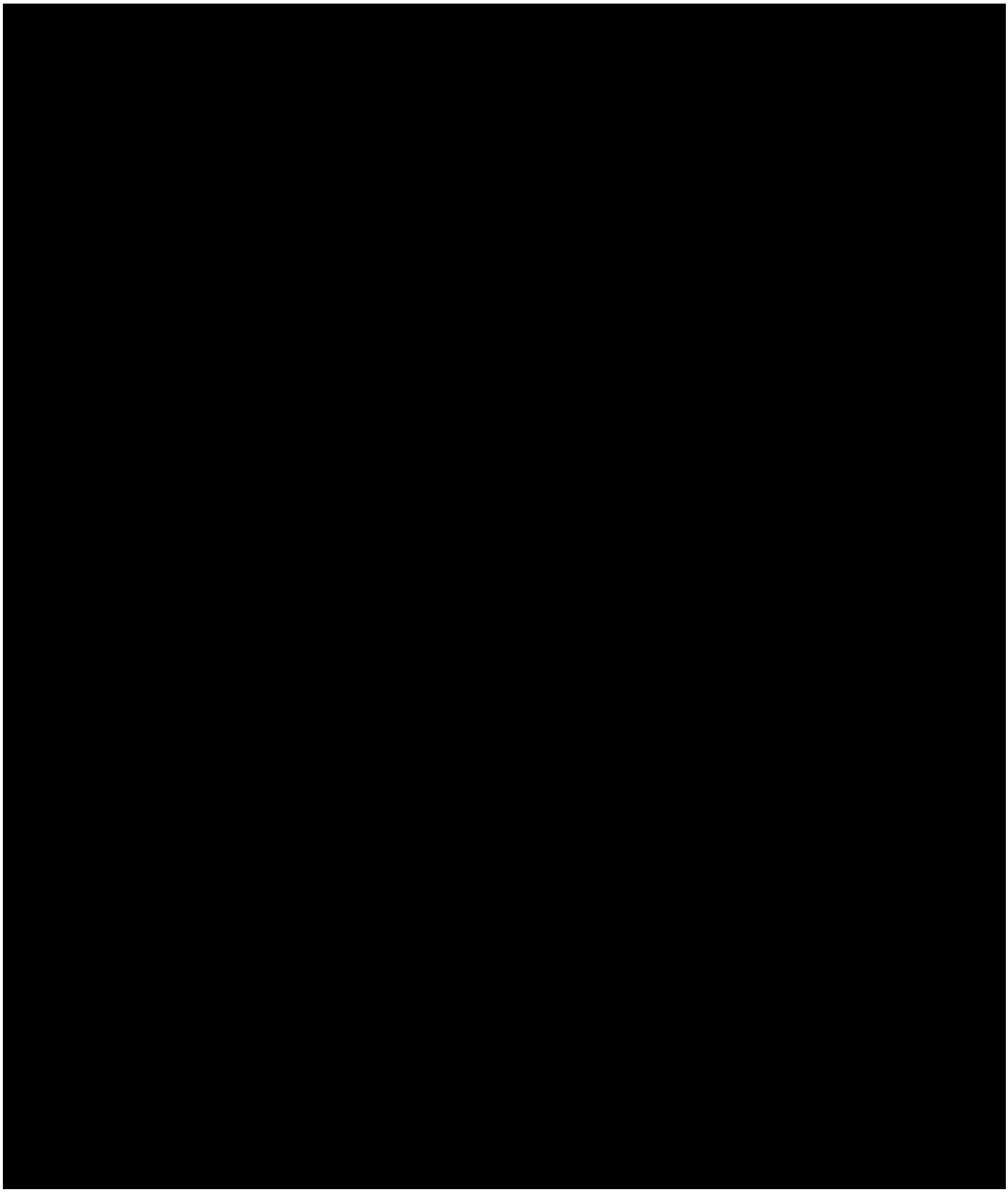
Abbreviations: CBC= complete blood count; CID= chemotherapy-induced diarrhea; CTC= Common Toxicity Criteria; IV= intravenous; NCI= National Cancer Institute; RT= radiotherapy; SC= subcutaneous; tid= three times per day.

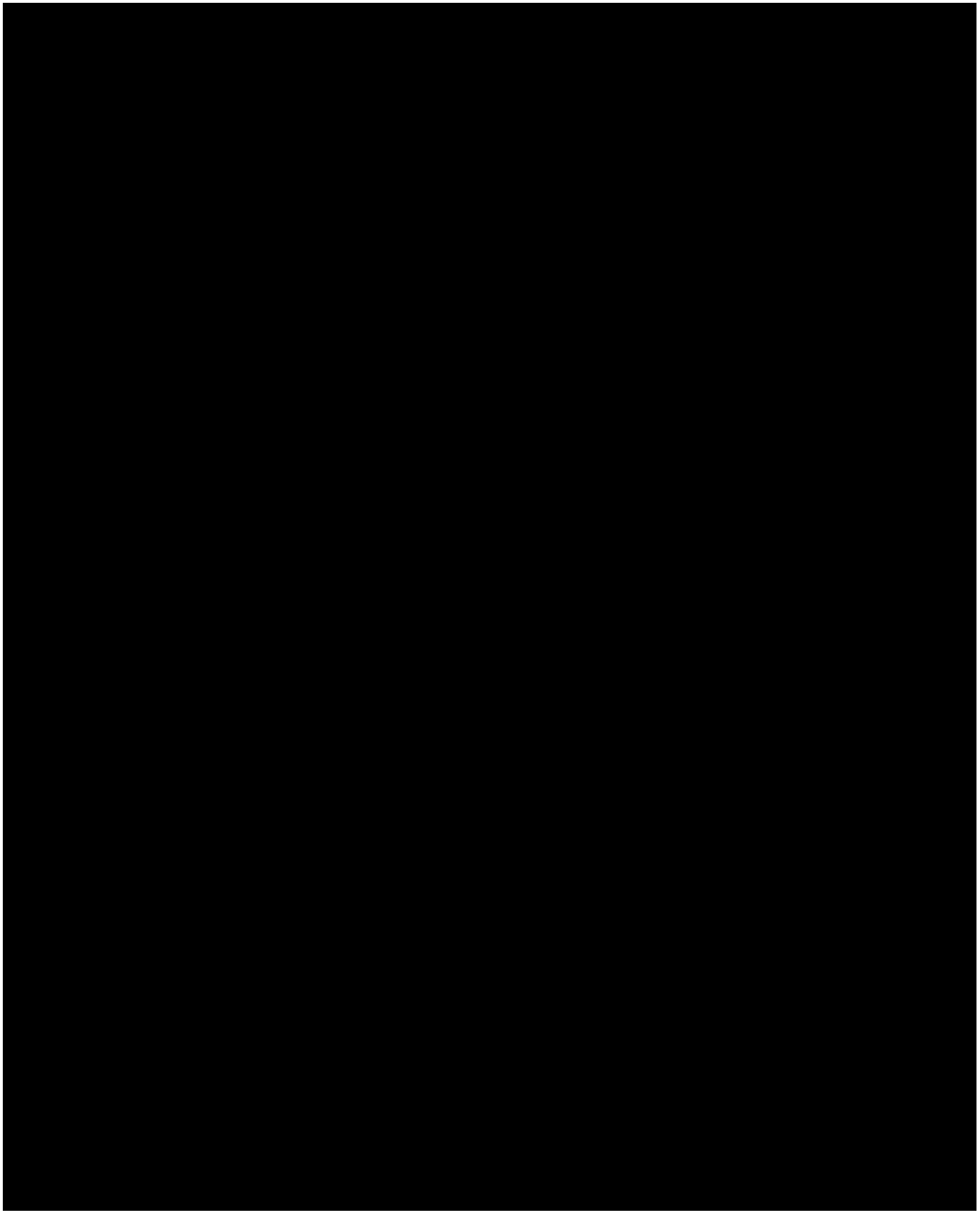
*For radiation-induced cases and select subjects with CID, consider intensive outpatient management, unless the subject has sepsis, fever, or neutropenia.

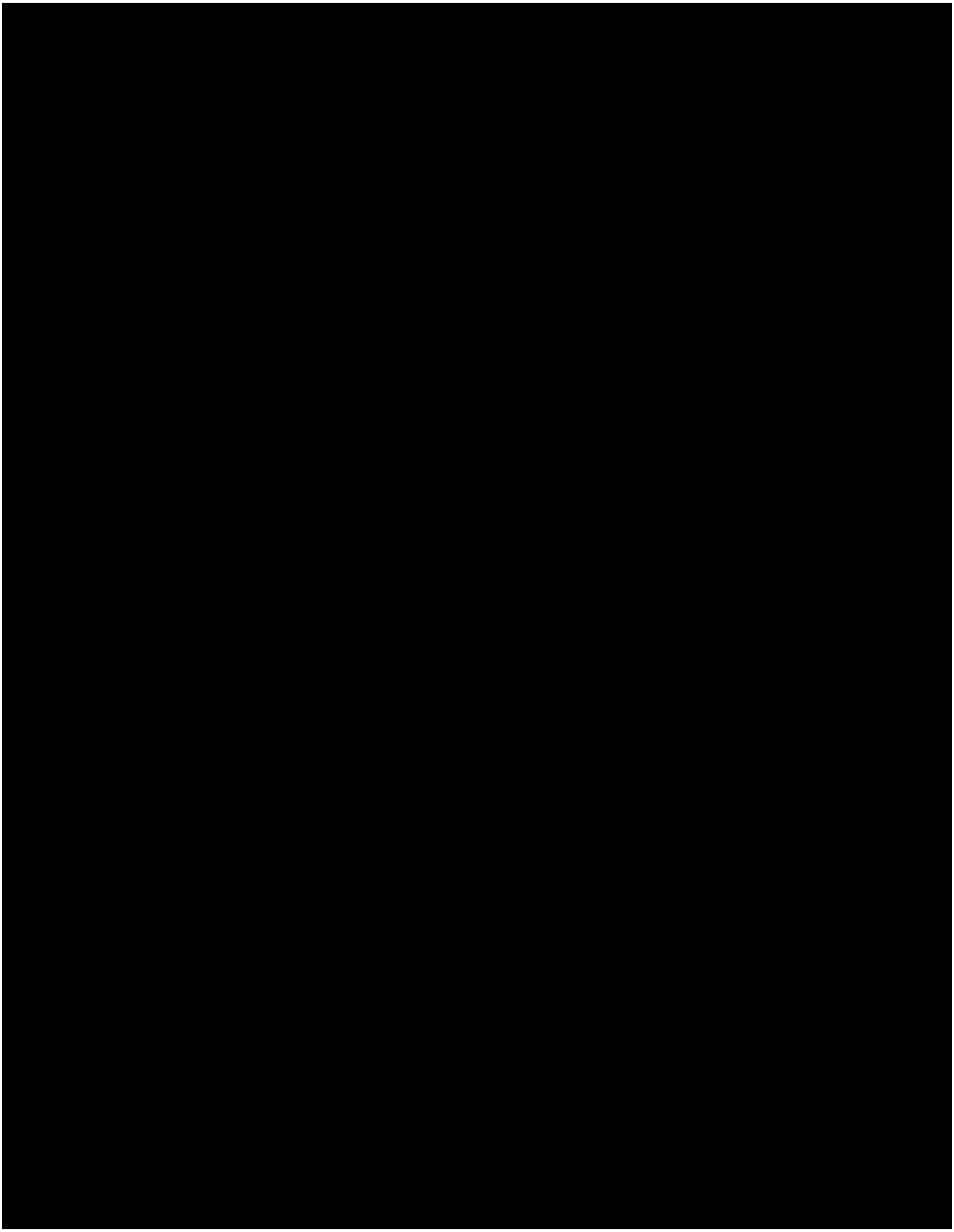
Source: Benson, 2004.

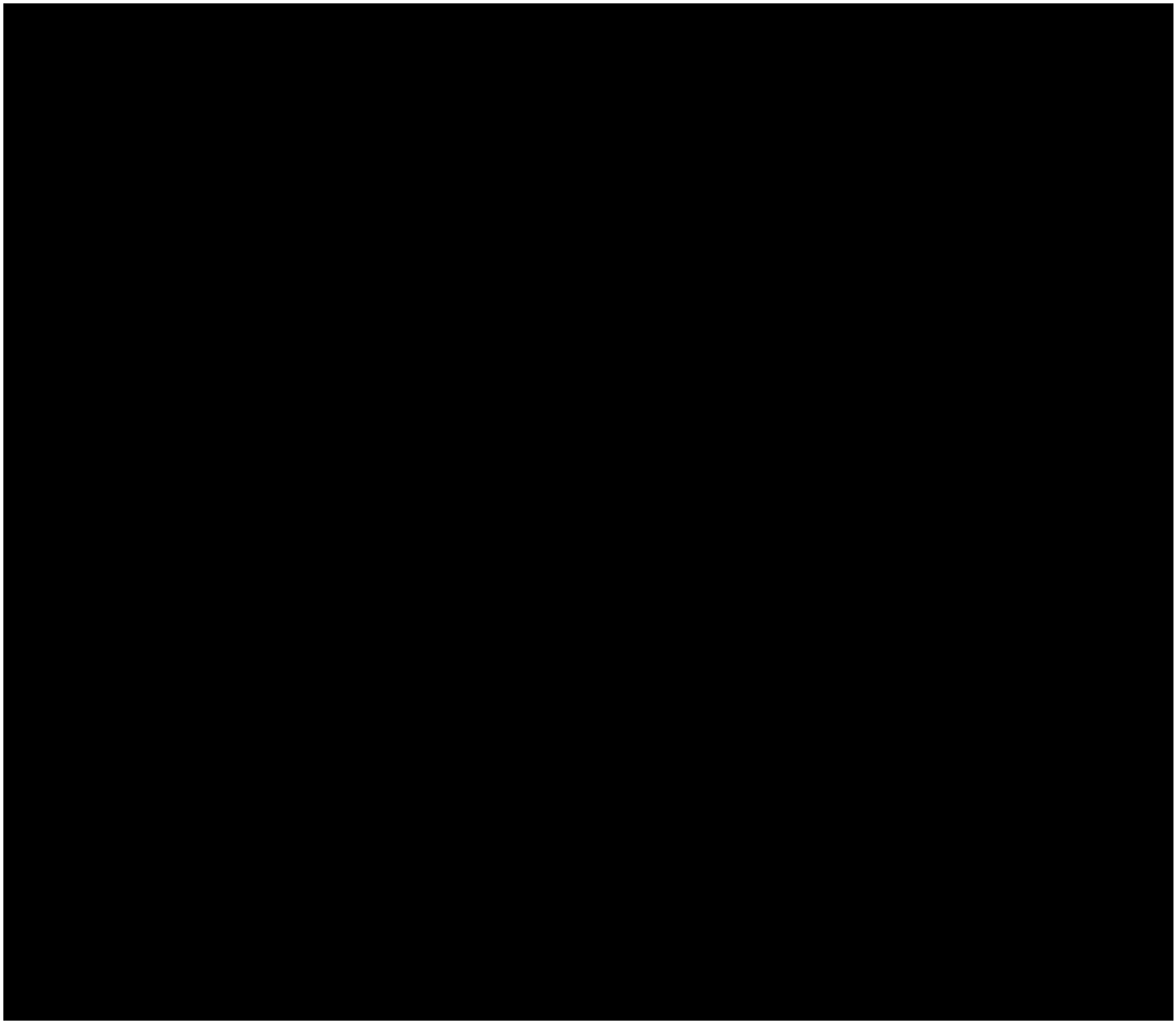
APPENDIX N PROTOCOL AMENDMENT SUMMARY OF CHANGE HISTORY

Overall Rationale for Protocol Amendment 2.0, 19 Dec 2022









1. JUSTIFICATION FOR AMENDMENT

The main purpose of this amendment is to reflect the revisions proposed by the Sponsor [redacted].

Significant changes included in this amendment are summarized below:

- **Modification of the Primary Objective to determine the recommended Phase 2 dose (RP2D)**

The maximal pharmacologic activity may be reached prior to reaching the [redacted], hence the determination of the [redacted] is removed from the study Primary objectives. The study seeks to define the dose with greatest clinical benefit without exceeding an acceptable rate of toxicity as specified in the protocol, which is the recommended Phase 2 dose (RP2D). The Primary objective is updated to define the RP2D of CC-95251 alone and in combination with antineoplastic agents in subjects with acute myeloid leukemia (AML) and myelodysplastic syndromes (MDS), and not the [redacted].

The Safety Review Committee (SRC) will make dose escalation/de-escalation recommendations [redacted]

Revised sections: Protocol Summary; Section 2 Study Objectives and Endpoints, Section 3.1.1 Part A, Section 3.1.2 Part B, Section 3.1.3 Part C, Section 7.2.1.1 CC-95251, Section 7.2.2 Dose Escalation Criteria, Section 7.2.4 Definition of [redacted], Section 7.2.6 Criteria for Dose Escalation in the Next Cohort of Subjects, Section 7.2.7.1 Criteria for Stopping a Dose Cohort, Section 7.2.10 Criteria for Dose Increase, Section 9.1 Overview, Section 9.3 Sample Size and Power Considerations, Section 9.7 Safety Analysis, Section 9.9.1 Statistical Method for Dose Escalation; [redacted]; Table 1 Study Objectives

- **Clarification of treatment regimen for cohorts in Part B**

The protocol has been updated to specify the treatment regimen including the sample size for CC-95251 monotherapy and in combination with azacitidine cohorts in Part B. [redacted] Additional cohorts of subjects testing CC-95251 in combination with additional antineoplastic agents in subjects with R/R AML or R/R MDS may be considered at the recommendation of the SRC and will be included by protocol amendment.

Revised sections: Protocol Summary; Section 1.3.2 Rationale for the Study Design, Section 3.1 Study Design, Section 3.1.2 Part B, Section 9.1 Overview, Section 9.3 Sample Size and Power Considerations, Section 9.9.2 Stopping Rules Regarding Toxicity in Dose Expansion; [redacted]

- **Statistical justification for sample sizes greater than [redacted] subjects in each of the expansion cohorts**

The protocol has been updated to provide more details of statistical justification for sample sizes greater than [redacted] subjects in each of the expansion cohorts by using a [redacted].

Revised sections: Section 9.3 Sample Size and Power Considerations

- **Modification of interim futility analysis for expansion cohorts**

Complete remission (CR) is the response endpoint reasonably likely to predict clinical benefit in patients with relapsed or refractory AML. Use of responses less than CR would not be sufficient to claim efficacy and continue accrual to a study, since use of an ineffective therapy may be detrimental to patients. [redacted]

A [redacted] analysis based on CRR has been added for Part C to avoid continued enrollment of previously untreated MDS subjects if preliminary results are not sufficiently promising.

Revised sections: Protocol Summary; Section 3.1.4.2 Treatment Period, Section 7.2.7.1 Criteria for Stopping a Dose Cohort, Section 9.9.2 Stopping Rules Regarding Toxicity in Dose Expansion; [redacted]

- **Modification of the Eligibility Criteria related to MDS population, calcineurin inhibitors, and creatinine clearance**

Specific eligibility criteria have been revised to ensure patient populations are not placed at excess risk. The revised International Prognostic Scoring System (IPSS-R) score for eligible relapsed or refractory MDS subjects has been updated to [redacted], the IPSS-R score for previously untreated MDS subjects has been updated to [redacted].

[redacted]

Subjects should have creatinine clearance of [redacted] ml/min using the Cockcroft-Gault equation.

Revised sections: Protocol Summary; Section 1.3.1 Study Rationale and Purpose, Section 1.3.2 Rationale for the Study Design, Section 3.1 Study Design, Section 3.1.2 Part B, Section 3.1.3 Part C, Section 4.2 Inclusion Criteria, Section 4.3 Exclusion criteria, Section 9.1 Overview, Section 9.3 Sample Size and Power Considerations

- **Modification of the hematologic dose-limiting toxicity (DLT) definition and the DLT criteria exceptions**

[redacted]

Specific non-hematologic toxicity exceptions to the DLT criteria were revised to ensure patient populations are not placed at excess risk.

[redacted]

Revised sections: Protocol Summary; Section 3.1.1 Part A, Section 3.1.4 Study Treatments, Section 7.2.3 Definition of a Subject Evaluable for DLT, Section 7.2.5 Definition of Dose-Limiting Toxicity (DLT); Footnote 'l' in Table 3, [redacted].

- **Modification of dose modifications for hematologic toxicities**

[redacted]

Revised sections: Section 7.2.12 Dose Modification Guidelines, Section 7.2.13.4 Hematological Toxicity; [redacted]

- **Addition of safety labs to monitor for the potential risk for hemolysis**

Subjects with MDS and AML often have severe baseline anemia and small shifts in hemoglobin may pose a significant safety risk. In order to monitor for hemolytic anemia, the protocol has been updated to check type and screen, [redacted]

Revised sections: [redacted], Section 6.2.6 Clinical Laboratory Tests, [redacted]

The amendment also includes other minor clarifications and corrections:

- Removal of 'subjects with non-progressive disease' from text describing study treatment and dosing of CC-95251 (Protocol Summary, Section 3.1.4 Study Treatments, Section 7.2.1.1 CC-95251).
- Addition of the statement that investigation of any other alternate dosing schedule beyond those stipulated in the current protocol version will be submitted in a protocol amendment (Protocol Summary, Section 1.3.3 Rationale for Dose, Schedule and Regimen Selection, Section 3.1.1 Part A, Section 3.1.4 Study Treatments, Section 7.2.1.1 CC-95251, Section 7.2.4 Definition of Maximum Tolerated Dose).
- Addition of post-dose PK samples at steady state in Cycle 2 (Section 6.5 Pharmacokinetics; [redacted]
- Clarification of the evaluation of minimal residual disease (MRD) to apply to the whole study (Section 2 Study Objectives and Endpoints, Section 6.4 Efficacy Assessment, Section 6.6 Biomarkers, Pharmacodynamics, Pharmacogenomics; Table 1 Study Objectives).
- Completion of Table 17 WHO classification of AML in Appendix B.
- Other clarifications including content alignment, corrections of minor typographical errors and incidental formatting changes were made throughout the document.