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Clinical Protocol CA204125

An Open Label, Randomized Phase 2 Trial of Pomalidomide/Dexamethasone With or Without Elotuzumab in relapsed and refractory Multiple Myeloma.

Revised Protocol Number: 01
Incorporates Amendment: 02

Study Director/Central Medical Monitor

Suresh Shelat, MD, PhD
Bristol Myers Squibb Company

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Replace all previous version(s) of the protocol with this revised protocol and please provide a copy of this revised protocol to all study personnel under your supervision, and archive the previous versions.

DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Revised Protocol 01	11-Nov-2015	Incorporates Amendment 02
Amendment 02	11-Nov-2015	Remove the Circulating Multiple Myeloma Cells (CMMC) assay and to replace with Gene Expression Profiling Clarify wording of pomalidomide risk management program and Pomalidomide Pregnancy Risk Prevention Plan throughout Minor formatting and typographical revisions
Original Protocol	02-Sep-2015	Not applicable

SYNOPSIS

Clinical Protocol CA204125

Protocol Title: An Open Label, Randomized Phase 2 Trial of Pomalidomide/Dexamethasone With or Without Elotuzumab in relapsed and refractory Multiple Myeloma

Investigational Product(s), Dose and Mode of Administration, Duration of Treatment with Investigational Product(s):

See **Study Schema** for details

Control Arm

Pomalidomide: 4 mg PO QD Days 1-21 of each cycle

Dexamethasone:

- Subjects \leq 75 years old: 40 mg PO Days (1, 8, 15 and 22) of each cycle
- Subjects $>$ 75 years old: 20 mg PO Days (1, 8, 15 and 22) of each cycle

Elotuzumab Arm

Elotuzumab:

- Cycle 1 - 2: 10 mg/kg IV Days 1, 8, 15 and 22 of each cycle
- Cycle 3 and beyond: 20mg/kg IV Day 1 of each cycle

Pomalidomide: 4 mg PO QD Days 1-21 of each cycle

Dexamethasone: Days 1, 8, 15 and 22 of each cycle

- Subjects \leq 75 years old: weeks with elotuzumab dosing: 28 mg PO + 8 mg IV and 40 mg PO on non-elotuzumab dosing weeks
- Subjects $>$ 75 years old: weeks with elotuzumab dosing: 8 mg PO + 8 mg IV and 20 mg PO on non-elotuzumab dosing weeks

A cycle is defined as 28 days. Treatment with study drug continues until disease progression, unacceptable toxicity (adverse event related to study drug), or subject meets other criteria for discontinuation of study drug outlined in [Section 3.5](#).

Study Phase: 2

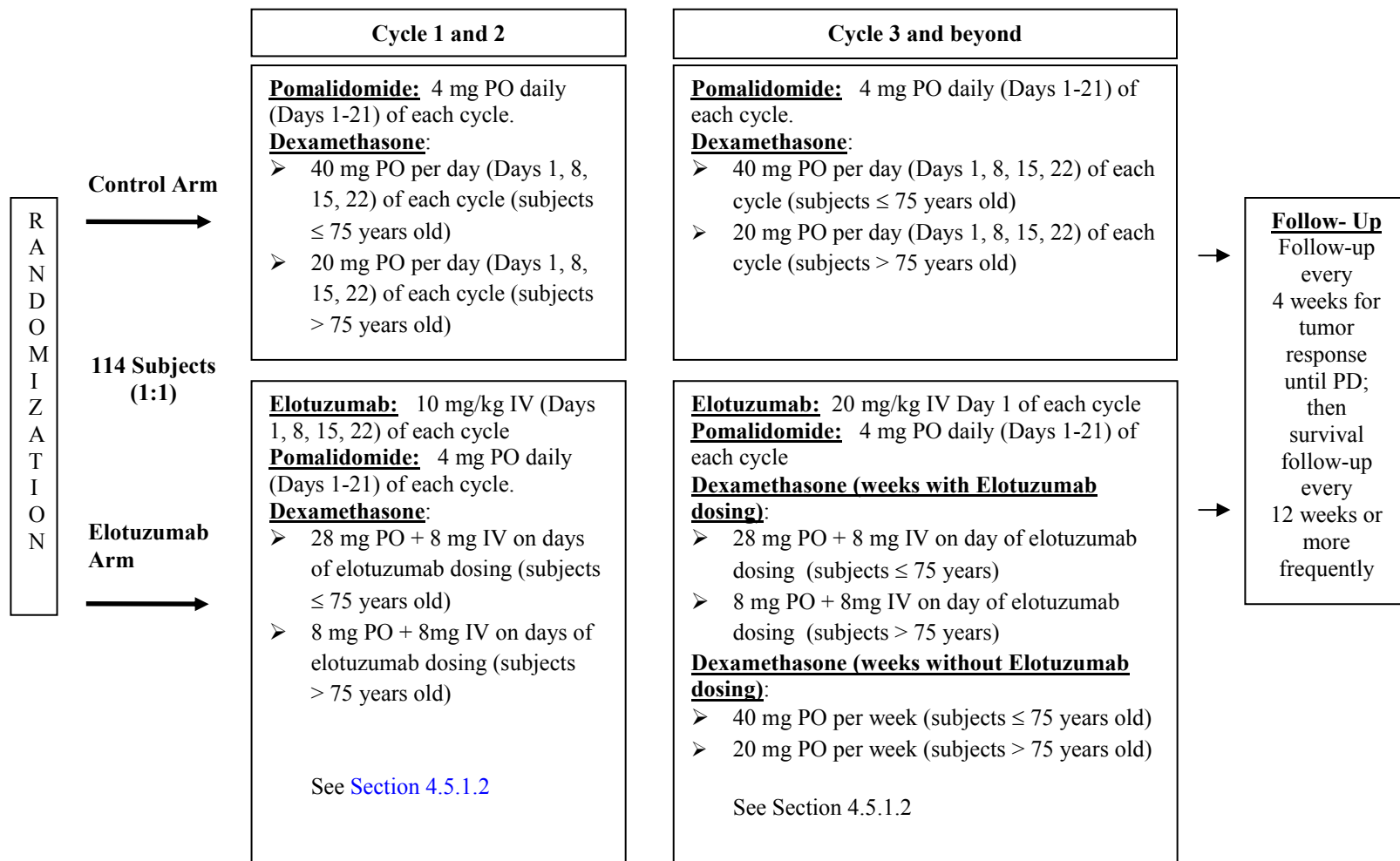
Primary Objective:

- To compare progression free survival (PFS) between treatment arms

Secondary Objectives:

- To compare objective response rate between treatment arms
- To compare overall survival between treatment arms

Study Schema



Study Population:

Subjects who are diagnosed with relapsed and refractory multiple myeloma defined as:

- 1) Must have received ≥ 2 prior lines of therapy (See [Appendix 1](#)) which must have included at least 2 consecutive cycles of lenalidomide and a proteasome inhibitor alone or in combination.
- 2) Documented refractory or relapsed and refractory (R/R) multiple myeloma
- 3) Refractory (progressed on or within 60 days of treatment) to their last treatment.
- 4) Subjects must have failed treatment with a proteasome inhibitor and lenalidomide in one of the following ways.
 - a) “Refractory” to proteasome inhibitor and lenalidomide, and to their last treatment.
 - b) “Relapsed and refractory”= patients had achieved at least a partial response to previous treatment with proteasome inhibitor or lenalidomide, or both, but progressed within 6 months, and were refractory to their last treatment

Study Drug: includes both Investigational [Medicinal] Products (IP/IMP) and Non-investigational [Medicinal] Products (Non-IP/Non-IMP) as listed:

Study Drug for CA204125		
Medication	Potency	IP/Non-IP
Elotuzumab	400mg/vial	IP
Pomalidomide Capsules	1 mg, 2 mg, 3 mg and 4 mg	Non-IP
Dexamethasone Tablets	2 mg and 4 mg & various strengths	Non-IP
Dexamethasone Solution	4 mg/mL, 8 mg/mL & various strengths	Non-IP

Study Assessments: Tumor response assessment by modified IMWG criteria ([Appendix 6](#)) will be evaluated during the trial for all randomized subjects. The primary endpoint of PFS will be based on the investigator’s assessment

Statistical Considerations:

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Endpoints:

Primary Endpoint:

PFS will be defined as the time, in months, from randomization to the date of the first documented tumor progression or death due to any cause. Clinical deterioration will not be considered progression. A subject who neither progresses nor dies will be censored on the date of their last tumor assessment. A subject who does not have any post-baseline tumor assessments and who has not died will be censored on the date at which they were randomized.

Secondary Endpoint:

- 1) Objective response rate is defined as the proportion of randomized subjects who achieve a best response of partial response (PR) or better using the criteria in [Appendix 6](#) as per investigator's assessment.
- 2) Overall survival is defined as the time from randomization to the date of death from any cause. If a subject has not died, their survival time will be censored at the date of last contact ("last known alive date"). A subject will be censored at the date of randomization if they were randomized but had no follow-up.

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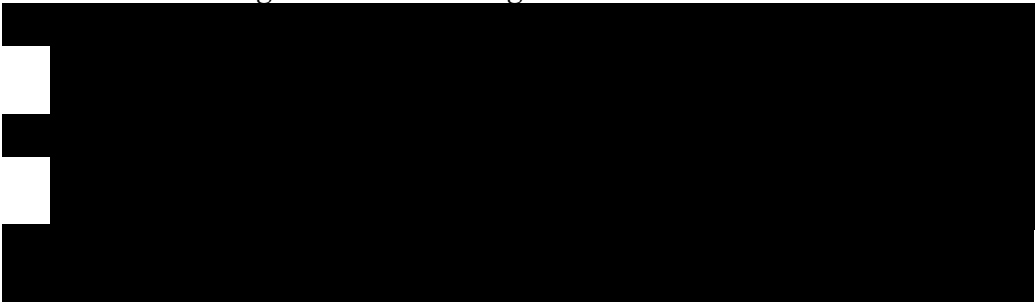


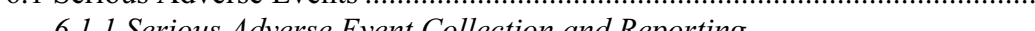
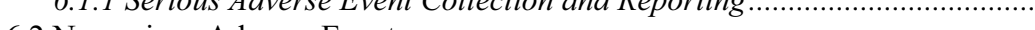
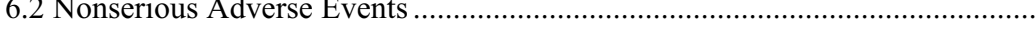


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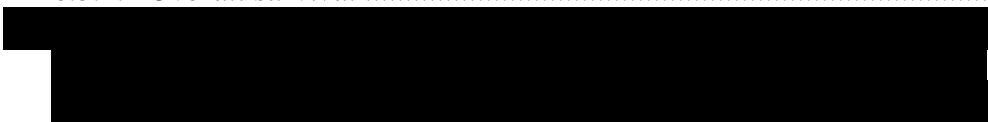
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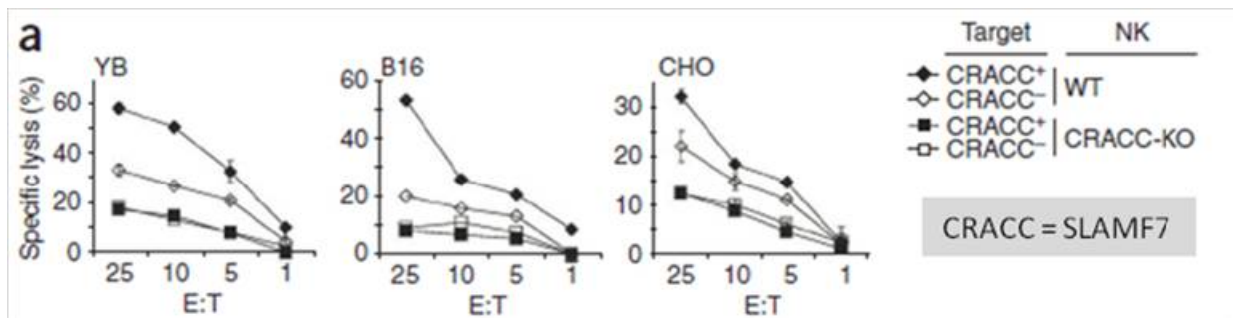
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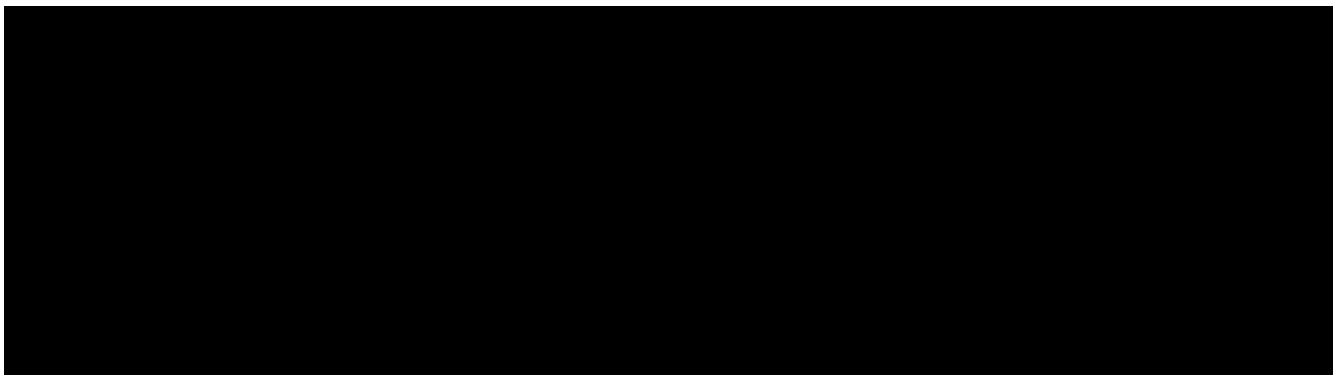
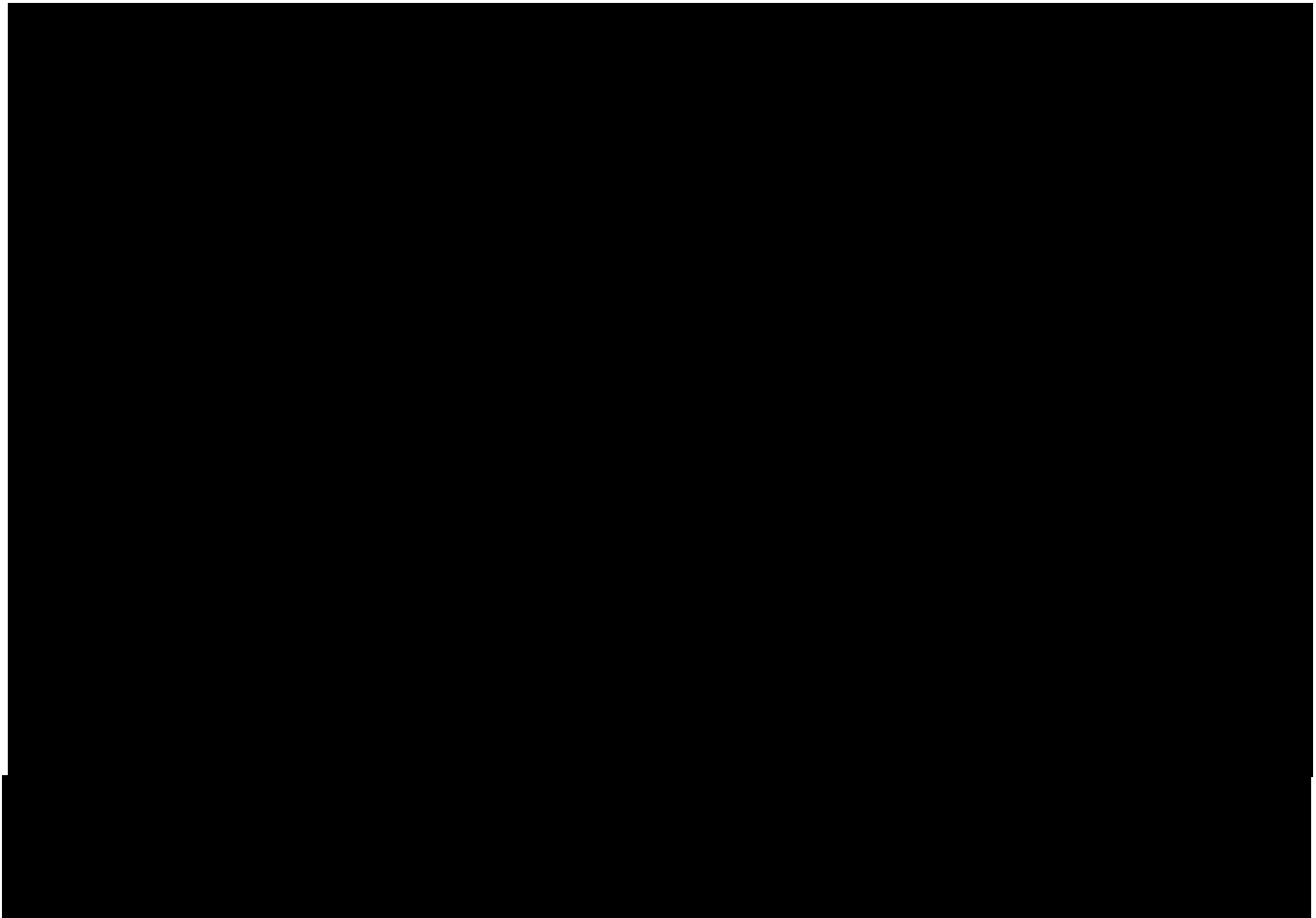
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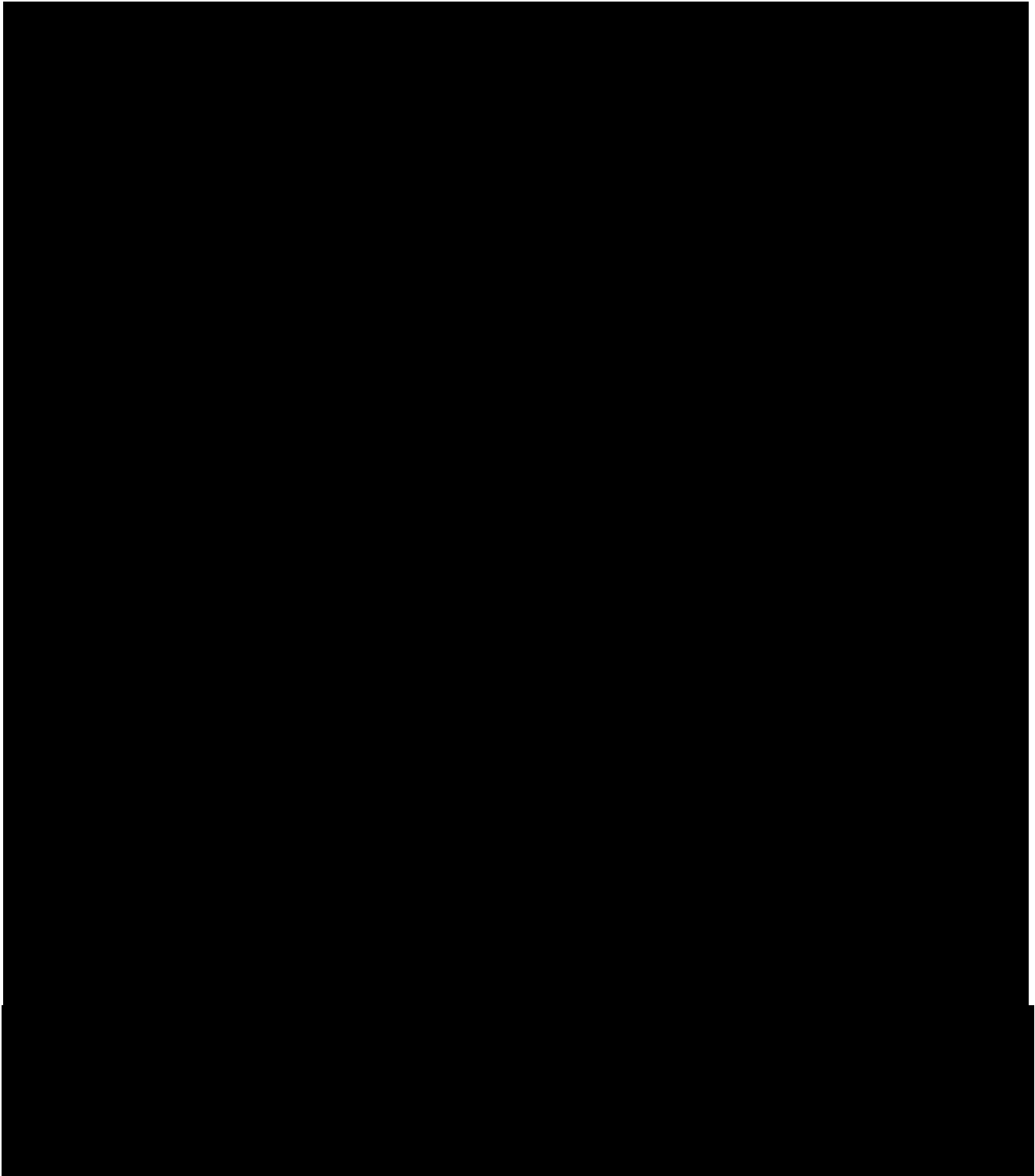
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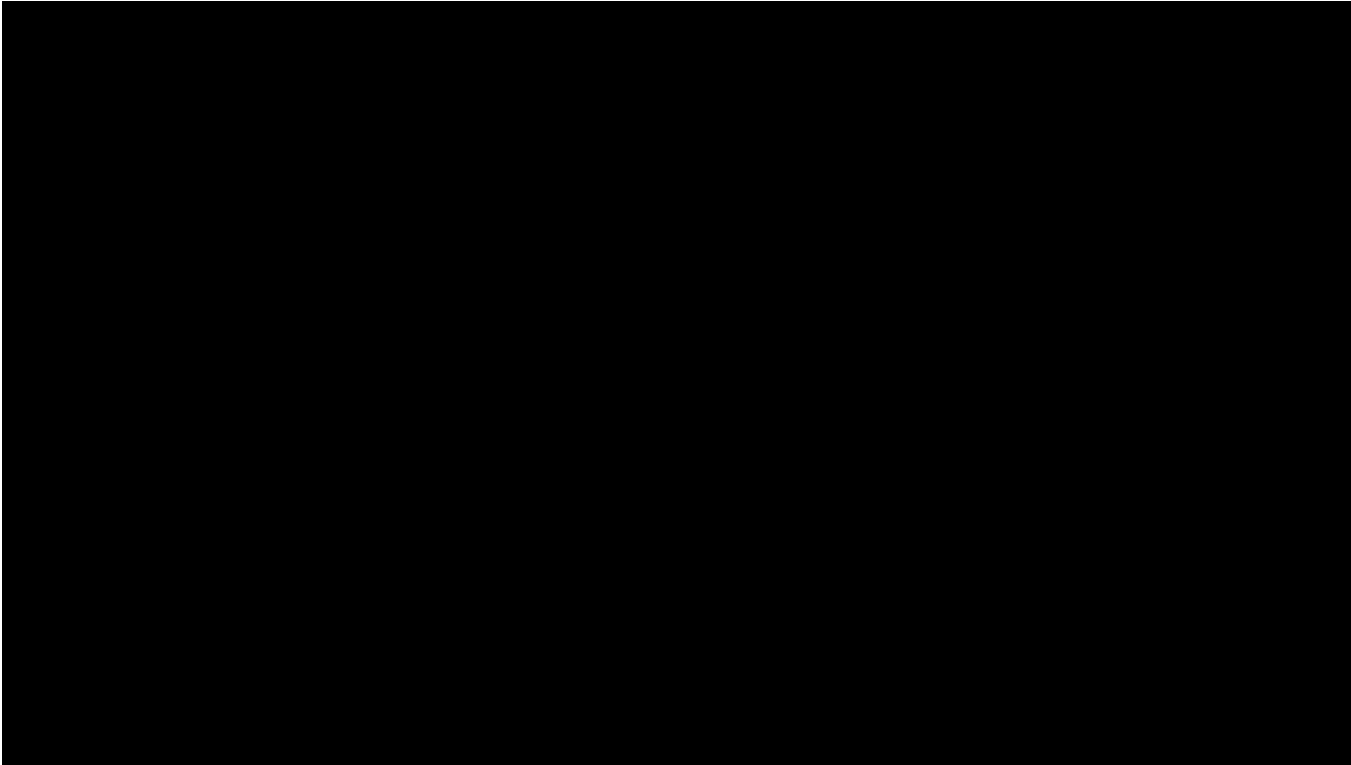
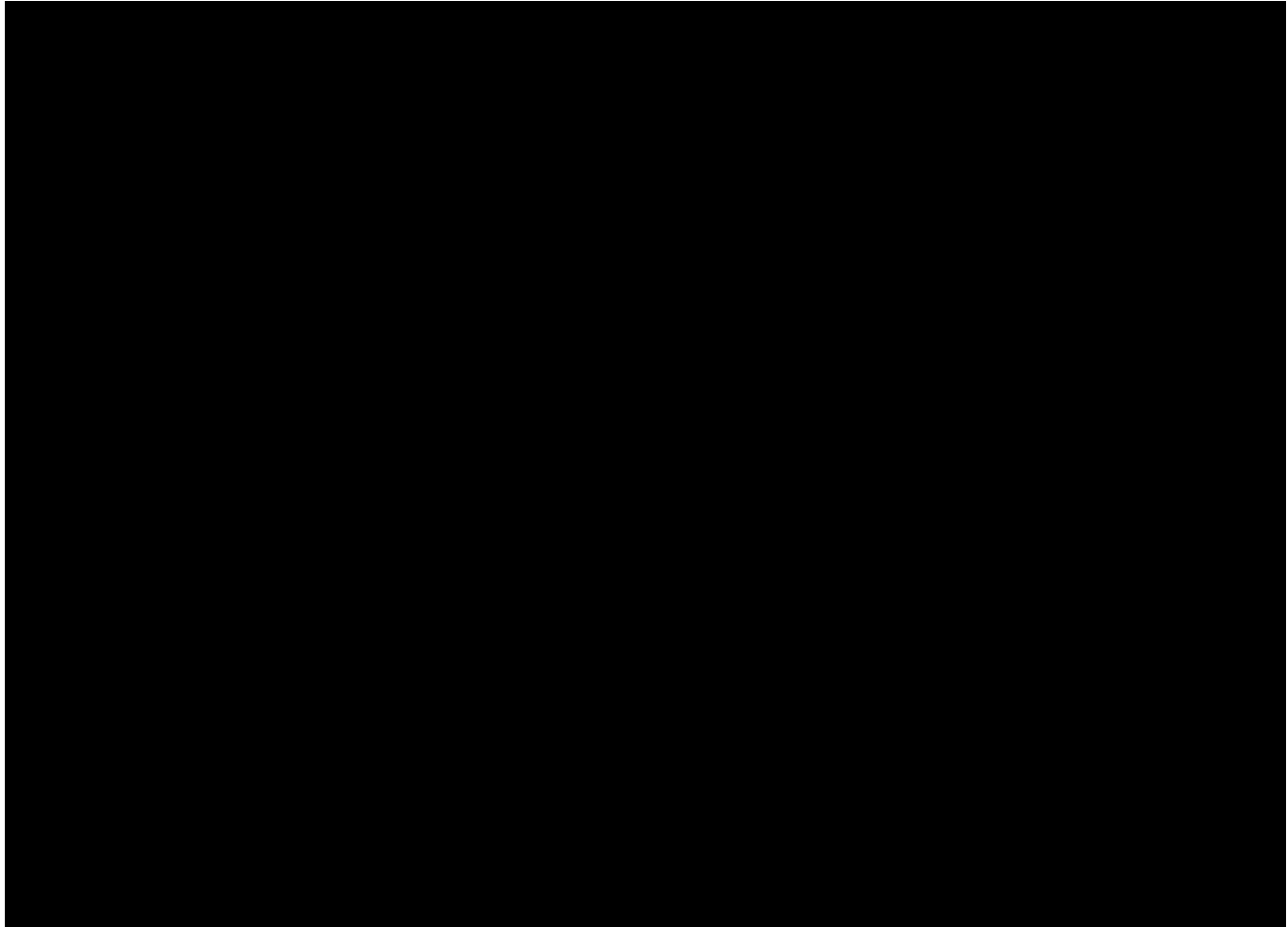
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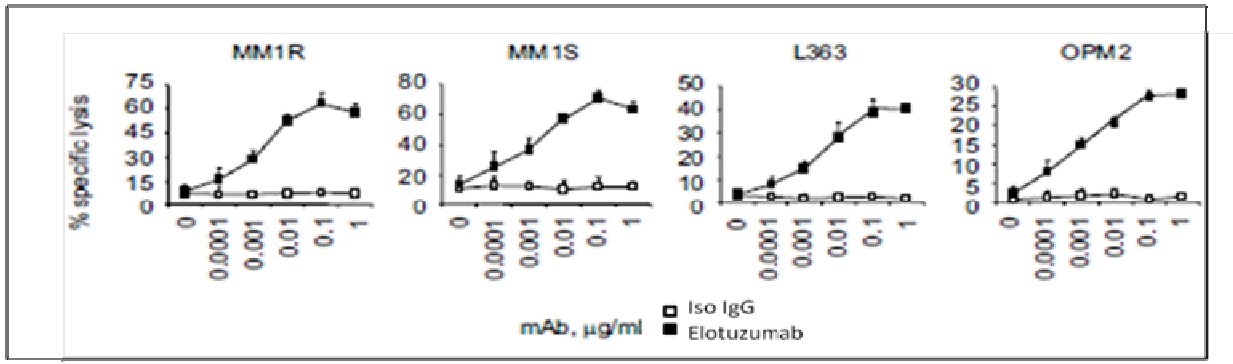
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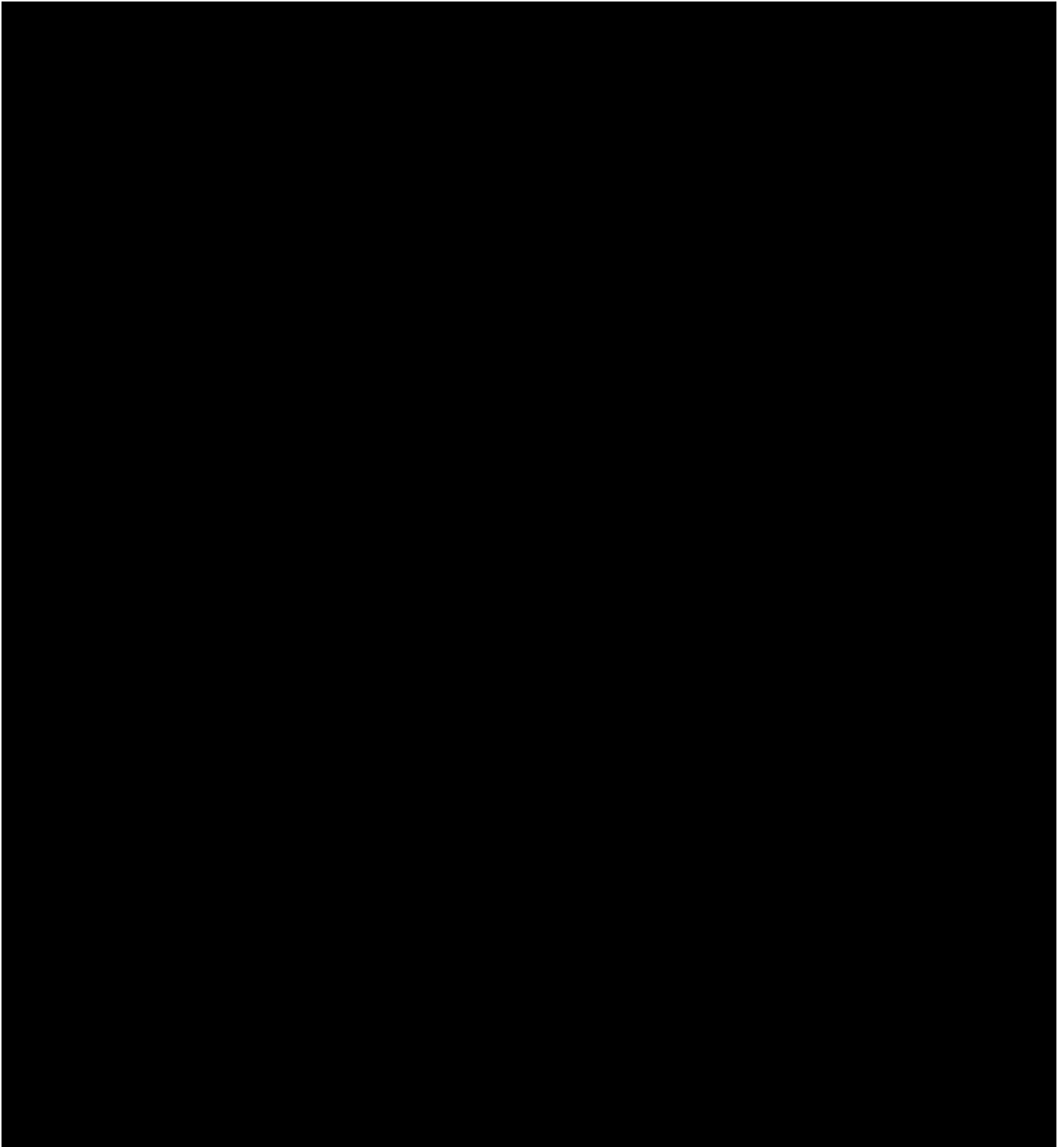


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1.3 Objectives(s)

1.3.1 Primary Objectives

- To compare progression free survival (PFS) between treatment arms.

1.3.2 Secondary Objectives

- To compare objective response rate between treatment arms
- To compare overall survival between treatment arms

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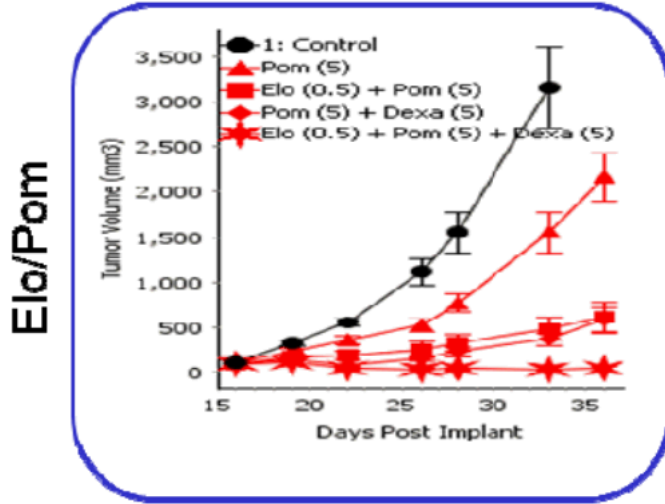
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combination with Ld at the accelerated infusion rate over approximately 60 min (a maximum

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2 ETHICAL CONSIDERATIONS

2.1 Good Clinical Practice

This study will be conducted in accordance with Good Clinical Practice (GCP), as defined by the International Conference on Harmonisation (ICH) and in accordance with the ethical principles underlying European Union Directive 2001/20/EC and the United States Code of Federal Regulations, Title 21, Part 50 (21CFR50).

The study will be conducted in compliance with the protocol. The protocol and any amendments and the subject informed consent will receive Institutional Review Board/Independent Ethics Committee (IRB/IEC) approval/favorable opinion prior to initiation of the study.

All potential serious breaches must be reported to BMS immediately. A serious breach is a breach of the conditions and principles of GCP in connection with the study or the protocol, which is likely to affect, to a significant degree, the safety or physical or mental integrity of the subjects of the study or the scientific value of the study.

Personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective tasks.

This study will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (eg, loss of medical licensure, debarment).

2.2 Institutional Review Board/Independent Ethics Committee

Before study initiation, the investigator must have written and dated approval/favorable opinion from the IRB/IEC for the protocol, consent form, subject recruitment materials (eg, advertisements), and any other written information to be provided to subjects. The investigator or BMS should also provide the IRB/IEC with a copy of the Investigator Brochure or product labeling information to be provided to subjects and any updates.

The investigator or BMS should provide the IRB/IEC with reports, updates and other information (eg, expedited safety reports, amendments, and administrative letters) according to regulatory requirements or institution procedures.

2.3 Informed Consent

Investigators must ensure that subjects are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which they volunteer to participate.

In situations where consent cannot be given to subjects, their legally acceptable representatives (as per country guidelines) are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which the subject volunteers to participate.

BMS will provide the investigator with an appropriate (ie, Global or Local) sample informed consent form which will include all elements required by ICH, GCP and applicable regulatory requirements. The sample informed consent form will adhere to the ethical principles that have their origin in the Declaration of Helsinki.

Investigators must:

Provide a copy of the consent form and written information about the study in the language in which the subject is most proficient prior to clinical study participation. The language must be non-technical and easily understood.

Allow time necessary for subject or subject's legally acceptable representative to inquire about the details of the study.

Obtain an informed consent signed and personally dated by the subject or the subject's legally acceptable representative and by the person who conducted the informed consent discussion.

Obtain the IRB/IEC's written approval/favorable opinion of the written informed consent form and any other information to be provided to the subjects, prior to the beginning of the study, and after any revisions are completed for new information.

If informed consent is initially given by a subject's legally acceptable representative or legal guardian, and the subject subsequently becomes capable of making and communicating his or her informed consent during the study, consent must additionally be obtained from the subject.

Revise the informed consent whenever important new information becomes available that is relevant to the subject's consent. The investigator, or a person designated by the investigator, should fully inform the subject or the subject's legally acceptable representative or legal guardian, of all pertinent aspects of the study and of any new information relevant to the subject's willingness to continue participation in the study. This communication should be documented.

The confidentiality of records that could identify subjects must be protected, respecting the privacy and confidentiality rules applicable to regulatory requirements, the subjects' signed ICF and, in the US, the subjects' signed HIPAA Authorization.

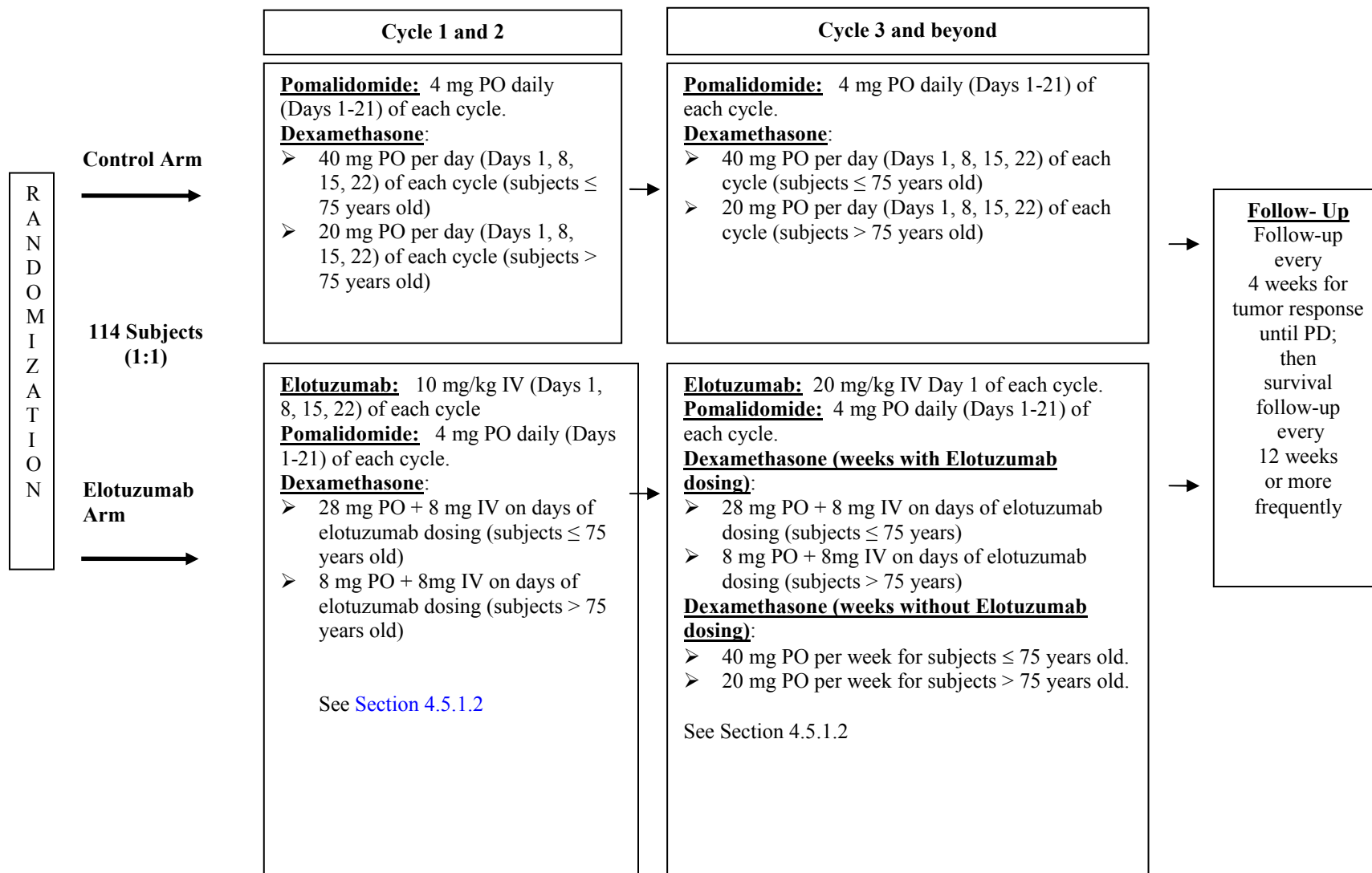
The consent form must also include a statement that BMS and regulatory authorities have direct access to subject records.

The rights, safety, and well-being of the study subjects are the most important considerations and should prevail over interests of science and society.

[REDACTED]

A cycle is defined as 28 days.

Table 3.1-1: Study Design Schematic



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3.2 Post Study Access to Therapy

At the conclusion of the study, subjects who continue to demonstrate clinical benefit will be eligible to receive study drug. Study drug will be provided via an extension of the study, a rollover study requiring approval by responsible health authority and ethics committee or through another mechanism at the discretion of BMS. BMS reserves the right to terminate access to study drug if any of the following occur: a) the marketing application is rejected by responsible health authority; b) the study is terminated due to safety concerns; c) the subject can obtain medication from a government sponsored or private health program; or d) therapeutic alternatives become available in the local market.

3.3 Study Population

For entry into the study, the following criteria MUST be met.

3.3.1 Inclusion Criteria

1) Signed Written Informed Consent

- a) Subject is, in the investigator's opinion, willing and able to comply with the protocol requirements.
- b) Subject has given voluntary written informed consent before performance of any study-related procedure not part of normal medical care, with the understanding that consent may be withdrawn by the subject at any time without prejudice to their future medical care.

2) Target Population

- a) Must have received ≥ 2 prior lines of therapy (See Appendix 1) which must have included at least 2 consecutive cycles of lenalidomide and a proteasome inhibitor alone or in combination.
- b) Documented refractory or relapsed and refractory (R/R) multiple myeloma
- c) Refractory (progressed on or within 60 days of treatment) to their last treatment.
- d) Subjects must have failed treatment with a proteasome inhibitor and lenalidomide in one of the following ways⁴¹.
 - i) "Refractory" to proteasome inhibitor and lenalidomide, and to their last treatment.
 - ii) "Relapsed and refractory"= patients had achieved at least a partial response to previous treatment with proteasome inhibitor or lenalidomide, or both, but progressed within 6 months, and were refractory to their last treatment.

- e) Measurable disease at screening, based on central lab results, defined as one or more of the following:
 - i) Serum IgG, IgA, or IgM M-protein ≥ 0.5 g/dL (5 g/L).
 - ii) Urine M-Protein ≥ 200 mg (0.2 g) excreted in a 24-hour collection sample
 - iii) Involved serum free light chain (sFLC) ≥ 100 mg/L (10 mg/dL) provided the FLC ratio is abnormal.
- f) Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2 .

3) Age and Reproductive Status

- a) Males and Females at least 18 years or legal age of consent per local regulations.
- b) Women of childbearing potential (WOCBP) must have two negative serum or urine pregnancy tests (minimum sensitivity 25 mIU/mL or equivalent units of HCG). One 10-14 days prior to start of the study drug and one 24 hours prior to the start of study drug. See [Section 3.3.3](#) for the definition of WOCBP.
- c) Women must not be breastfeeding.
- d) WOCBP must agree to follow instructions for method(s) of contraception for 4 weeks before the start of treatment with study drugs, for the duration of treatment with study drugs, and for a total of 120 days post-treatment completion.
- e) Males who are sexually active with WOCBP must always use a latex or synthetic condom during any sexual contact with females of reproductive potential, even if they have undergone a successful vasectomy. They must also agree to follow instructions for method(s) of contraception for 4 weeks before the start of treatment with study drugs, for the duration of treatment with study drugs, and for a total of 180 days post-treatment completion.
- f) Male patients must not donate sperm, for up to 180 days post treatment completion.
- g) Azoospermic males and WOCBP who are not heterosexually active are exempt from contraceptive requirements. However they must still undergo pregnancy testing as described in this section.
- h) All Subjects must not donate blood for 90 days post treatment completion.
- i) All subjects must be willing and able to comply with the local pomalidomide risk management program or the Pomalidomide Pregnancy Risk Prevention Plan.
- j) All subjects must agree not share study medication.

Investigators shall counsel WOCBP and male subjects who are sexually active with WOCBP on the importance of pregnancy prevention and the implications of an unexpected pregnancy. Investigators shall advise WOCBP and male subjects who are sexually active with WOCBP on the use of highly effective methods of contraception. Highly effective methods of contraception have a failure rate of $< 1\%$ when used consistently and correctly.

At a minimum, subjects must agree to the use of two methods of contraception, with one method being highly effective and the other method being either highly effective or less effective as listed in the informed consent document.

3.3.2 Exclusion Criteria

1) Target Disease Exceptions

- a) Subjects with solitary bone or extramedullary plasmacytoma as the only evidence of plasma cell dyscrasia.
- b) Subjects with monoclonal gammopathy of undetermined significance (MGUS), smoldering multiple myeloma (SMM), amyloidosis, Waldenstrom's macroglobulinemia, or POEMS syndrome (plasma cell dyscrasia with poly neuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes)
- c) Subjects with active plasma cell leukemia (defined as either 20% of peripheral blood white blood cell count comprised of plasma/CD138+ cells or an absolute plasma cell count of $2 \times 10^9/L$)

2) Medical History and Concurrent Diseases

- a) Any uncontrolled or severe cardiovascular or pulmonary disease determined by the investigator, including:
 - i) NYHA functional classification III or IV, congestive heart failure, unstable or poorly controlled angina, hypertension, arrhythmia, or myocardial infarction in the past 12 months.
- b) Active infection that requires parenteral anti-infective treatment > 14 days
- c) Unable to tolerate thromboembolic prophylaxis while on the study
- d) Hypersensitivity reaction to prior IMiD (thalidomide or lenalidomide)
- e) Grade ≥ 2 peripheral neuropathy (per NCI CTCAE v3.0)
- f) Known active hepatitis A, B, or C
- g) Known HIV infection
- h) Gastrointestinal disease that may significantly alter the absorption of pomalidomide
- i) Prior or concurrent malignancy, except for the following:
 - i) Adequately treated basal cell or squamous cell skin cancer.
 - ii) Any cancer (other than in-situ) from which the subject has been disease free for > 3 years prior to study entry.

3) Prior Therapy or Surgery

- a) Prior treatment with pomalidomide.
- b) Prior participation in an elotuzumab clinical trial regardless of treatment assignment.
- c) Use of any anti-myeloma drug therapy, within 14 days of the initiation of study drug treatment or use of any experimental drug therapy or plasmapheresis within 28 days (or 5 half-lives) whichever is longer of the initiation of study drug treatment (includes dexamethasone). Bisphosphonate use permitted.
- d) Treatment with melphalan or monoclonal antibodies within 6 weeks of the first dose of study drug
- e) Prior autologous stem cell transplant within 12 weeks of the first dose of study drug.
- f) Prior allogeneic stem cell transplant—except subjects who have completed the stem cell transplant > 12 months prior to first dose of study drug, have no history of graft versus host disease, and are not on topical or systemic immunosuppressive therapy

- g) Treatment with corticosteroids within 3 weeks of the first dose of study drug, except for the equivalent of ≤ 10 mg prednisone per day or corticosteroids with minimal to no systemic absorption (ie, topical or inhaled steroids) or for short course (≤ 4 days) of 40 mg dexamethasone or equivalent for emergency use (baseline M proteins must be drawn after this short course and prior to randomization).
- h) Major cardiac surgery within 8 weeks prior to the first dose of study drug; all other major surgery within 4 weeks prior to the first dose of study drug. (Kyphoplasty is not considered major surgery); subjects should have been fully recovered from any surgical related toxicities.

4) Physical and Laboratory Test Findings

- a) Corrected serum calcium ≥ 11.5 mg/dl (see equation in [Section 5.4.2](#)) within 2 weeks of randomization (despite appropriate measures such a short course of steroids, bisphosphonates, hydration, calcitonin).
- b) Absolute neutrophil count $< 1 \times 10^9/L$ (1000/uL). No growth factors allowed within 1 week of first dose of study drug. No pegylated growth factors within 3 weeks of randomization.
- c) Platelets $< 75 \times 10^9/L$ (75,000/uL) ($< 30 \times 10^9/L$ if $\geq 50\%$ of bone marrow nucleated cells were plasma cells). Qualifying laboratory value must occur at most recent measurement prior to randomization and must be no more than 14 days prior to randomization. No transfusions are allowed within 72 hours prior to qualifying laboratory value.
- d) Hemoglobin < 80 g/L (8g/dL). Qualifying laboratory value must occur at most recent measurement prior to randomization and must be no more than 14 days prior to randomization. No transfusions are allowed within 72 hours prior to qualifying laboratory value
- e) Creatinine clearance < 45 ml/min according to the Cockcroft-Gault formula.
 - 1) Female $CrCl = \frac{(140 - \text{age in years}) \times \text{body weight in kg} \times 0.85}{72 \times \text{serum creatinine in mg/dl}}$
 - 2) $72 \times \text{serum creatinine in mg/dl}$
 - 3) Male $CrCl = \frac{(140 - \text{age in years}) \times \text{body weight in kg} \times 1.00}{72 \times \text{serum creatinine in mg/dl}}$
 - 4) $72 \times \text{serum creatinine in mg/dl}$

Qualifying serum creatinine value must occur at most recent measurement prior to randomization and must be no more than 14 days prior to randomization.

- f) Total bilirubin $\geq 2 \times ULN$
 - i) Subjects with known Gilbert's syndrome must NOT have a total bilirubin $\geq 3 \times ULN$ and must have a direct bilirubin within the institutional limit of normal
- g) Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) $\geq 3 \times ULN$

5) Other Exclusion Criteria

- a) Known hypersensitivity or intolerance to lenalidomide, dexamethasone, or any excipients in elotuzumab, formulation or recombinant protein.

- b) Sexually active fertile men not using 2 forms of effective birth control if their partners are WOCBP.
- c) Prisoners or subjects who are involuntarily incarcerated.
- d) Subjects who are compulsorily detained for treatment of either a psychiatric or physical (eg, infectious disease) illness.

Eligibility criteria for this study have been carefully considered to ensure the safety of the study subjects and that the results of the study can be used. It is imperative that subjects fully meet all eligibility criteria.

3.3.3 Women of Childbearing Potential

Women of childbearing potential (WOCBP), as defined by the local pomalidomide risk management program or the Pomalidomide Pregnancy Risk Prevention Plan, must also include all females who are menstruating, amenorrheic from previous medical treatments, under 50 years of age, and/or perimenopausal, and do not qualify for the category “females not of reproductive potential”.

Females not of reproductive potential, as defined by the local pomalidomide risk management program or the Pomalidomide Pregnancy Risk Prevention Plan, include females who have been in natural menopause for at least 24 consecutive months, or who have had a hysterectomy and/or bilateral oophorectomy.

Females treated with hormone replacement therapy, (HRT) are likely to have artificially suppressed FSH levels and may require a washout period in order to obtain a physiologic FSH level. The duration of the washout period is a function of the type of HRT used. The duration of the washout period below are suggested guidelines and the investigators should use their judgment in checking serum FSH levels. If the serum FSH level is > 40 mIU/ml at any time during the washout period, the woman can be considered postmenopausal:

- 1 week minimum for vaginal hormonal products (rings, creams, gels)
- 4 week minimum for transdermal products
- 8 week minimum for oral products

Other parenteral products may require washout periods as long as 6 months.

3.4 Concomitant Treatments

3.4.1 Required

Subjects must receive thrombo-embolic prophylaxis, per institutional guidelines or PI discretion. Examples of commonly used thrombo-embolic prophylaxis medications include aspirin, low molecular weight heparin, and vitamin K antagonists.

Subjects must receive pre-medications ([Sections 4.5.1.4](#) and [4.5.1.5](#)) prior to each dose of elotuzumab.

3.4.2 Permitted at Investigator's Discretion

IV corticosteroids, diphenhydramine, or hydroxyzine, acetaminophen/ paracetamol, H2 inhibitors (ie, cimetidine), leukotriene inhibitors (montelukast sodium) for the management of infusion reactions. Additional supportive measures should be provided as indicated including:

- oxygen inhalation
- epinephrine
- bronchodilators
- oral antiviral and antimicrobial prophylaxis
- anti-emetics
- bisphosphonates

Per the ASCO 2007 Clinical Practice Guidelines⁴², bisphosphonate therapy should be administered for a period of 2 years. At 2 years, the investigator should seriously consider discontinuing bisphosphonates in subjects with at least stable disease, although further use is at the discretion of the investigator.

Routine clinical practice for monitoring and prevention of osteonecrosis of the jaw (ie, comprehensive dental exam, treating active oral infections, eliminating sites of high risks for oral infection, excellent oral hygiene and avoiding invasive dental procedures while on treatment) must be followed.

- Erythropoietin (EPO) or erythropoiesis stimulating agents (prior and ongoing use according to the package insert and institutional guidelines)
- Red blood cell or platelet transfusion
- Prophylactic administration of G-CSF for neutropenic subjects or therapeutic use in subjects with serious neutropenic complications (such as tissue infection, sepsis syndrome or fungal infection) may be considered at the investigator's discretion, consistent with American Society of Clinical Oncology guidelines (American Society of Clinical Oncology 2006).

3.4.3 Prohibited and/or Restricted Treatments

Any systemic, anti-myeloma therapy other than pomalidomide, dexamethasone, and elotuzumab are prohibited while on study therapy. Concomitant steroids, other than weekly dexamethasone [Section 4.5.1](#) or steroids allowed (as defined in eligibility criteria) are prohibited unless used to treat an adverse event. Guidelines for selection and use of other concomitant medications should be derived from the pomalidomide and dexamethasone prescribing information.

Avoid co-administration of pomalidomide with strong inhibitors of CYP1A2 unless medically necessary. Co-administration of pomalidomide with drugs that are strong inhibitors of CYP1A2 (eg, ciprofloxacin, enoxacin and fluvoxamine) and CYP3A4/5 (eg, ketoconazole) or P-gp could increase pomalidomide exposure and should be avoided, unless medically necessary^{43, 44}.

Other than study medications, administration of any therapeutic or diagnostic investigational agent (for any indication) is prohibited while on study therapy without prior Sponsor approval.

3.4.4 Surgery and Radiation

Use of radiotherapy or surgical intervention must be recorded on the appropriate Case Report Form.

Localized radiation therapy to a site of pre-existing disease may be permitted while on study. Following approval by the medical monitor, the patient may continue with protocol therapy without interruption during the course of palliative radiation therapy if the investigator believes that the risk of excessive bone marrow suppression or other toxicity is acceptable, and it is in the best interest of the patient to do so.

If the subject develops a definite increase in the size of existing bone lesions or soft tissue plasmacytomas that meets the criteria for disease progression ([Appendix 6](#)), treatment must be discontinued for progressive disease regardless of whether radiation therapy is initiated (Section 3.5).

Kyphoplasty, vertebroplasty, or emergency orthopedic surgery is permitted.

3.5 Discontinuation of Subjects following any Treatment with Study Drug

Subjects MUST discontinue investigational product (and non-investigational product at the discretion of the investigator) for any of the following reasons:

- Withdrawal of informed consent (subject's decision to withdraw for any reason)
- Any clinical adverse event (AE), laboratory abnormality or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the subject.
- Pregnancy (Subjects must discontinue elotuzumab and pomalidomide).
- Termination of the study by Bristol-Myers Squibb (BMS).
- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness.
- Progressive Disease ([Appendix 6](#))
- Subjects who receive any non-protocol specified systemic anti-myeloma therapy before documented progression will be discontinued from all study treatment (including pomalidomide/dexamethasone); however, tumor assessments will continue at 4 week intervals until documented progression.
- Subjects experiencing a Grade 4 infusion reaction must discontinue elotuzumab. Subjects may continue pomalidomide and dexamethasone treatment. Refer to [Section 4.5.2.3](#).
- Subjects experiencing angioedema, Grade 4 rash, exfoliative or bullous rash, Stevens-Johnson syndrome, or toxic epidermal necrolysis related to pomalidomide must discontinue pomalidomide. Subjects in the elotuzumab arm may continue elotuzumab and dexamethasone.
- Subjects experiencing a 56 day delay in all study drugs (pomalidomide, dexamethasone, and elotuzumab) due to an adverse event(s) related to study treatment must be discontinued from

study drug. Subjects experiencing delays unrelated to study therapy, for example due to radiation therapy, may delay study treatment up to 84 days. Further delays may be allowed after discussion with the BMS Medical Monitor. Delays greater than 28 days must be discussed with the medical monitor.

In the case of pregnancy, the investigator must immediately notify the BMS Medical Monitor/designee of this event. In most cases, the study drug will be permanently discontinued in an appropriate manner. If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study drug, a discussion between the investigator and the BMS Medical Monitor/designee must occur.

All subjects who discontinue study drug should comply with protocol specified follow-up procedures as outlined in [Table 5.1-3](#). The only exception to this requirement is when a subject withdraws consent for all study procedures or loses the ability to consent freely (ie, is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).

If study drug is discontinued prior to the subject's completion of the study, the reason for the discontinuation must be documented in the subject's medical records and entered on the appropriate case report form (CRF) page.

3.6 Post Study Drug Study Follow up

PFS and OS are key endpoints of the study. Post treatment study follow-up is essential to preserving subject safety and the integrity of the study. Subjects who discontinue study treatment prior to progression must continue to be followed for collection of protocol-defined PFS. Subjects who discontinue study therapy must also continue to be followed for overall survival data until death or the conclusion of the study.

BMS may request that survival data be collected on all randomized subjects outside of the protocol defined window, [Table 5.1-3](#). At the time of this request, each subject will be contacted to determine their survival status unless the subject has withdrawn consent for all contact.

3.6.1 Withdrawal of Consent

Subjects should be encouraged to continue participation in the trial until the laboratory definition of disease progression is met ([Appendix 6](#)). **Subjects who discontinue study therapy before progression (eg, due to toxicity) should be encouraged to allow the necessary laboratory results (eg, M-protein data, sFLC data, radiologic data, calcium results) to be collected until disease progression criteria are fulfilled, even if the subject is on subsequent therapy (see [Section 8.3.1](#)).** Central laboratory assessments are preferred; however assessments may also be completed locally. Local lab data can be obtained by the subjects' local health care provider or the site staff. Site staff will enter local lab data into the CRF/database. Withdrawal of consent should be minimized because:

1. The subject in this trial who discontinues study therapy before progression will most likely be followed by a healthcare provider locally or at the site via routine standard of care assessments (ie, monthly M-protein data, calcium, etc) and

2. In most cases, this protocol would not require any additional samples beyond those considered standard of care.

If there is uncertainty about the disease progression criteria, investigators are encouraged to contact the BMS Medical Monitor/study director prior to:

1. starting a subject on another myeloma regimen or
2. performing the end of treatment visit for progression

Subjects who request to discontinue study drug will remain in the study and must continue protocol specified follow-up procedures. The only exception to this is when a subject specifically withdraws consent for any further contact with him/her or persons previously authorized by subject to provide this information. Subjects should notify the investigator of the decision to withdraw consent from future follow-up **in writing**, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator as to whether the withdrawal is from further:

1. Study medication but subject is willing to continue to perform visits for PFS follow-up.
2. Study medication and study visits for PFS but agrees to provide the results of future myeloma assessments from another site/local site.
3. Study treatments and results from another site/local sites, but agrees to be contacted for overall survival follow-up.
4. Study treatments and results from another site/local sites, and does not agree to be contacted for overall survival follow-up.

In the event that vital status (whether the subject is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law

3.6.2 Lost to Follow-Up

All reasonable efforts must be made to locate subjects to determine and report their ongoing status. This includes follow-up with persons authorized by the subject as noted above. Lost to follow-up is defined by the inability to reach the subject after a minimum of three documented phone calls, faxes, or emails as well as lack of response by subject to one registered mail letter. All attempts should be documented in the subject's medical records. If it is determined that the subject has died, the site will use permissible local methods to obtain the date and cause of death.

If investigator's use of third-party representative to assist in the follow-up portion of the study has been included in the subject's informed consent, then the investigator may use a Sponsor-retained third-party representative to assist site staff with obtaining subject's contact information or other public vital status data necessary to complete the follow-up portion of the study. The site staff and representative will consult publicly available sources, such as public health registries, obituary listings, and databases, in order to obtain updated contact information.

If after all attempts, the subject remains lost to follow-up, then the last known alive date as determined by the investigator should be reported and documented in the subject's medical records

4 STUDY DRUG

All protocol-specified investigational and non-investigational products are considered study drug

Table 4-1: Study Drugs for CA204125					
Product Description / Class and Dosage Form	Potency	IMP/Non-IMP	Blinded or Open Label	Packaging / Appearance	Storage Conditions (per label)
Elotuzumab Powder for Solution for Infusion	400 mg/vial	IMP	Open Label	20 mL Vial/ Sterile, white to off-white, preservative-free, lyophilized cake	Store at 2°C - 8°C
Dexamethasone Tablets	2 mg and 4 mg & various strengths	Non-IMP	NA	Various packing configurations	Refer to label on container or package insert / summary of product characteristics
Dexamethasone Solution	4 mg/mL, 8 mg/mL & various strengths	Non-IMP	NA	Various packing configurations	Refer to label on container or package insert / summary of product characteristics
Pomalidomide Capsules	1 mg, 2 mg, 3 mg and 4 mg	Non-IMP	Open label	Various packing configurations	Refer to label on container or package insert

Dexamethasone tablets and solution for IV infusion may be obtained by the investigating site’s standard prescribing procedures. Pomalidomide (Pomalyst[®]) may be supplied by BMS centrally or through site standard prescribing procedure.

4.1 Investigational Product

An investigational product, also known as investigational medicinal product in some regions, is defined a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical study, including products already with a marketing authorization but used or assembled (formulated or packaged) differently than the authorized form, or used for an unauthorized indication, or when used to gain further information about the authorized form.

The investigational product should be stored in a secure area according to local regulations. It is the responsibility of the investigator to ensure that investigational product is only dispensed to study subjects. The investigational product must be dispensed only from official study sites by authorized personnel according to local regulations.

In this protocol, investigational product is: Elotuzumab powder for solution for infusion.

4.1.1 *Elotuzumab*

Before administration the drug product should be stored and prepared as per the instructions in [Appendix 5](#). The dose of elotuzumab to be administered to a subject will be calculated by multiplying the subject's weight (kg) by 10 mg/kg in Cycles 1 and 2 (20 mg/kg for Cycle 3 and beyond). The subject's predose weight on Day 1 of each cycle will be used to calculate the dose for each cycle. Each dose should be infused as per instructions in [Appendix 5](#). The infusion start and stop time will be recorded in the CRF. If the infusion is stopped mid-session for any reason, the stop/start time must be recorded together with an explanation.

4.2 Non-Investigational Product

Other medications used in the study as support or escape medication for preventative, diagnostic, or therapeutic reasons, as components of the standard of care for a given diagnosis, are considered non-investigational products.

In this protocol, non-investigational product(s) are: Pomalidomide (Pomalyst[®]) capsules 1 mg, 2 mg, 3 mg, and 4 mg, dexamethasone tablets and concentrate for solution for IV infusion, or products used for Elotuzumab premedication ([Section 4.5.1.4](#)) or thromboprophylaxis ([Section 3.4.1](#)).

4.2.1 *Pomalidomide*

Pomalidomide is an analogue of thalidomide. Thalidomide is a known human teratogen that causes severe life-threatening human birth defects. If pomalidomide is taken during pregnancy, it may cause birth defects or death to an unborn baby. Females must not get pregnant: (1) for at least 4 weeks before starting pomalidomide, (2) while taking pomalidomide, (3) during any interruptions in pomalidomide treatment and (4) for at least 120 days after their last dose of pomalidomide. Furthermore, subjects taking pomalidomide should refrain from donating blood (until at least 90 days) or sperm (until at least 180 days) after last dose of pomalidomide.

Because of this potential toxicity and to avoid fetal exposure to pomalidomide, pomalidomide is only available under a special restricted distribution program. Each risk management program is country or region specific. Under these programs, only prescribers and pharmacists registered

with the program can prescribe and dispense the product. In addition, pomalidomide must only be dispensed to subjects who are registered and meet all the conditions of the local pomalidomide risk management program or meet all the conditions of the Pomalidomide Pregnancy Risk Prevention Plan. Subjects who have the potential of pregnancy must be instructed about contraception and undergo the scheduled pregnancy tests.

All study participants must be registered into the local, mandatory pomalidomide risk management program or follow the Pomalidomide Pregnancy Risk Prevention Plan, and be willing and able to comply with all requirements.

Please see the US package insert/SmPC for additional information for prescribing to female subjects and male subjects about this restricted distribution program.

Subjects should not break, chew or open the capsules. Pomalidomide should be taken without food (at least 2 hours before or 2 hours after a meal). Only enough pomalidomide for one cycle of therapy will be supplied to the patient each cycle in accordance with the local pomalidomide risk management program or the Pomalidomide Pregnancy Risk Prevention Plan.

WOCBP must have negative pregnancy testing and use contraception methods before initiating pomalidomide.

The trade name of pomalidomide may vary in other countries. In such cases, refer to country trade name.

4.2.2 Dexamethasone

Dexamethasone tablets and solution for IV infusion is considered NIMP for this study and will not be provided by the sponsor. It will be obtained by the investigating sites standard prescribing procedures except where it may be supplied by BMS due to country availability and specific regulatory requirements. Marketed product will be utilized for this study and should be stored in accordance with the package insert or summary of product characteristics (SmPC). See [Table 4.5.1.5-1](#) for dexamethasone dose reduction information if infusion reaction is observed.

4.3 Storage and Dispensing

The product storage manager should ensure that the study drug is stored in accordance with the environmental conditions (temperature, light, and humidity) as determined by BMS. If concerns regarding the quality or appearance of the study drug arise, do not dispense the study drug and contact BMS immediately.

The investigator (or assigned designee, ie, study pharmacist) will dispense the proper number of each strength tablet to the subject to satisfy dosing requirements until the subject's next visit. The subject must be instructed to return all unused study medications in the provided packaging at each subsequent visit.

Procedures for proper handling and disposal of anticancer drugs should be considered.

Study drug not supplied by BMS will be stored in accordance with the package insert.

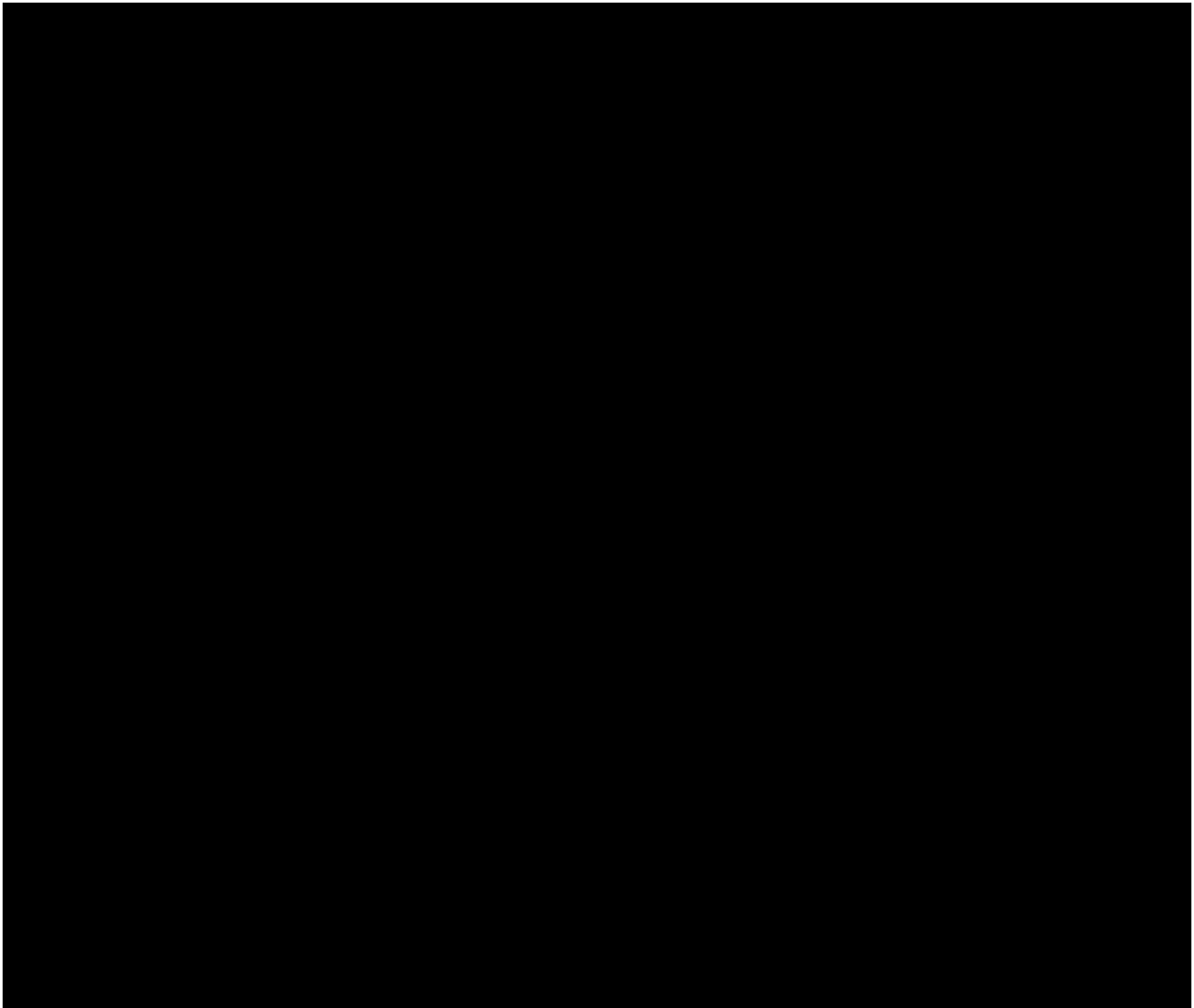
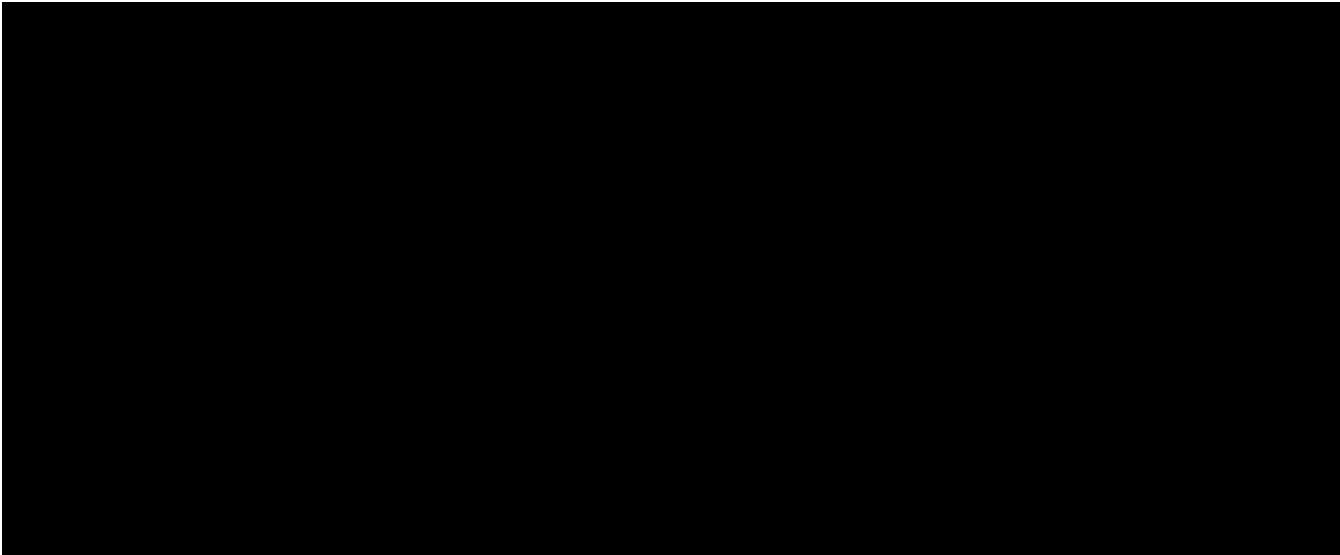
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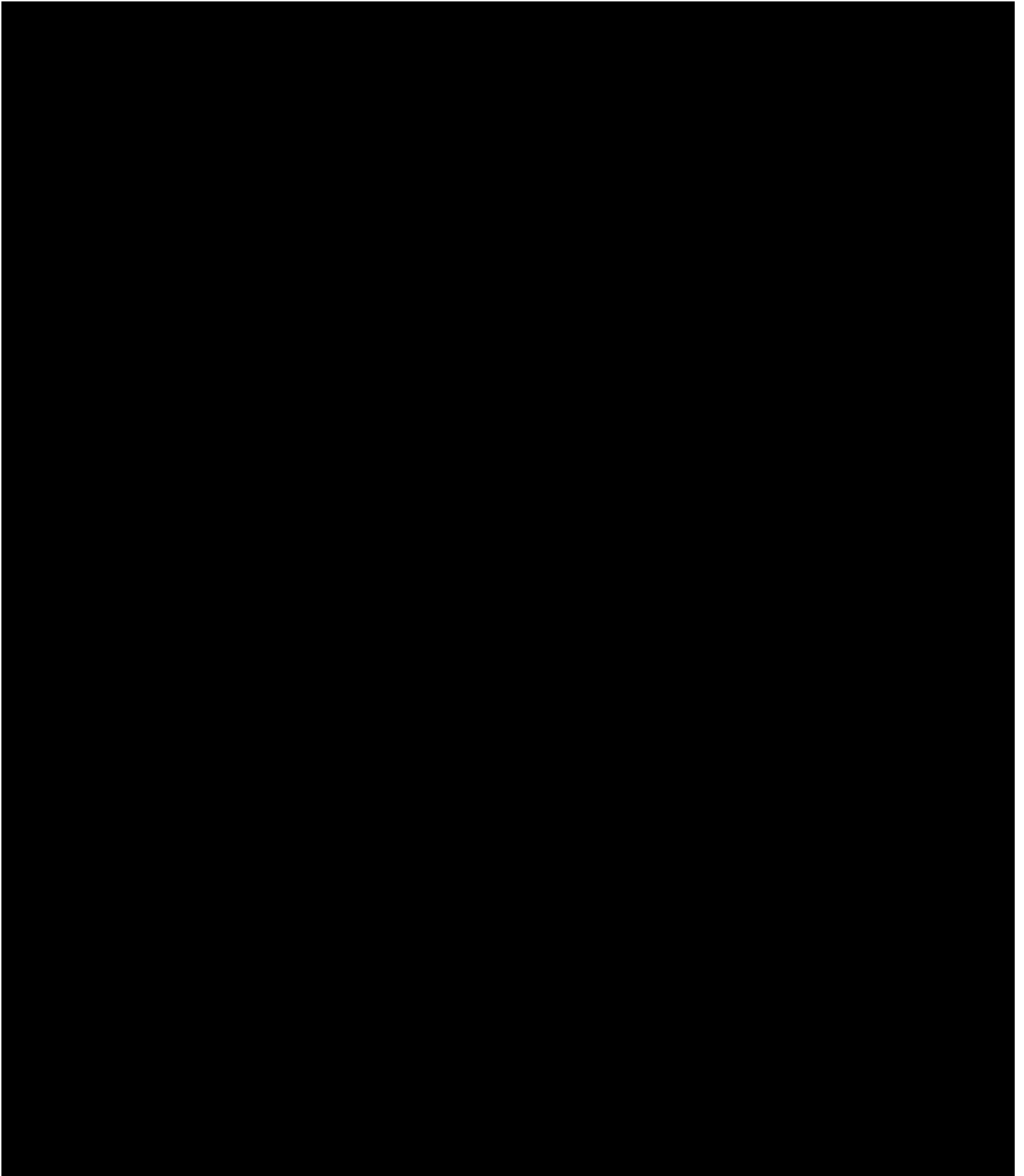
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4.5.2 Guidelines for Elotuzumab Infusion in Subjects with Infusion Reactions

4.5.2.1 Grade 1 Infusion Reaction

For Grade 1 elotuzumab infusion-related reactions, by definition, do not require intervention. However, increased monitoring is recommended.

4.5.2.2 Grade \geq 2 Infusion Reaction

Infusion reactions during the elotuzumab infusion: For a Grade \geq 2 elotuzumab infusion-related reaction, the infusion must be interrupted. The subject should be treated as clinically indicated with one or more of the following medications or interventions: antiemetics, antihistamines, analgesics, corticosteroids, leukotriene inhibitors, oxygen inhalation, epinephrine, bronchodilators, or other supportive measures as indicated. Subjects with a Grade 4 elotuzumab infusion reaction, see Section 4.5.2.3.

For Grade 2 or 3 infusion reactions, once the elotuzumab infusion-related reaction has resolved to Grade \leq 1, the infusion can be restarted at 0.5 mL/minute. If symptoms do not recur after 30 minutes, the infusion rate may be increased in a stepwise fashion starting at a rate per investigator's discretion, and increasing up to a rate per investigator's discretion, up to a maximum of 5 mL/minute.

Subjects who experience an infusion reaction require vital signs to be monitored every 30 minutes for 2 hours after the end of the elotuzumab infusion. If the elotuzumab infusion reaction recurs, the infusion must be stopped and not restarted on that day. Appropriate therapy should be administered to address the subject's signs and symptoms. The infusion can be reattempted at the next protocol defined infusion time point at the investigator's discretion with additional premedication as described in [Table 4.5.1.5-1](#).

Infusion reactions after the completion of elotuzumab infusion: Should a Grade \geq 2 infusion reaction occur following completion of an elotuzumab infusion, the subject should be treated as above.

Elotuzumab infusions on subsequent weeks after a prior Grade 2 or 3 infusion reaction: Subjects with a prior Grade 2 or 3 infusion reaction during Cycle 1 should have the subsequent infusion started at 0.5 mL/min. The infusion rate may be escalated in a stepwise fashion (0.5 mL/minute every 30 minutes) to a maximum of 5 mL/minute on that day. If no Grade \geq 2 infusion reaction occurs, the next infusion may be increased in a stepwise fashion starting at a rate per investigators' discretion, and up to a maximum of 5 mL/minute. If tolerated, all subsequent infusions may start at a rate per investigator's discretion, up to a maximum rate of 5 mL/minute.

Contact the Medical Monitor with any questions regarding elotuzumab infusion rate escalation.

4.5.2.3 Grade 4 Infusion Reaction

Acute symptoms should be managed as described in Section 4.5.2.2. Elotuzumab must be permanently discontinued. Subjects may continue with pomalidomide and dexamethasone per protocol.

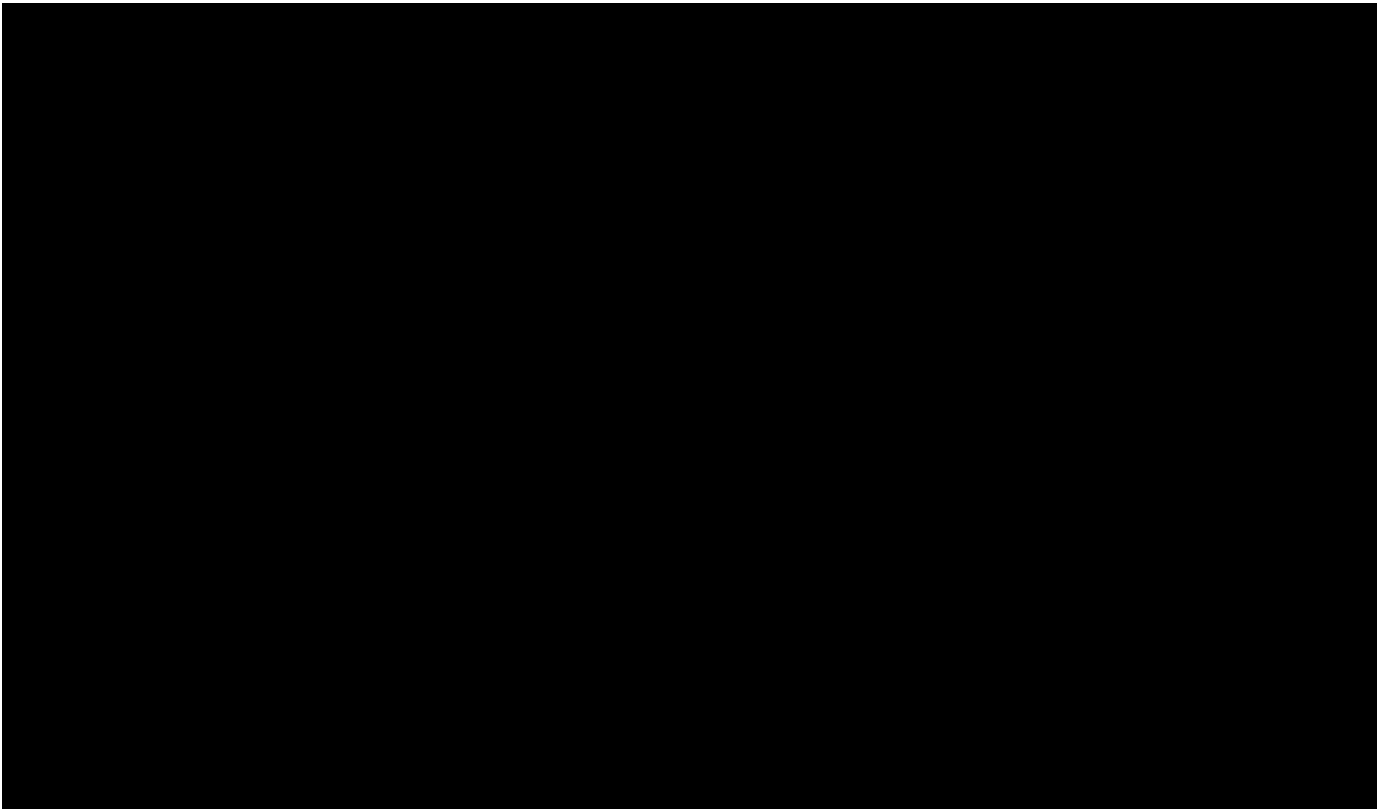
4.5.3 Dose Delay, Interruption, or Discontinuation, All Subjects

If the dose of one drug in the regimen (ie, pomalidomide, dexamethasone, or elotuzumab) is delayed, interrupted, or discontinued, the treatment with the other drugs may continue as scheduled. However, if dexamethasone is delayed or discontinued discuss ongoing elotuzumab administration with the medical monitor. Also see [Section 3.5](#) for delays in study drugs.

Each cycle is 28 days. While dose delays or interruptions are permitted, the start of each cycle cannot be delayed and is fixed (ie, anchored) relative to Cycle 1 Day 1. Adjustments to the Cycle 1 Day 1 anchored schedule should not be performed. Should the start of a cycle be delayed, it is expected the following cycle begin as anchored to Cycle 1 Day 1. For example, if a subject is unable to start Cycle (X) until 3 days after the anchored start date, all assessments should be recorded on Cycle (X) Day 3. The following cycle should begin on Day 1 (not Day 3) of Cycle (X+1). Missed doses should be skipped, not delayed, if not given within the allowed window.

Subjects may continue on study therapy even if components of the study therapy must be discontinued. For example, a subject on pomalidomide and dexamethasone may continue on study therapy even if dexamethasone must be discontinued for an adverse event. Likewise, a subject on the elotuzumab arm may continue on study therapy if elotuzumab must be discontinued for an adverse event or other reason. Subjects are considered still on study therapy even if they continue solely on pomalidomide or dexamethasone.

Please consult the BMS Medical Monitor or any questions regarding dose interruption or study



Subjects should be instructed that if a dose of pomalidomide has been missed and it has been less than 12 hours since the subject’s regular dosing time, to take pomalidomide as soon as the subject remembers. If it has been more than 12 hours, the dose must be skipped. Subjects should not take 2 doses at the same time

4.5.4 Recommended Dose Reduction

The criteria presented in this section for dose modification of dexamethasone and pomalidomide are meant as general guidelines. They are based on current US standards of clinical practice. Local standards may differ and may be followed. Dose modification may occur in the setting of lower grade toxicity if the investigator, in consultation with the Medical Monitor/Sponsor, believes that it is in the interest of subject safety.

4.5.4.1 Elotuzumab

No dose reduction is allowed for elotuzumab.

4.5.4.2 Dexamethasone

Dexamethasone dose reductions for toxicity must be performed as clinically indicated. Recommended management is described in Table 4.5.4.2-1 and Table 4.5.4.2-2. Deviations to the recommended dose reductions are allowed based on the clinical judgment of the investigator.

CTCAE Category	Adverse Event	Treatment Adjustment
Gastrointestinal	Dyspepsia, gastric or duodenal ulcer, gastritis Grade 1 - 2 (requiring medical management)	Treat with a proton pump inhibitor. If symptoms persist despite above measures, decrease by 1 dose level.
	≥ Grade 3 (requiring hospitalization or surgery)	Hold dexamethasone until symptoms are adequately controlled. Reduce by 1 dose level and resume along with concurrent therapy with a proton pump inhibitor. If symptoms persist despite above measures, reduce to dose level -3 (dose withheld).
	Acute pancreatitis	Reduce to dose level -3(dose withheld).
Cardiovascular	Edema ≥ Grade 3 (limiting function and unresponsive to therapy or anasarca)	Use diuretics as needed, and decrease dexamethasone by 1 dose level. If edema persists despite above measures, decrease by another dose level.
Neurology	Confusion or Mood alteration ≥ Grade 2 (interfering with function ± interfering with activities of daily living)	Hold dexamethasone until symptoms resolve. Decrease by 1 dose level and resume. If symptoms persist despite above measures, decrease by another dose level.

Table 4.5.4.2-1: Dexamethasone Dose Reductions		
CTCAE Category	Adverse Event	Treatment Adjustment
Musculoskeletal	Muscle weakness \geq Grade 2 (symptomatic and interfering with function \pm interfering with activities of daily living)	Hold dose until muscle weakness is \leq Grade 1. Decrease dexamethasone by 1 dose level and resume. If weakness persists despite above measures, decrease by another dose level.
Metabolic	Hyperglycemia \geq Grade 3 or higher	Treat with insulin or oral hypoglycemics as needed. If uncontrolled despite above measures, decrease by 1 dose level until glucose levels are satisfactory.
Constitutional	Insomnia \geq Grade 2	Decrease by 1 dose level and resume.

Dose reduction for persistent Grade 2 or Grade \geq 3 AEs believed to be related to dexamethasone and not listed above are permitted. Dose reductions should follow the guidance in [Table 4.5.4.2-1](#) and [Table 4.5.4.2-2](#).

For subjects receiving elotuzumab, regardless of dexamethasone dose reduction, at least 8 mg of the weekly dexamethasone dose must be administered IV as part of the premedication for elotuzumab with the remainder of the weekly dexamethasone dose administered orally as described in [Section 4.5.1](#). Contact the Medical Monitor to discuss dexamethasone IV premedication for subjects in the investigational arm who reach dose level -3 and must discontinue dexamethasone due to dose limiting toxicity.

On days without elotuzumab, no IV dexamethasone should be administered.

Table 4.5.4.2-2: Dexamethasone Dose Levels				
Dose Level	Reducing Dexamethasone on Weeks with Elotuzumab		Reducing Dexamethasone on Weeks Without Elotuzumab	
	PO	IV	PO	IV
0	\leq 75 years old - 28 mg	8 mg	\leq 75 years old - 40 mg	N/A
	$>$ 75 years old - 8 mg		$>$ 75 years old - 20 mg	
-1	\leq 75 years old - 12 mg	8 mg	\leq 75 years old - 20 mg	N/A
	$>$ 75 years old - 2 mg		$>$ 75 years old - 12 mg	
-2	\leq 75 years old - 0 mg	8 mg	\leq 75 years old - 12 mg	N/A
	$>$ 75 years old - 0 mg		$>$ 75 years old - 8 mg	
-3	\leq 75 years old - 0 mg	Contact Medical Monitor	\leq 75 years old - 0 mg	N/A
	$>$ 75 years old - 0 mg		$>$ 75 years old - 0 mg	

4.5.4.3 Pomalidomide

Below are the recommended dose adjustments for the management of thrombocytopenia and neutropenia judged by the investigator to be related to pomalidomide. Information in Table 4.5.4.3-1 and Table 4.5.4.3-2 is based on pomalidomide prescribing information, which contains additional guidance on pomalidomide dosing^{43 44}.

Table 4.5.4.3-1: Treating Thrombocytopenia Related to Pomalidomide	
When Platelet Count:	Recommended Course:
<ul style="list-style-type: none"> Fall to < 25,000 per mm³ Return to > 50,000 per mm³ 	<ul style="list-style-type: none"> Interrupt pomalidomide treatment, follow Complete Blood Count weekly. Resume pomalidomide at 3 mg daily
<ul style="list-style-type: none"> For each subsequent drop < 25,000 mm³ Return to ≥ 50,000 mm³ 	<ul style="list-style-type: none"> Interrupt pomalidomide treatment Resume pomalidomide at 1 mg less than previous dose

Table 4.5.4.3-2: Treating Neutropenia Related to Pomalidomide	
When Neutrophil Count:	Recommended Course:
<ul style="list-style-type: none"> Fall to < 500 per mm³ or febrile neutropenia (fever ≥ 38.5°C and ANC < 1,000 mm³) ANC returns to ≥ 1000 per mm³ 	<ul style="list-style-type: none"> Interrupt pomalidomide treatment, follow Complete Blood Count weekly. Resume pomalidomide at 3 mg daily
<ul style="list-style-type: none"> For each subsequent drop < 500 mm³ Return to ≥ 1000 mm³ 	<ul style="list-style-type: none"> Interrupt pomalidomide treatment Resume pomalidomide at 1 mg less than previous dose

ANC, absolute neutrophil count. In case of neutropenia, consider the use of growth factors in subject management.

If necessary to co-administer strong inhibitors of CYP1A2 in the presence of strong inhibitors of CYP3A4 and P-glycoprotein, consider reducing pomalidomide dose by 50%.^{43,44}

4.6 Blinding/Unblinding

Not applicable.

4.7 Treatment Compliance

Starting at Cycle 1, all treated subjects will be assessed for drug compliance of all treatments administered during the course of the study. Treatment compliance will be monitored by drug accountability and recorded in the subject's medical record. For those medications taken at home (PO dexamethasone and pomalidomide), subjects will be provided with a medication diary in which to record study drug doses and will be instructed to bring this diary and study drug containers to clinic visits.

4.8 Destruction and Return of Study Drug

4.8.1 Destruction of Study Drug

For this study, study drugs (those supplied by BMS or sourced by the investigator) such as partially used study drug containers, vials and syringes may be destroyed on site.

Any unused study drugs can only be destroyed after being inspected and reconciled by the responsible BMS Study Monitor unless study drug containers must be immediately destroyed as required for safety, or to meet local regulations (eg, cytotoxics or biologics).

On-site destruction is allowed provided the following minimal standards are met:

- On-site disposal practices must not expose humans to risks from the drug.
- On-site disposal practices and procedures are in agreement with applicable laws and regulations, including any special requirements for controlled or hazardous substances.
- Written procedures for on-site disposal are available and followed. The procedures must be filed with the site's SOPs and a copy provided to BMS upon request.
- Records are maintained that allow for traceability of each container, including the date disposed of, quantity disposed, and identification of the person disposing the containers. The method of disposal, ie, incinerator, licensed sanitary landfill, or licensed waste disposal vendor must be documented.
- Accountability and disposal records are complete, up-to-date, and available for the Monitor to review throughout the clinical trial period.

If conditions for destruction cannot be met the responsible BMS Study Monitor will make arrangements for return of study drug.

It is the investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local, and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

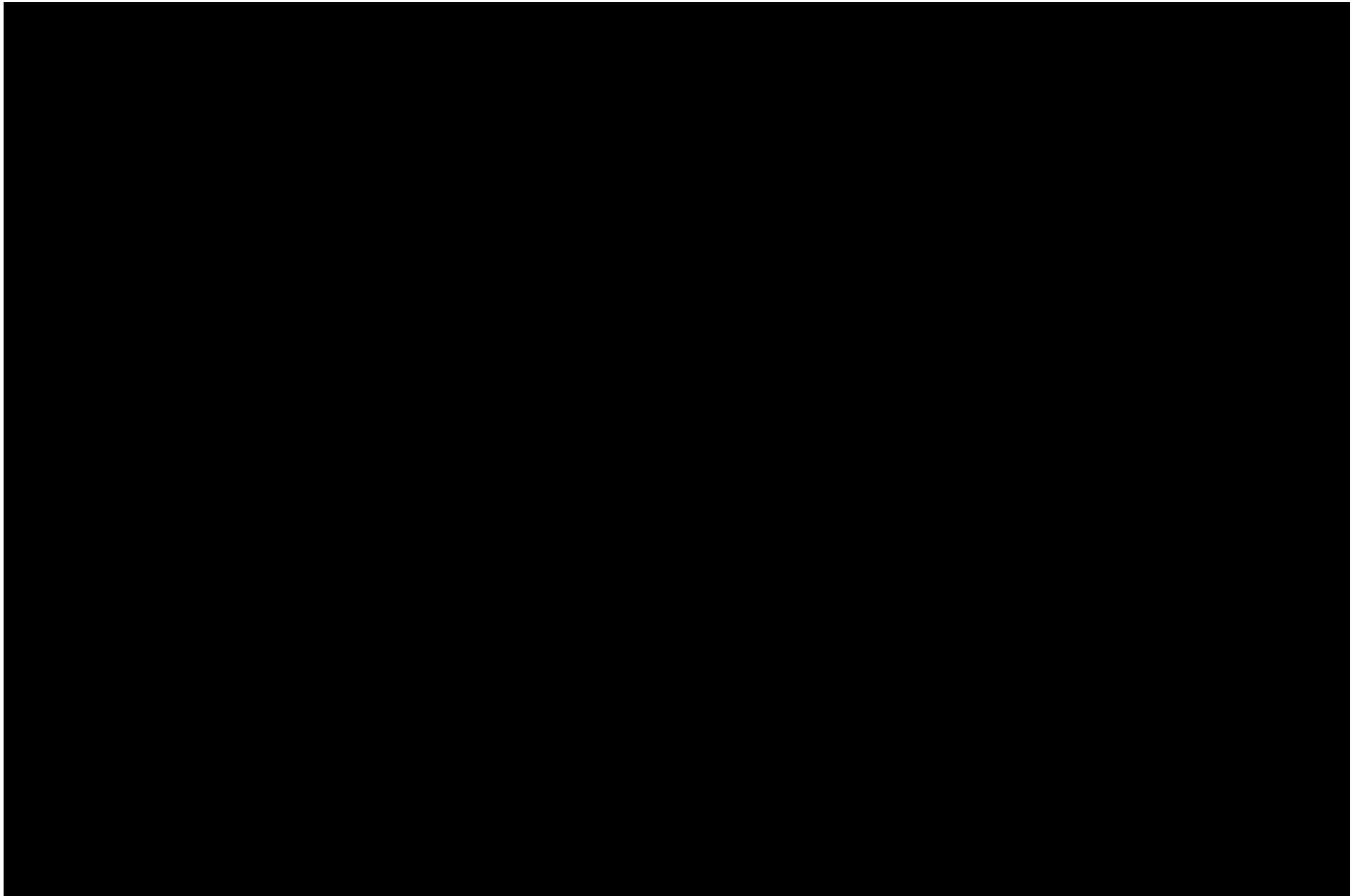
4.9 Return of Study Drug

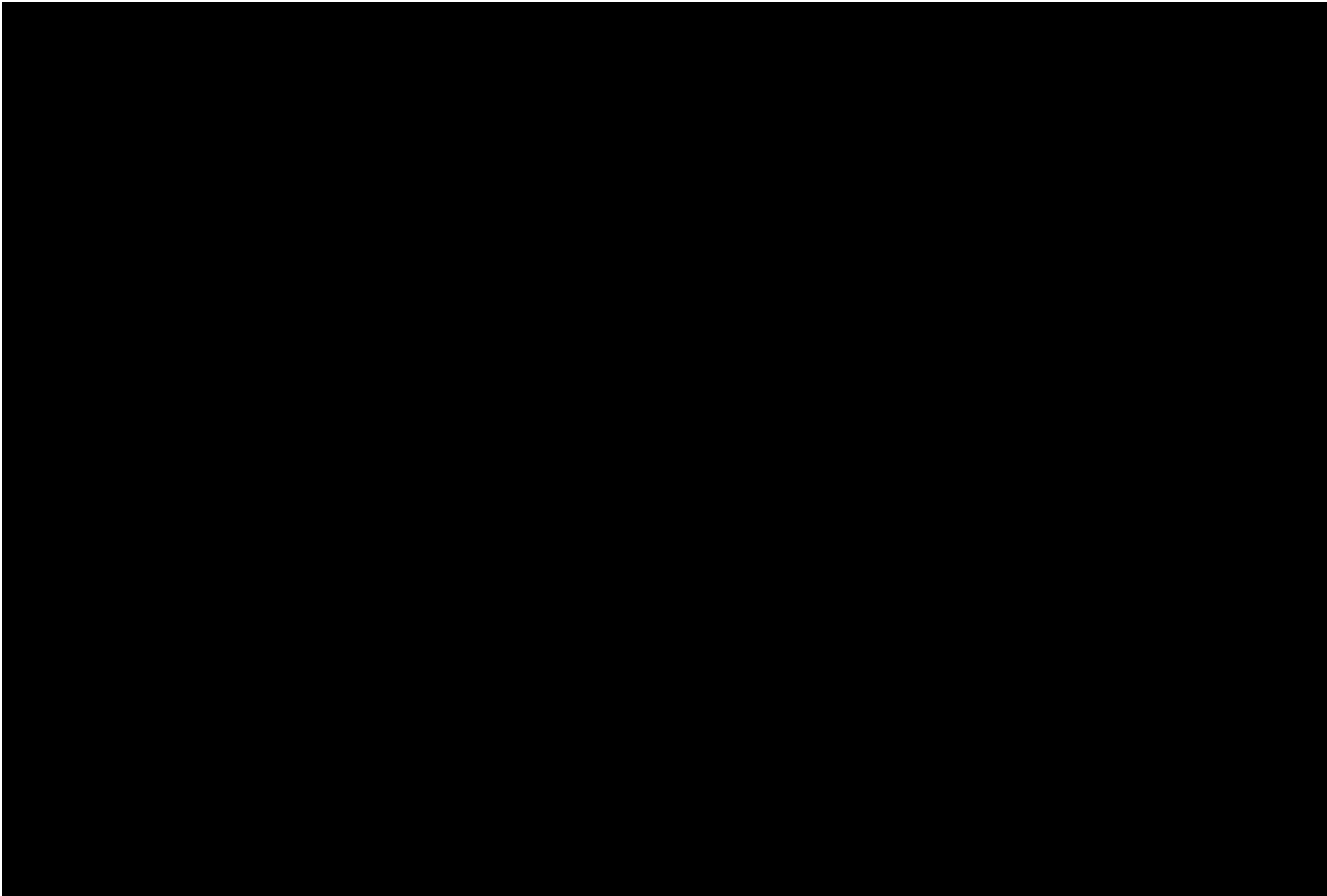
If study drug will not be destroyed upon completion or termination of the study, all unused and/or partially used study drug that was supplied by BMS must be returned to BMS. The return of study drug will be arranged by the responsible BMS Study Monitor.

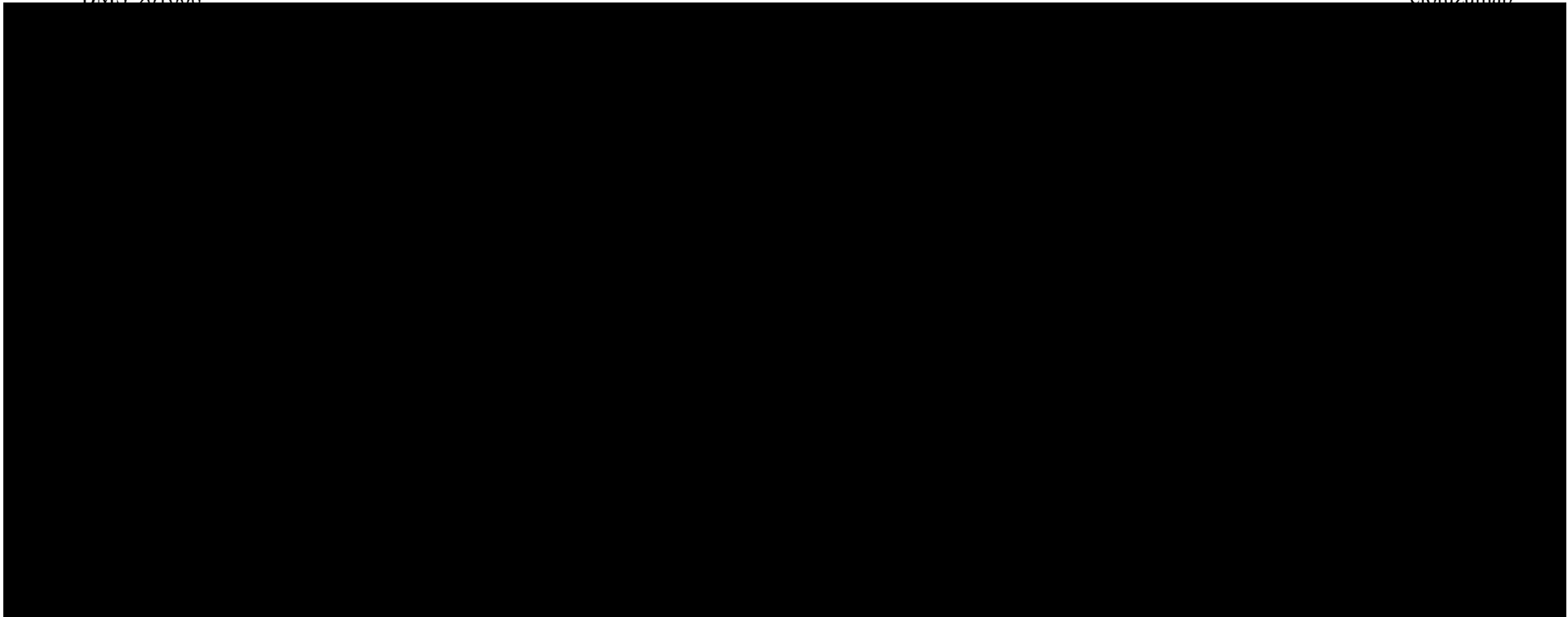
It is the investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local, and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

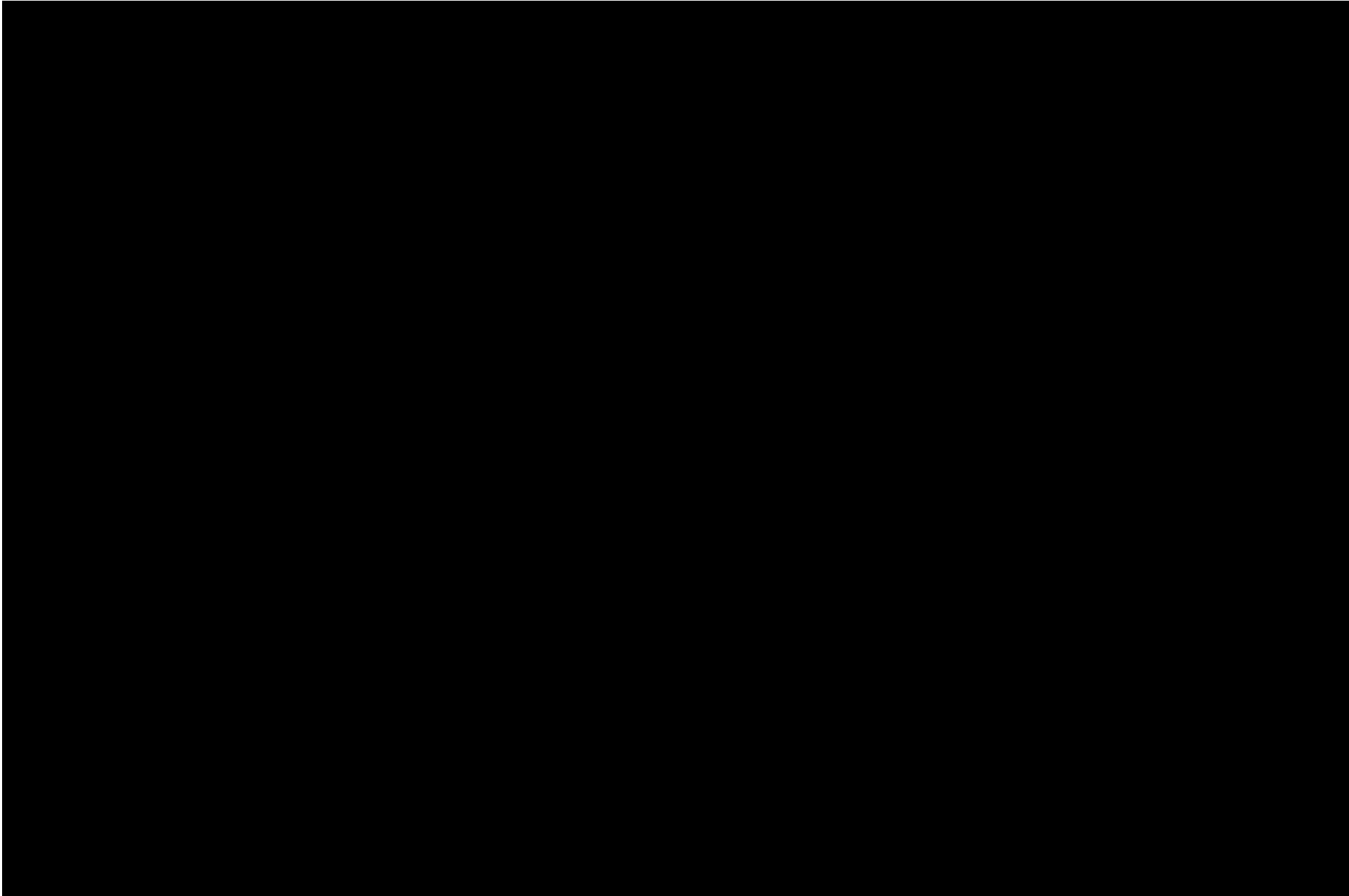
4.10 Retained Samples for Bioavailability / Bioequivalence

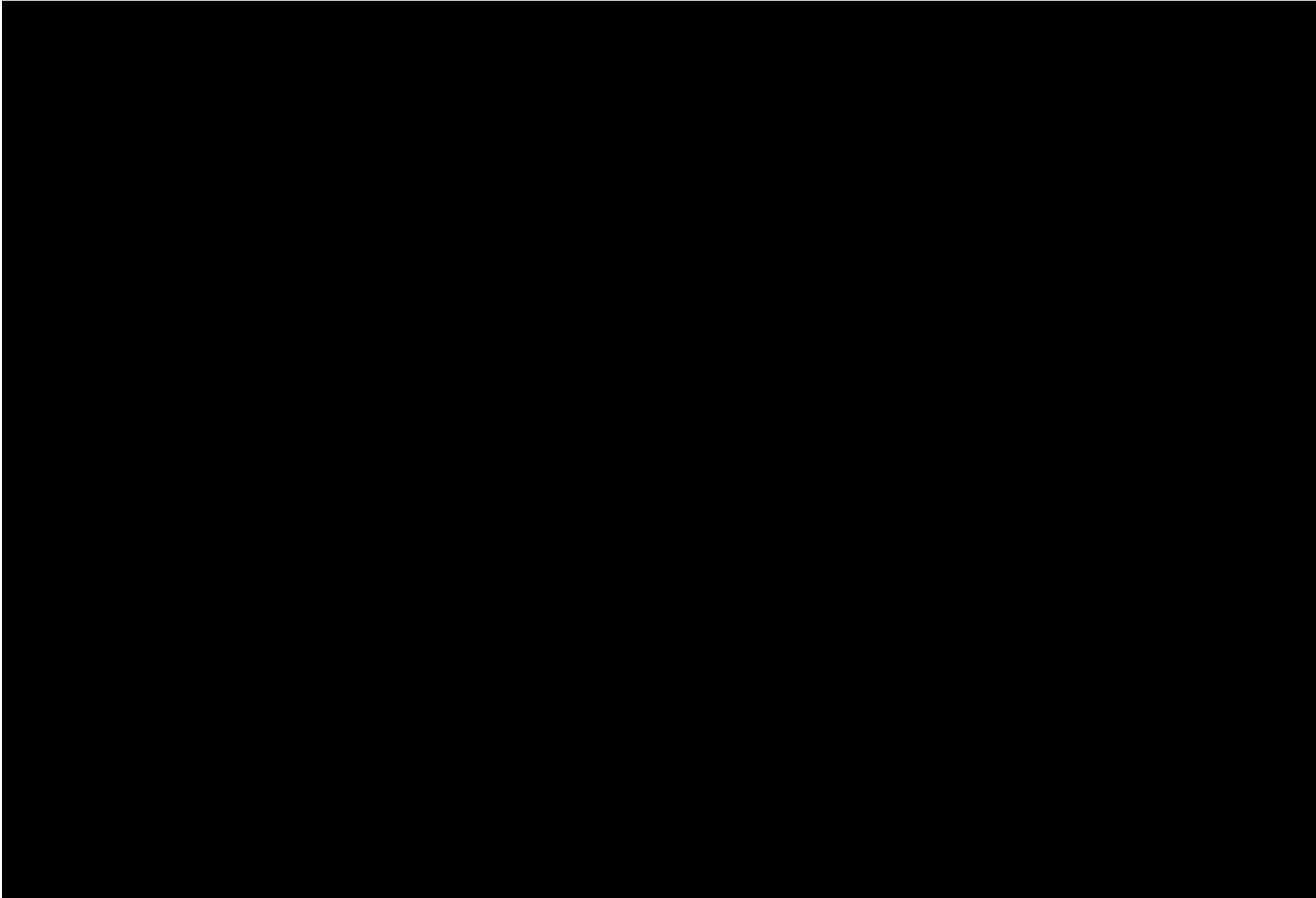
Not applicable.

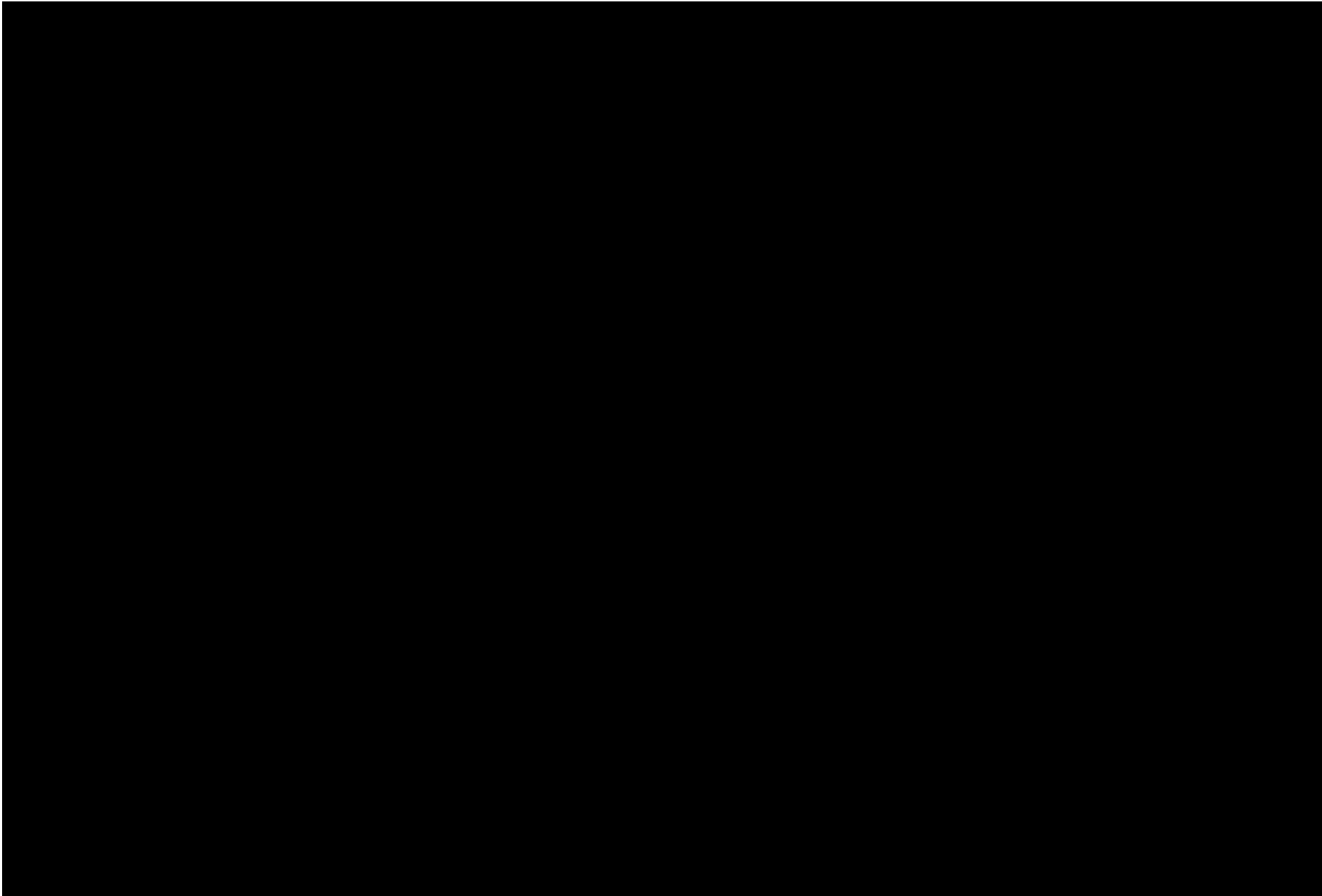


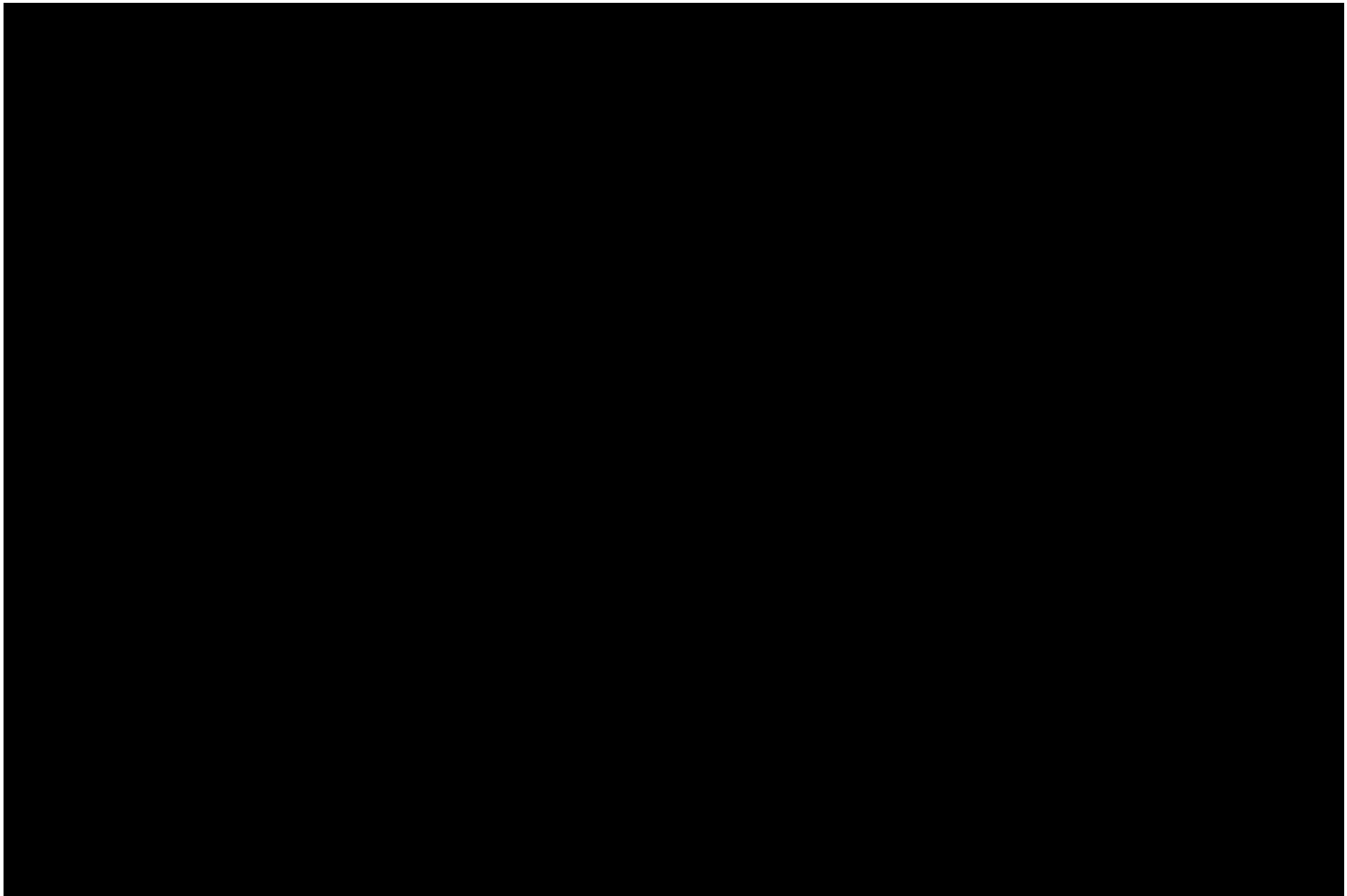


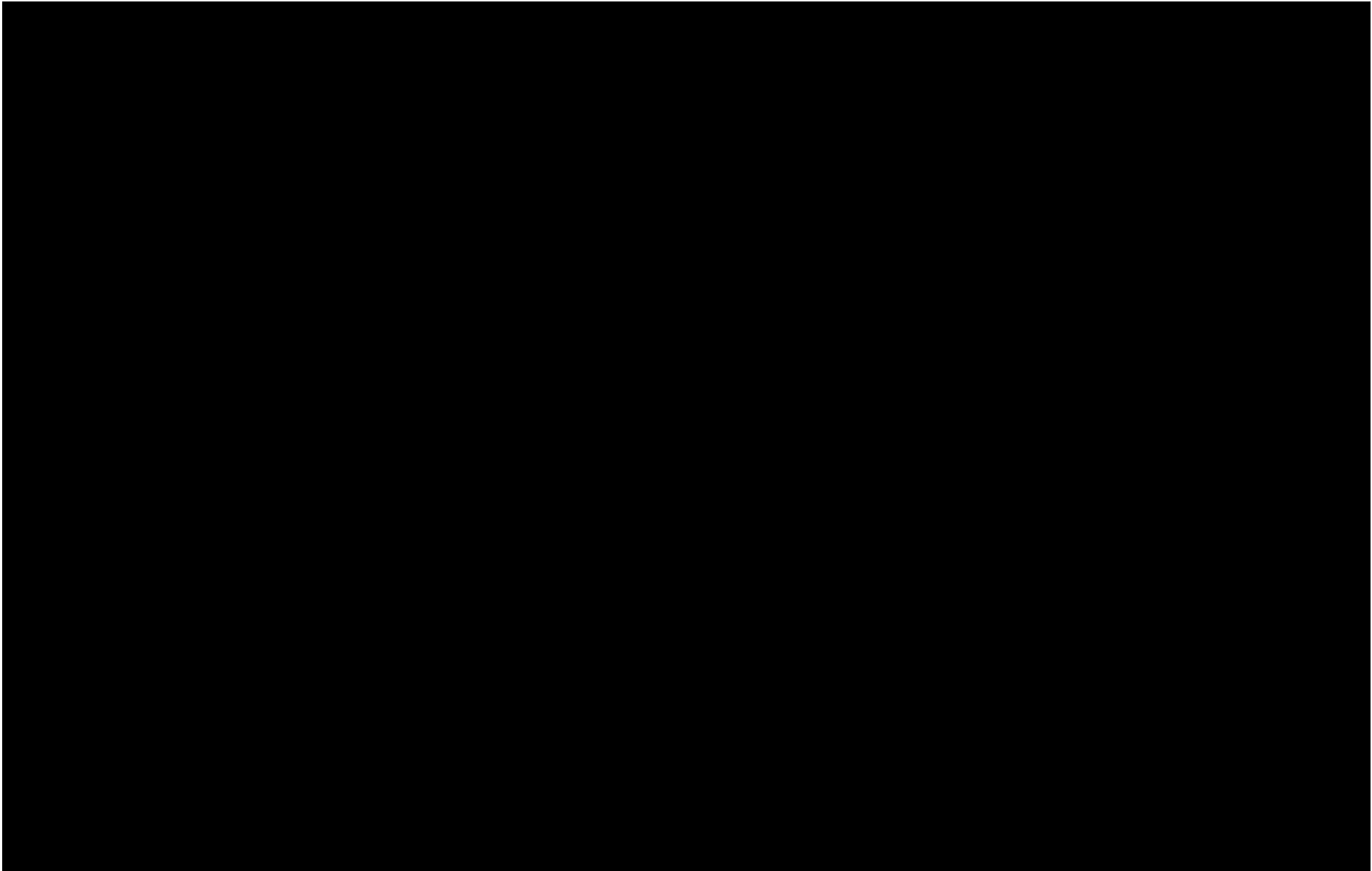


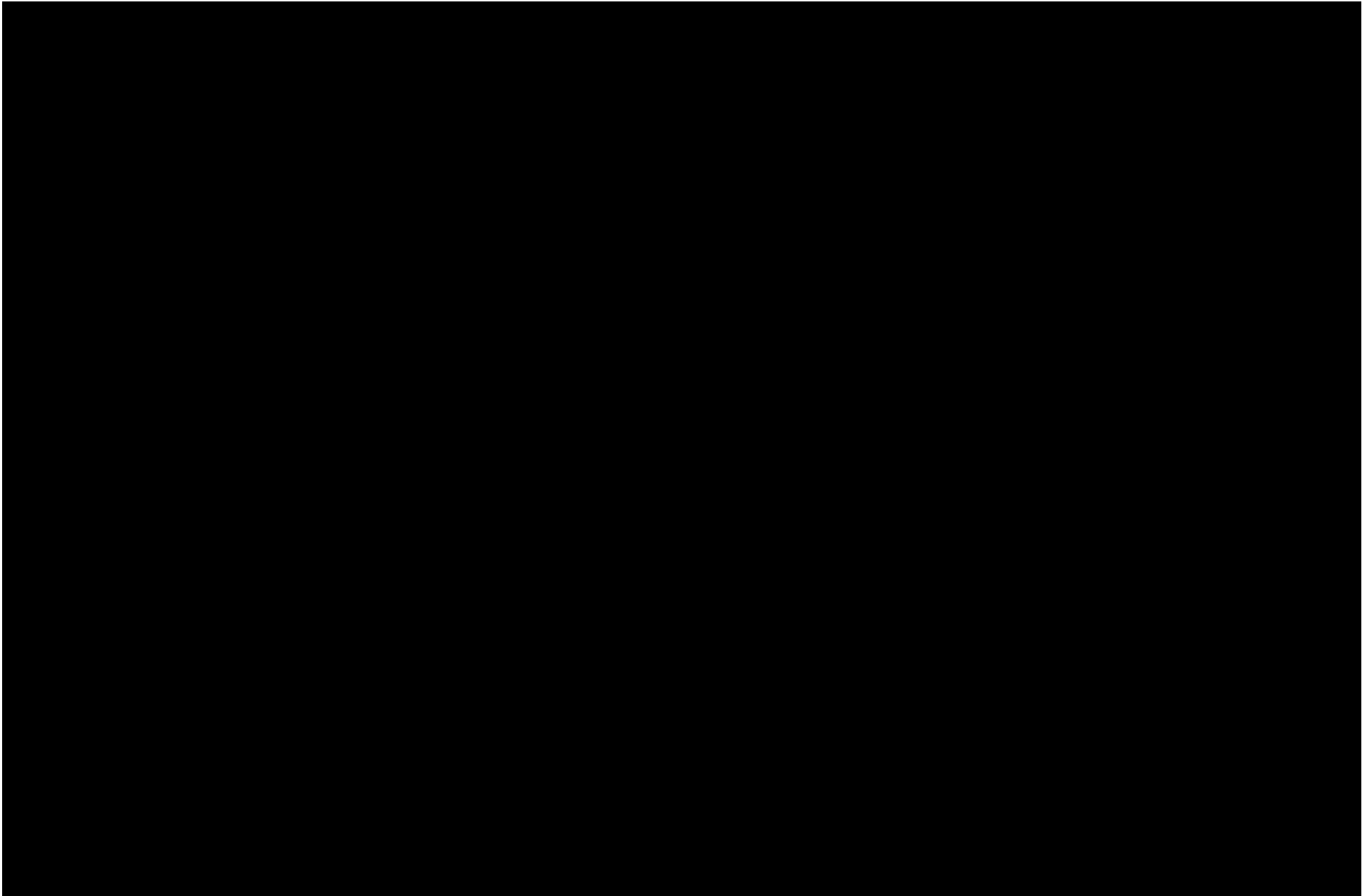


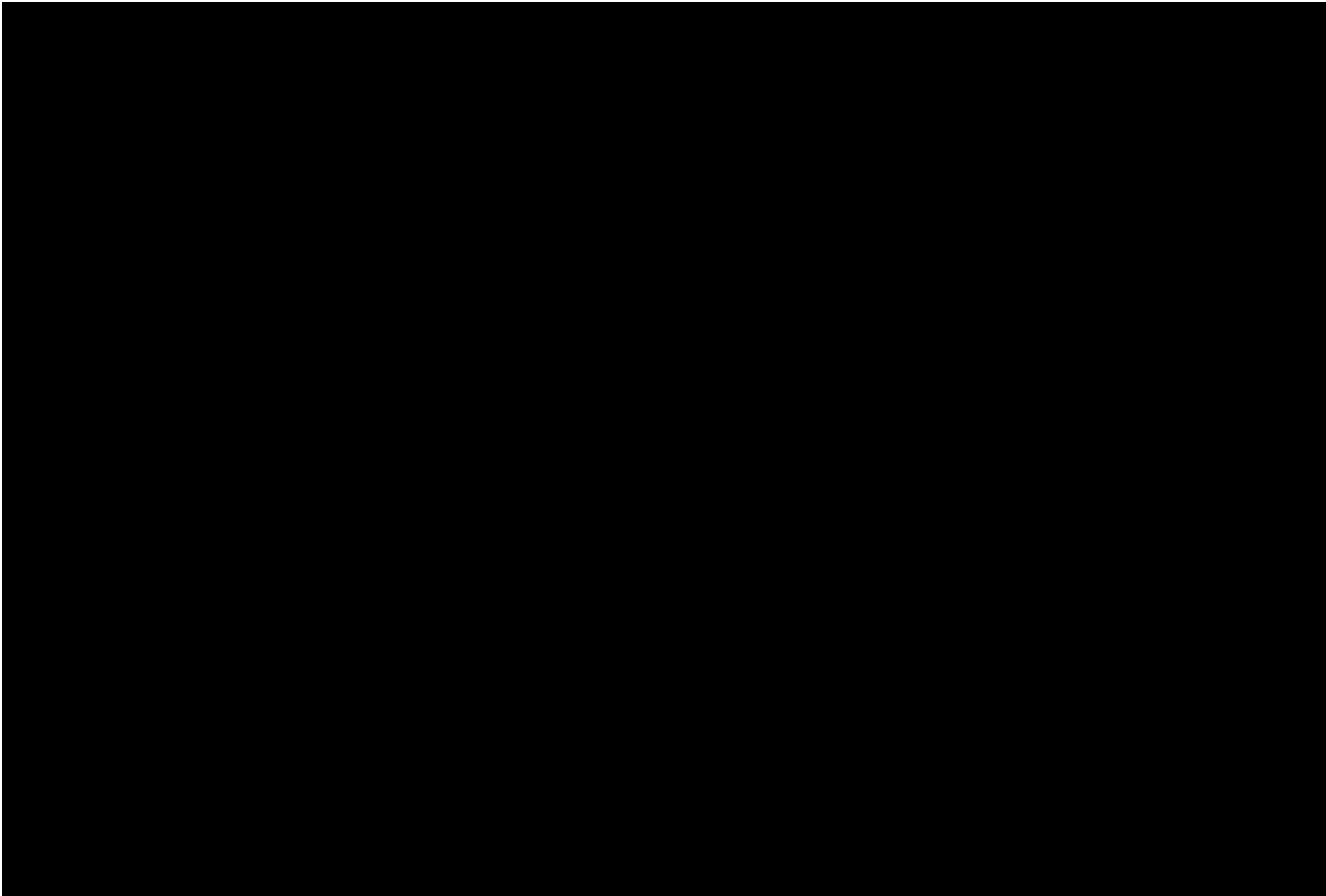


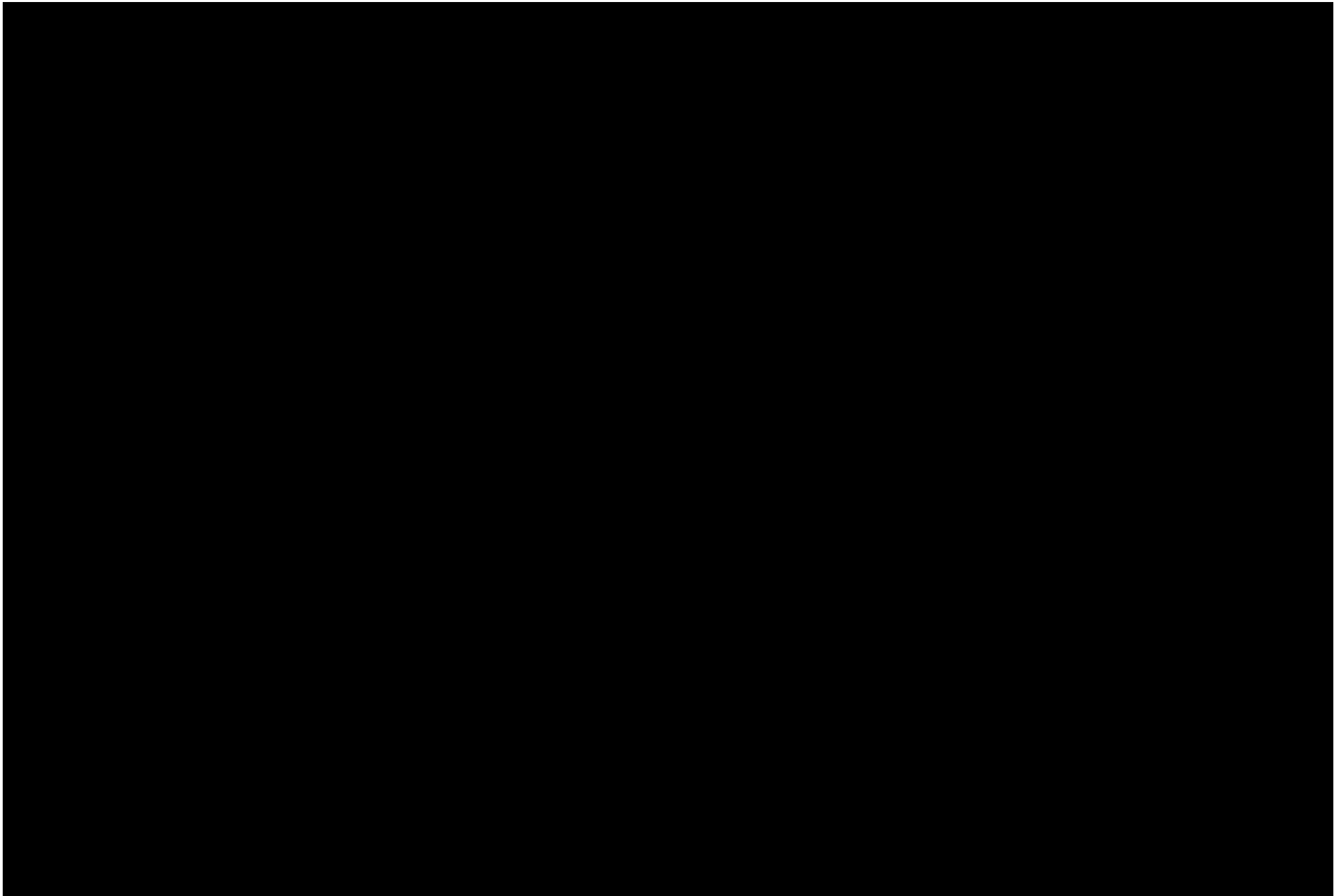


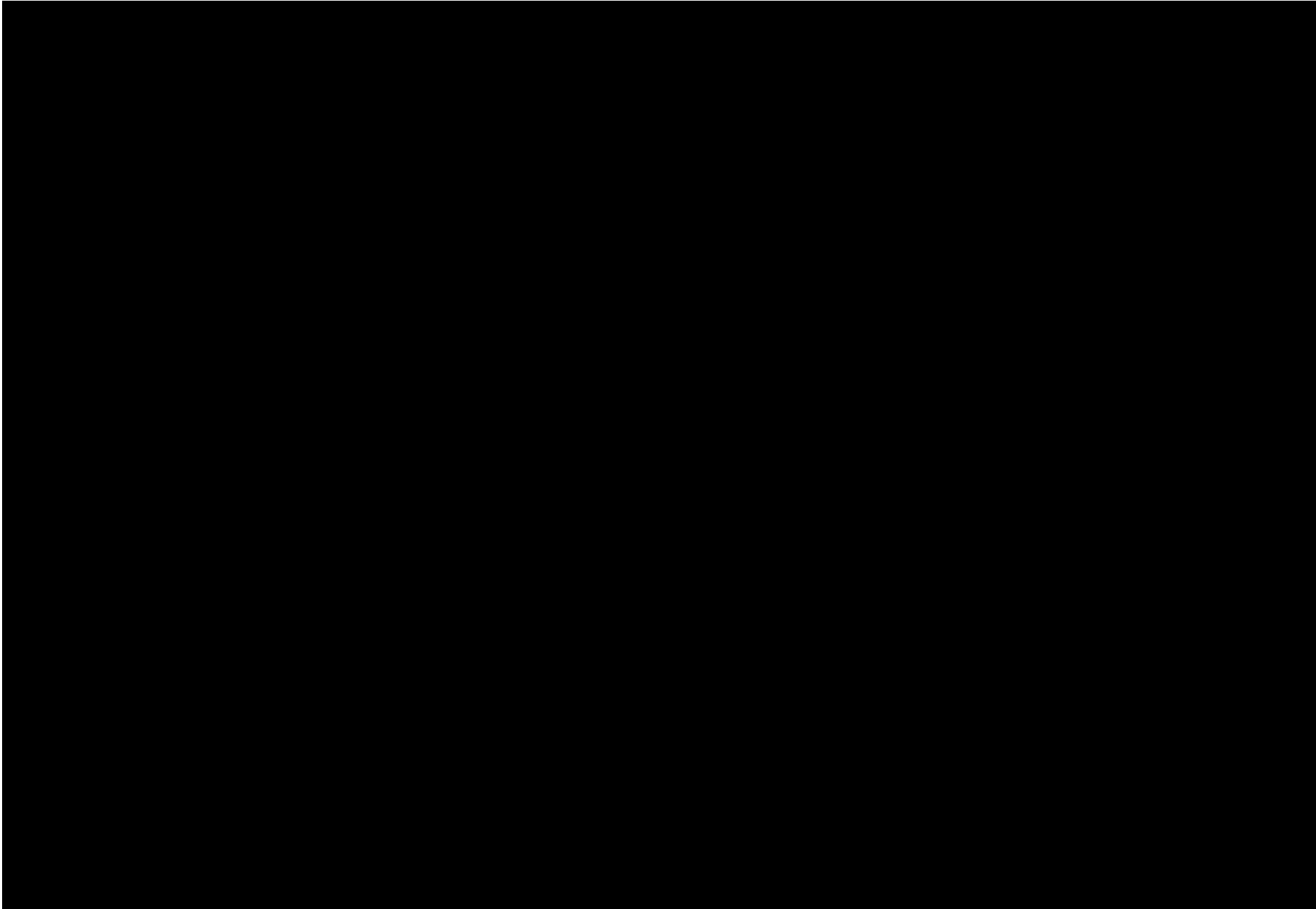


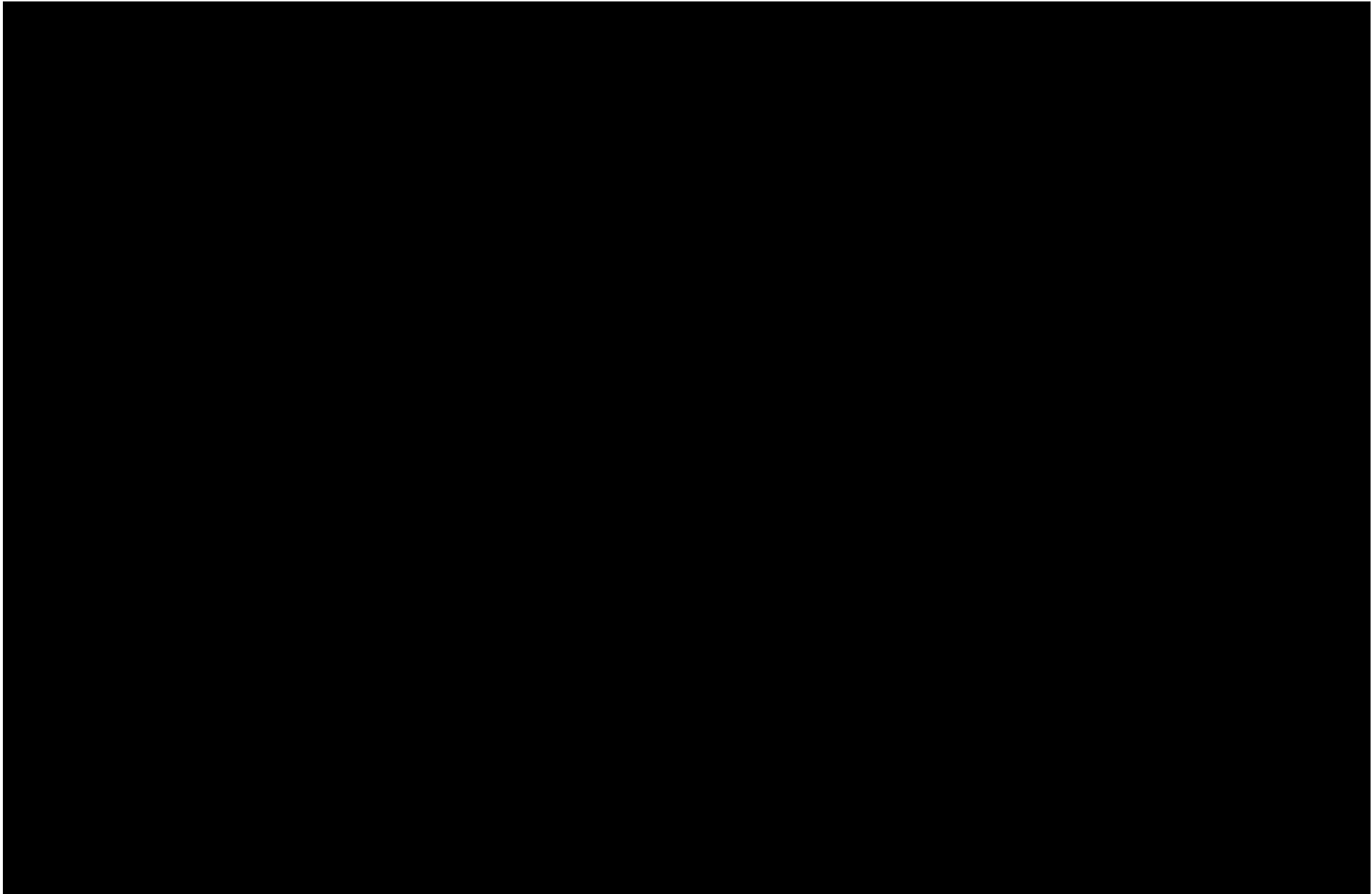


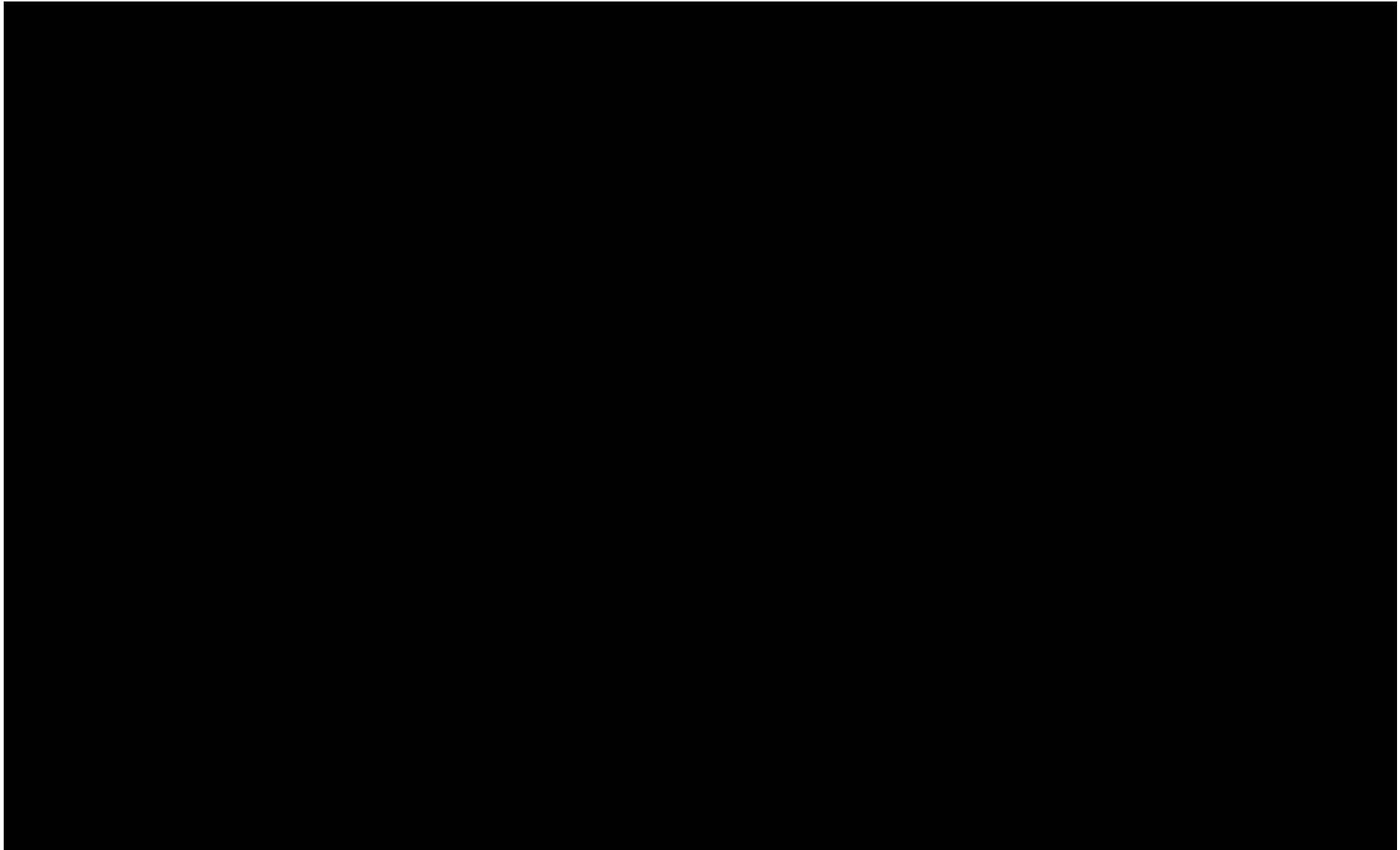


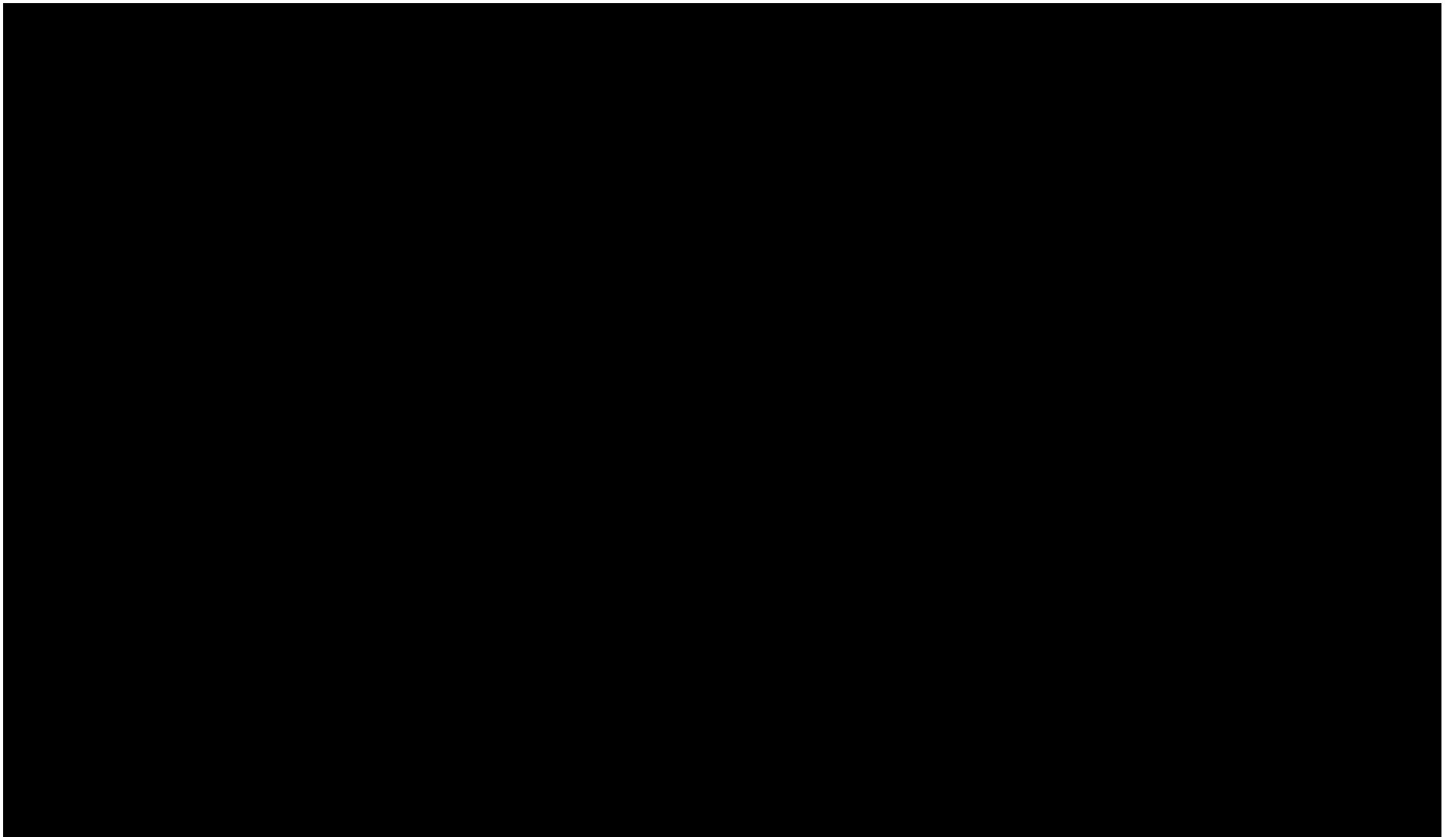


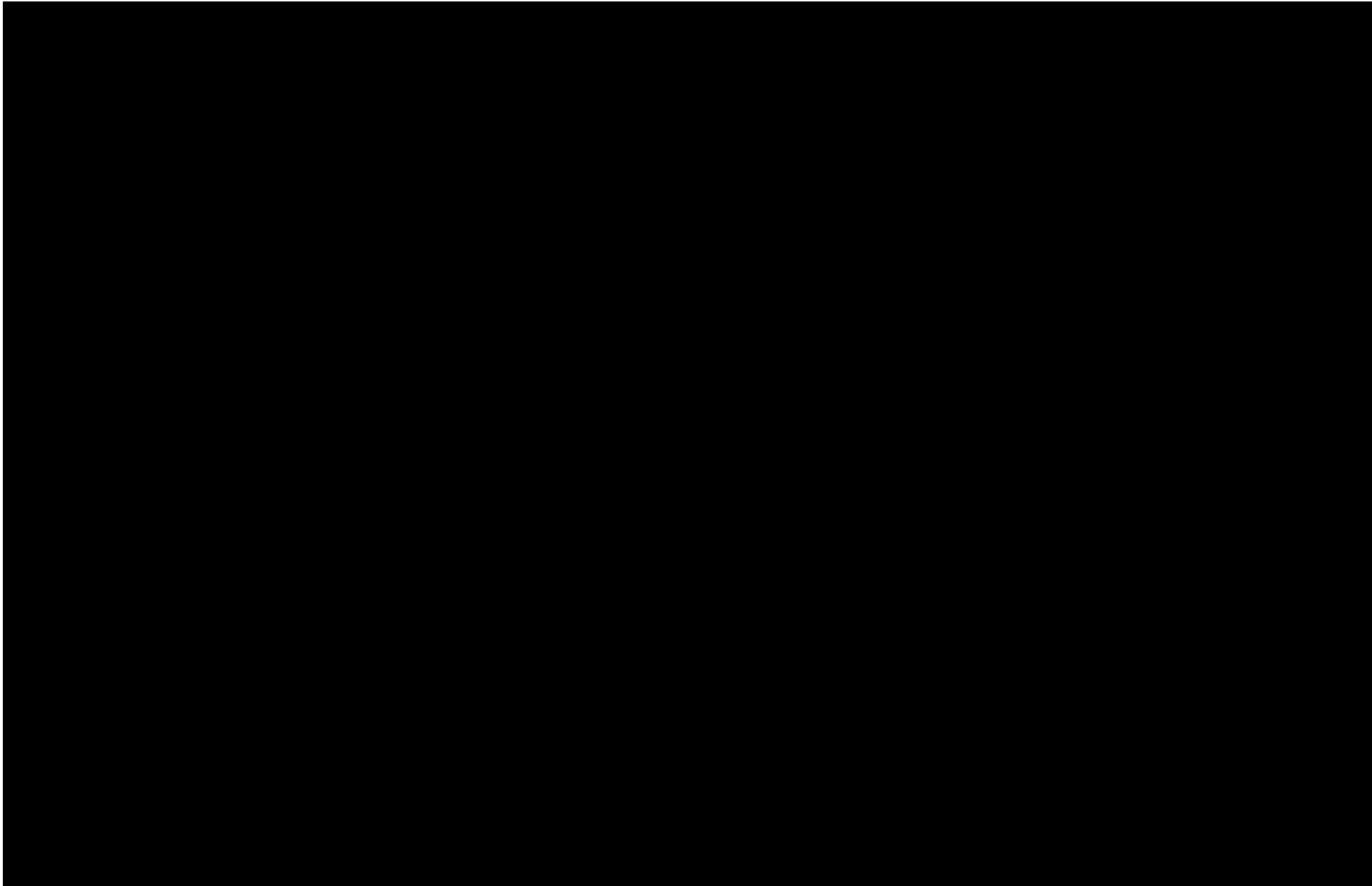












5.1.1 Retesting During Screening Period

Retesting of laboratory parameters and/or other assessments within the Screening period will be permitted (in addition to any parameters that require a confirmatory value).

Any new result will override the previous result (ie, the most current result prior to starting study drug) and is the value by which study inclusion will be assessed, as it represents the subject's most current, clinical state.

Laboratory parameters and/or assessments that are included in [Table 5.1-1](#), Screening Procedural Outline may be repeated in an effort to find all possible well-qualified subjects. Consultation with the Medical Monitor may be needed to identify whether repeat testing of any particular parameter is clinically relevant.

5.2 Study Materials

The following will be distributed to sites for use in this study:

- NCI CTCAE booklets version 3.0
- Elotuzumab Investigator Brochure
- Pomalidomide (Pomalyst®) Package Insert
- Site Manual for operation of IVRS
- Subject Dosing Diary
- Subject Quality of Life Questionnaires
- Serious Adverse Event (SAE) Case Report Form (CRF) pages
- Pregnancy Surveillance Forms

5.3 Safety Assessments

Only data for the procedures and assessments specified in this protocol should be submitted to BMS. Additional procedures and assessments may be performed as part of standard of care; however, the data for these assessments should remain in the subject's medical record and should not be provided to BMS, unless specifically requested from the Sponsor. Safety assessments must be done prior to dosing. The local safety labs (complete blood count, chemistry panel) and procedures may be collected or performed up to 3 days prior to the visit. For subjects who skip a dose, local safety labs results must be submitted to BMS at least once per cycle. In addition, all safety lab results that lead to dose delay or discontinuation must be submitted to BMS.

All subjects will be assessed for safety. Safety evaluations include assessments of AEs, clinical laboratory tests (hematology, chemistry), vital sign measurements, and physical examination with assessment of ECOG PS. Investigators are responsible for monitoring the safety of subjects who have entered this study and for alerting the Sponsor to any event that seems unusual, even if this event may be considered an unanticipated benefit to the subject. The investigator is responsible for appropriate medical care of subjects during the study.

5.3.1 Imaging Assessment for the Study

Any incidental findings of potential clinical relevance that are not directly associated with the objectives of the protocol should be evaluated and handled by the Study Investigator as per standard medical/clinical judgment.

5.3.2 Vital Signs, Physical Measurements, and Physical Examination

Vital signs (body temperature, seated blood pressure and heart rate) will be recorded as outlined in [Table 5.1-1](#), [Table 5.1-2](#) and [Table 5.1-3](#). Blood pressure and heart rate should be measured after the subject has been seated quietly for at least 5 minutes prior to dosing. Subjects in the control arm will have vital signs measured once at each visit. Subjects randomized to the elotuzumab arm will have additional vital signs as follows:

- Prior to pre-medication administration
- Prior to the start of the elotuzumab infusion
- Thirty minutes after the start of infusion
- At the end of the infusion
- For Cycles 1 and 2: Thirty minutes and 120 minutes post completion of the elotuzumab infusion.
- For Cycle 3 and beyond: post infusion vital signs will be measured at 30 minutes.
- Subjects who experience a Grade ≥ 2 infusion reaction require vital signs to be monitored every 30 minutes for 2 hours after the end of the elotuzumab infusion.

Height will be recorded at screening. Weight will be measured at study visits as indicated in [Table 5.1-1](#), [Table 5.1-2](#) and [Table 5.1-3](#)

A full physical examination will be performed at the screening visit, whereas a targeted exam will occur at Day 1 and during on-treatment up to 3 days prior to dosing and post-treatment visits. A targeted physical examination may be performed by a qualified professional guided by the examiner's observations and/or subject complaints on new or changed conditions, symptoms, or concerns. Targeted physical exam includes assessment of heart, lung, and abdomen.

5.3.3 Performance Status

Performance assessment will be performed as indicated in [Table 5.1-1](#), [Table 5.1-2](#) and [Table 5.1-3](#) using ECOG performance scale and criteria as described in [Appendix 2](#). The assessment should be completed prior to any study-related procedures, treatment or clinician assessment.

5.3.4 Cardiac Assessments

A MUGA scan or 2-dimensional echocardiogram and electrocardiogram (ECG) will be performed at screening within 28 days of randomization.

5.3.5 Laboratory Assessments for Safety

Laboratory assessments for safety will be performed at local laboratories. Safety laboratory assessments are listed in [Table 5.3.5-1](#).

Table 5.3.5-1: Safety Laboratory Assessments		
Safety Laboratory Assessments		
	Screening as outlined in Table 5.1-1 Within 14 days of randomization	Study Visits as outlined in Table 5.1-2 and Table 5.1-3
Serum Hematology		
CBC	X	X
Differential (absolute counts: neutrophils, lymphocytes, monocytes, basophils, eosinophils)	X	X
Platelets	X	X
Serum Chemistry		
Sodium	X	X
Potassium	X	X
Chloride	X	X
Carbon Dioxide or Bicarbonate ^a	X	X
Albumin	X	X
Alkaline Phosphatase	X	X
ALT (SGPT)	X	X
AST (SGOT)	X	X
Total Bilirubin	X	X
Direct Bilirubin ^b	X	
Lactate Dehydrogenase	X	X
BUN (or Urea)	X	X
Creatinine	X	X
Glucose	X	X
Calcium	X	X
Total Protein	X	X
Magnesium	X	X
Pregnancy Test		
Urine or Serum Pregnancy	X (2 tests: one 10 - 14 days prior to the start of study drug and one within 24 hours prior to the start of study drug)	X

^a To be done in sites where this is a standard part of the chemistry panel. In sites where testing for CO₂/HCO₃ is not standard, the test is optional

^b Only required for subjects with Gilbert's Syndrome. See [Section 3.3.2](#)

5.4 Efficacy Assessments

Efficacy endpoints will be based on analysis of serum and urine electrophoresis (SPEP and UPEP), sFLC (for those with sFLC disease only), corrected calcium (serum calcium and serum albumin), imaging and bone marrow assessments, all at predefined intervals as specified in [Table 5.1-1](#), [Table 5.1-2](#) and [Table 5.1-3](#). Assessments done at local labs versus central labs are indicated in [Table 5.1-1](#), [Table 5.1-2](#), [Table 5.1-3](#), and [Table 5.4.2-1](#). Assessments for SPEP, UPEP and sFLC will be based on central lab results, whereas assessments of bone marrow, bone lesions, extramedullary plasmacytomas, and corrected calcium will be based on local analysis at the site.

5.4.1 Primary Efficacy Assessment

Response criteria in [Appendix 6](#)^{32,33} will be used for the efficacy analysis. For the purposes of this study, all subjects' tumor assessments by myeloma laboratory tests (SPEP M protein and UPEP M protein quantification, corrected calcium (calcium and albumin), and serum free light chain) should be re-evaluated per the protocol-stated frequency relative to the date of first dose of study drug until disease progression based on [Appendix 6](#), irrespective of dose delays or treatment cycle. **If subject does not have documented disease progression as defined in [Appendix 6](#) at the time of study drug discontinuation, then tumor assessments must continue to be performed according to the same schedule described above until disease progression even if a subsequent anti-myeloma treatment is initiated prior to disease progression.** Subjects will be followed every 12 weeks, or more frequently, after disease progression for survival, subsequent myeloma therapy, and development of second primary malignancy.

All efficacy laboratory assessments (SPEP, UPEP, serum/urine immunofixation, and sFLC) should be done through the central laboratory, except corrected calcium (serum calcium and serum albumin), and bone marrow assessments for plasma cell percentage and light chain restriction (clonality by IHC or flow cytometry). All bone marrow aspirate and core biopsy samples should be assessed locally. For any SPEP, UPEP, or sFLC assessment performed locally, in lieu of a central lab assessment, (ie, if the subject cannot complete a visit at the study site), M protein absolute quantification (eg, g/dL or g/L) or sFLC (eg, mg/L or mg/dL) must be performed. Any laboratory samples analyzed locally, including for efficacy, must be entered on the appropriate CRF/eCRF as requested by the Sponsor to properly assess efficacy per protocol criteria.

5.4.2 Laboratory Assessments for Myeloma

All laboratory efficacy assessments must be performed until disease progression or withdrawal of consent, even if the subject is discontinued from study therapy and has started new myeloma therapy. Confirmation of \geq PR is required on 2 consecutive assessments for Serum, Urine and sFLC.

- 1) **Serum:** SPEP for M protein quantification, total serum protein, serum immunofixation, and quantitative immunoglobulin assay.
 - a. Serum Immunofixation is required at baseline and to confirm CR regardless of whether measurable M-protein was present at baseline.
 - b. Subjects with measurable disease in SPEP will be assessed for response based on SPEP and not by the serum FLC assay.
 - c. Subjects with measurable disease in both SPEP and UPEP will be assessed for response based on these two tests and not by the serum FLC assay.
 - d. All other serum tests will be followed at each tumor assessment.
- 2) **Serum free light chain (sFLC):**
 - a. Subjects without measurable serum M-protein (ie, < 0.5 g/dL (5 g/L)) or urine M-protein (ie, < 200 mg (0.2 g) per 24 hours) and considered oligosecretory must have sFLC assessed at each cycle until until progression.
 - b. Serum must be collected at screening and time of serum and urine IFE negativity to confirm CR and be sent to the central lab for sFLC analysis. This measurement is required to assess for sCR
- 3) **Urine:** 24-hour urine collection for M protein quantification, urinary light chains, and immunofixation. 24-hour urine must be collected with each cycle for all subjects.
 - a. Urine Immunofixation is required at baseline and to confirm CR, regardless of whether measurable M-protein was present at baseline.
 - b. All other urine tests will be followed at each tumor assessment.
- 4) **Bone marrow aspiration/biopsy:**

Table 5.4.2-1: Bone Marrow Samples		
Sample	Local Laboratory	Central Laboratory
Aspirate	1) Samples required at the following times to evaluate percentage plasma cells: <ol style="list-style-type: none"> a) Screening (within 35 days of randomization) b) When subject is immunofixation negative in both serum and urine (second bone marrow sample not required for confirmation) <ol style="list-style-type: none"> i) In addition, evaluate flow cytometry to assess plasma cell clonality (ie, lambda and kappa IHC or flow cytometry to assess light chain restriction. c) At time of suspected disease progression, if needed (see Section 5.4.4) to assess PD in subjects whose myeloma become nonsecretory. Evaluation of percentage of plasma cells should be performed locally per	a) Screening (within 35 days of randomization) <ol style="list-style-type: none"> i) Genetic assessments (FISH) should be performed by the central laboratory on a fresh bone marrow sample. However, if a new bone marrow sample collection is not feasible and if this assessment was performed locally within the 35 days of randomization, the local results must be entered into the eCRF. Contact BMS medical monitor in these cases. b) Aspirate samples are required for biomarker assessments (section 5.6.1).

Table 5.4.2-1: Bone Marrow Samples		
Sample	Local Laboratory	Central Laboratory
	institution standard practice; Plasma cell percentage and light chain restriction assessments are required. If not available, IHC can be performed on bone marrow core biopsy.	
Biopsy	Not required by protocol unless an aspirate sample (at any time point above) is not available due to a dry tap or due to laboratory preferences of the local pathologist	

- 5) **Serum Corrected Calcium:** Serum corrected calcium should be collected with each cycle for all subjects until disease progression.

$$\text{Corrected Calcium, mg/dL} = (0.8 \times [\text{Normal Albumin, g/dL} - \text{Subject's Albumin, g/dL}] + \text{Serum Ca, mg/dL}$$

5.4.3 Imaging Assessments for Myeloma

5.4.3.1 Skeletal Survey

Skeletal survey, by conventional radiography, for metastatic disease will be performed within 28 days of randomization in all subjects. Skeletal survey will be performed on study if clinically indicated (development of compression fracture does not exclude response). Use of conventional or low dose CT scan (ie, of the spine) or MRI bone survey is acceptable. If imaging is performed on treatment for assessment of progression, the site must use the same modality of imaging as used in screening. The number and location of skeletal lesions and whether they are lytic should be recorded on the eCRF. On treatment survey should record whether there is an increase in the number or size of lytic lesions.

5.4.3.2 Assessment of Extramedullary Plasmacytoma

Computed tomography or MRI should be performed at screening, if clinically indicated or if patient had a previous extramedullary or bone plasmacytoma. To minimize unnecessary radiation in myeloma subjects where progression is primarily based on serum and urine M-protein, on study assessments should only be performed if clinically indicated (ie, pain, concern for disease progression), whether or not present at baseline, and at the time of CR/sCR assessment.

A sum of the products of the longest diameters and longest perpendicular diameter for all measurable lesions will be calculated at screening. This sum will be used as the reference for on study assessments by which to characterize the objective tumor response.

All tumor measurements must be made in millimeters. All documented measurable and non-measurable lesions are to be followed throughout the trial. All assessments to be used for tumor response evaluation, including the baseline assessment, must be performed using the same method for repeat assessment. CT and MRI scanning are the preferable methods of assessment. Conventional CT and MRI should be performed with contiguous cuts of 10 mm or less or with cuts of 5 (or 10) mm if spiral CT scanning is used. Imaging-based evaluation is preferred to evaluation by clinical examination. Evaluation by chest x-ray is less preferable than CT or MRI, and should only be used for well-defined lesions surrounded by aerated lung. Clinical examination is only acceptable when lesions are superficial, such as a skin nodule or palpable lymph node. Skin lesions must be documented by a photograph with a ruler. Ultrasound is not acceptable for documentation of measurable disease.

Duplicate copies of all imaging studies used for tumor response evaluation will be made available for review by the Sponsor upon request.

Measurable disease are lesions that can be accurately measured in 2 dimensions and both diameters must be ≥ 20 mm when evaluated by standard CT scanning or ≥ 10 mm when evaluated by spiral CT scanning or MRI. The minimum diameter size should be at least twice the slice thickness.

Non-measurable disease are all other lesions (or sites of disease), including those that are too small (ie, do not meet above criteria), occur within a previously irradiated area (unless they are documented as new lesions since the completion of radiation therapy), bone lesions, leptomeningeal disease, ascites, pleural or pericardial effusion (exception for effusions documented by cytology as not malignant or present at baseline without progression), lymphangitis cutis/pulmonis, abdominal masses that are not pathologically/cytologically confirmed and followed by imaging techniques, and cystic lesions.

5.4.4 Definitions of Response and Progression Criteria

See [Appendix 6](#) for definitions of response and progression. All criteria are derived from IMWG^{46,47,48}, except for minor (minimal) response, which is derived from EBMT. All response categories require 2 consecutive assessments made before initiation of any new therapy.

5.5 Pharmacokinetic Assessments

Blood samples for pharmacokinetic (PK) assessment will be drawn according to the PK sampling schedule provided in [Table 5.5.1-1](#). Development of anti-drug antibodies (ADA) will be evaluated in all subjects receiving elotuzumab at specified time points as noted in [Table 5.5.1-1](#). Blood samples for the analysis of serum concentrations of elotuzumab should be drawn from the arm not used for infusion of study drug. Detailed instructions for the collection, processing, handling, labeling, storage, and shipment of PK and ADA samples will be provided in the central laboratory manual.

It is important to record the actual time of sample collection, even if this deviates from the protocol specified time.

5.5.1 Anti-Drug Antibody (ADA) Assessments

Development of Anti-Drug elotuzumab Antibodies (ADA) will be evaluated in subjects receiving elotuzumab at specified time points as noted in Table 5.5.1-1.

Table 5.5.1-1: PK and ADA Sampling Schedule				
Cycle Number	Study Day	Time (Event)	PK Collection^a	ADA Collection^a
1	1	0 H (pre-dose)	X	X
		2 hours post-end of infusion	X	
	8	0 H (pre-dose)	X	
		2 hours post-end of infusion	X	
	15	0 H (pre-dose)	X	
		22	0 H (pre-dose)	X
		2 hours post-end of infusion	X	
		2	1	0 H (pre-dose)
		2 hours post-end of infusion	X	
		22	0 H (pre-dose)	X
			2 hours post-end of infusion	X
		3	1	0 H (pre-dose)
				2 hours post-end of infusion
		4	1	0 H (pre-dose)
5	1			0 H (pre-dose)
		6	1	0 H (pre-dose)
7	1			0 H (pre-dose)
				2 hours post-end of infusion
Every 3rd Cycle after Cycle 7 (ie Cycle 10, 13...etc)	1			0 H (pre-dose)
End of Study / Discontinuation ^b			X	X
30-Day Follow-Up ^b			X	X
60 Day Follow-Up ^b			X	X

^a Subjects who miss a PK and ADA collection, because elotuzumab was not given, should collect PK and ADA samples on the day (predose) that elotuzumab is restarted (noting the actual time of collection and dosing), and then continue following the schedule in Table 5.5.1-1

^b If elotuzumab is discontinued, but the subject remains on study drug(s), PK and ADA samples will be collected at: the day of the last elotuzumab dose, 30 days after the last elotuzumab dose and 60 days after the last elotuzumab dose

5.5.2 Pharmacogenomic/Pharmacogenetic Assessments

Genetic assessment (FISH) of myeloma cells will be performed by a central laboratory on the fresh bone marrow, during the screening period. If a fresh aspirate is not available, but local genetic assessment has been performed since completing the last regimen, but prior to entering this study, these results must be entered into the CRF/eCRF. This assessment is considered to be standard of care for myeloma. Contact BMS medical monitor in these cases. Assessment may include but not be limited to FISH analyses in Section 5.6. In addition, potential biomarkers of resistance or sensitivity to pomalidomide or elotuzumab may be explored in these tumor samples.

5.6.1 Bone Marrow Aspirate Samples:

Bone marrow aspirates for Biomarker Assessments will be evaluated at a Central Lab:

- 1) Cytometry of:
 - a) Plasma cell (PC) subsets: Evaluation of, but not limited to SLAMF7 (target of elotuzumab) and PD-L1 on enumerated CD138⁺/CD38⁺ PCs. PC subsets will be further subdivided into normal and aberrant (malignant) based on differential expression of CD19 and CD56.
 - b) Lymphoid and myeloid subsets: will be enumerated and evaluated for expression of but not limited to SLAMF7 and PD-1. In addition to the absolute lymphocyte count, enumeration and percentage of cell subsets will be determined by multiparameter cytometry to assess major NK cells subsets, naïve and memory T cell subsets, T_{reg} cells, Th17 cells, MDSCs, and pDCs.
- 2) Gene expression: CD138 magnetic separation and enrichment of CD138⁺ (plasma cells) and CD138⁻ (which includes lymphocytes) cells and RNAseq of PCs and lymphocytes in the bone marrow microenvironment.
- 3) Protein analysis (marrow): Following separation of CD138⁺ and CD138⁻ cell cellular fractions from the bone marrow aspirate (see “Gene expression analysis”), the soluble (non-cellular) fraction will be assessed for proteins, including but not limited to soluble SLAMF7 (sSLAMF7) and potentially immune regulators such as cytokines/chemokines.
- 4) Fluorescence in-situ hybridization (FISH): bone marrow aspirates obtained at screening will be used to identify prognostic cytogenetic markers that may include but are not limited to: t(4 ;14), t(14 ;16), t(11 ;14), t(6;14), t(14;20), 1q gains/amp, del(17p), del(1p), and del(13). FISH analysis will be limited to bone marrow aspirates obtained at screening (mandated) and at EOT (if available).
- 5) Molecular minimum residual disease (MRD) assessment by Adaptive® ClonoSIGHT assay.
- 6) Cytometry MRD: using a portion of the bone marrow sample collected at time of CR/sCR.

5.6.2 Peripheral Blood Samples:

Peripheral Blood samples for Biomarker Assessments will be evaluated at a Central Lab:

- 1) Lymphoid and myeloid subsets: (same population as with marrow).
- 2) Molecular (MRD) whole blood assessment by Adaptive® ClonoSIGHT assay.
- 3) Protein analysis (serum): Assessment of soluble proteins in circulation that include but are not limited to sSLAMF7 and potentially immune regulators such as cytokines/chemokines.
- 4) Fc-γR polymorphisms: for genotyping of Fc receptor genes (minimally CD16a and CD32a) and other host genes that may be related to regulators of immune response and anti-tumor activity.
- 5) Gene Expression Profiling: gene expression levels and changes (along with gene networks or pathways) to better understand the complex nature of the immune response.

5.7 Outcomes Research Assessments

5.7.1 Patient-reported Outcomes (PRO) Assessments

To assess the impact of treatment on patient-reported outcomes, two questionnaires will be used:

- 1) M.D. Anderson Symptom Inventory Multiple Myeloma module MDASI-MM (Appendix 4), which measures symptoms.
- 2) EuroQol Group's EQ-5D (Appendix 5), which measures utilities, and is a preference-based measure of health status.

Questionnaires will be administered to all subjects per the schedule in [Table 5.1-1](#), [Table 5.1-2](#) and [Table 5.1-3](#).

All questionnaires will be administered at (1) baseline (prior to randomization); (2) on Day 1 of each 4 week treatment cycle; (3) at the end of treatment or study withdrawal; (4) at each survival follow-up at the post treatment phase of the study via telephone. Traditional telephone communication between research staff and patient, or automated interactive voice response (IVR) system may reduce the burden of missing data in monitoring patient reported outcomes while they are away from the clinical sites. EQ-5D has been validated in paper, telephone interview, as well as IVR formats. Telephone interview scripts in local languages, detailed training and instructions will be provided to field staff administering the questionnaire.

Subjects should fill out the questionnaire prior to any study-related procedures, treatment or clinical assessment in order to prevent these variables from influencing PRO results. PRO instruments are provided as part of the CRF. Questionnaires will be provided in the subject's preferred language.

M. D. Anderson Symptom Inventory (MDASI) is reliable, valid instrument that was designed for ease of administration and that asks patients to rate 13 symptoms (“core” items) and 6 symptom-related interference items that are common across cancer types and treatments. The multiple myeloma module of the MDASI (MDASI-MM) is a site-specific module that augments the 19 core MDASI symptom and interference items with additional items identified as unique to multiple myeloma. Along with the core MDASI’s 13 symptom items and 6 interference items, the MDASI-MM also assesses 7 multiple myeloma-specific symptom items: bone aches, muscle weakness, sore mouth/throat, rash, difficulty concentrating, constipation, and diarrhea.

EuroQol Group’s EQ-5D:

Because oncology therapies may positively or negatively affect a patient’s quality of life, a common methodological approach is used to quantify this effect by “quality adjusting” survival in comparative treatment arms. The result, quality adjusted life years (QALYs), is a measure of both the length and quality of life and is used as a measure of benefit in cost-utility analysis. Unfortunately, general PRO instruments such as the EORTC QLQ C30 are not designed to measure subject preferences (or utilities) in a way that is suitable for calculating QALYs. Therefore, a separate validated instrument, in this case the EuroQol EQ 5D, will be used to quantify utilities to calculate QALYs for cost utility analyses.

The EQ 5D is a 5-item questionnaire and a “thermometer” visual analogue scale ranging from 0 (worst imaginable health state) to 100 (best imaginable health state) that will be administered at the same intervals as the other PRO instruments, including at the Screening Visit to assess the comparability of the groups at study initiation. The time referent is “today” for this instrument.

Enhancing Compliance

It is necessary to implement specific measures to ensure optimal compliance in PRO data collection. Both staff and patients will be provided with the necessary training and resources for optimal data collection at the appropriate times. Collaboration between the study coordinator, the data center responsible for the day to day administration of the study and the individual investigators can lead to organizational improvements. More specific measures will be targeted at the patient, the physician and the data manager or the research nurse, though there is considerable overlap.

Missing Data

If a questionnaire is missing during the acceptable time delay, a reason should be recorded (eg, refusal, nurse forgot, etc.), and the patient should be contacted by telephone and mail with the questionnaire and a reply paid envelope. An acceptable time delay or “window” during which the questionnaire must be completed is ± 1 week during treatment, at EOT, and the first two visits post treatment, to ensure evaluation of short-term toxicity and response. During follow up for EQ-5D, a wider window (± 3 weeks) would be acceptable after the first two post-treatment visits.

5.7.2 Healthcare Resource Utilization

During the study, healthcare resource utilization (HRU) data associated with medical encounters related to disease or treatments or both will be collected for all subjects. Specifically, HRU is evaluated based on the number of medical care encounters such as hospital admissions and their duration, outpatient visits, diagnostic tests and procedures, and concomitant medications. HRU data will be collected from all sites. The medical resource utilization data will be utilized to conduct economic analyses.

5.8 Other Assessments

Not applicable.

5.9 Results of Central Assessments

All efficacy laboratory assessments should be performed by the central laboratory. Investigative site staff will receive reports of the results on an ongoing basis for treatment decisions and patient management throughout the study. If the investigator chooses to perform any additional serum and urine myeloma lab tests locally, the results must be reported in the CRF

6 ADVERSE EVENTS

An *Adverse Event (AE)* is defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a clinical investigation subject administered study drug and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (such as an abnormal laboratory finding), symptom, or disease temporally associated with the use of study drug, whether or not considered related to the study drug.

The causal relationship to study drug is determined by a physician and should be used to assess all adverse events (AE). The causal relationship can be one of the following:

Related: There is a reasonable causal relationship between study drug administration and the AE.

Not related: There is not a reasonable causal relationship between study drug administration and the AE.

The term "reasonable causal relationship" means there is evidence to suggest a causal relationship.

Adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject. (In order to prevent reporting bias, subjects should not be questioned regarding the specific occurrence of one or more AEs.)

6.1 Serious Adverse Events

A *Serious Adverse Event (SAE)* is any untoward medical occurrence that at any dose:

- results in death
- is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)

- requires inpatient hospitalization or causes prolongation of existing hospitalization (see **NOTE** below)
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [eg, medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.) Potential drug induced liver injury (DILI) is also considered an important medical event. (See [Section 6.6](#) for the definition of potential DILI.)

Suspected transmission of an infectious agent (eg, pathogenic or nonpathogenic) via the study drug is an SAE.

Although pregnancy, overdose, cancer, and potential drug induced liver injury (DILI) are not always serious by regulatory definition, these events must be handled as SAEs. (See [Section 6.1.1](#) for reporting pregnancies).

Any component of a study endpoint that is considered related to study therapy (eg, death is an endpoint, if death occurred due to anaphylaxis, anaphylaxis must be reported) should be reported as SAE (see [Section 6.1.1](#) for reporting details).

NOTE:

The following hospitalizations are not considered SAEs in BMS clinical studies:

- a visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered an important medical or life-threatening event)
- elective surgery, planned prior to signing consent
- admissions as per protocol for a planned medical/surgical procedure
- routine health assessment requiring admission for baseline/trending of health status (eg, routine colonoscopy)
- medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases
- admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (eg, lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason).
- Admission for administration of anticancer therapy in the absence of any other SAEs (applies to oncology protocols)

6.1.1 Serious Adverse Event Collection and Reporting

Sections 5.6.1 and 5.6.2 in the Investigator Brochure (IB) represent the Reference Safety Information to determine expectedness of serious adverse events for expedited reporting. Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures. All SAEs must be collected that occur during the screening period and within 60 days of discontinuation of dosing or within 30 days of the last visit for screen failures. The investigator must report any SAE that occurs after these time periods and that is believed to be related to study drug or protocol-specified procedure.

An SAE report must be completed for any event where doubt exists regarding its seriousness.

If the investigator believes that an SAE is not related to study drug, but is potentially related to the conditions of the study (such as withdrawal of previous therapy or a complication of a study procedure), the relationship must be specified in the narrative section of the SAE Report Form.

SAEs, whether related or not related to study drug, and pregnancies must be reported to BMS (or designee) within 24 hours of awareness of the event. SAEs must be recorded on the SAE Report Form; pregnancies on a Pregnancy Surveillance Form (electronic or paper forms). The preferred method for SAE data reporting collection is through the eCRF. The paper SAE/pregnancy surveillance forms are only intended as a back-up option when the eCRF system is not functioning. In this case, the paper forms are to be transmitted via email or confirmed facsimile (fax) transmission to:

SAE Email Address: Refer to Contact Information list.

SAE Facsimile Number: Refer to Contact Information list.

For studies capturing SAEs through electronic data capture (EDC), electronic submission is the required method for reporting. In the event the electronic system is unavailable for transmission, paper forms must be used and submitted immediately. When paper forms are used, the original paper forms are to remain on site.

SAE Telephone Contact (required for SAE and pregnancy reporting): Refer to Contact Information list.

If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports must include the same investigator term(s) initially reported.)

If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, the SAE report must be updated and submitted within 24 hours to BMS (or designee) using the same procedure used for transmitting the initial SAE report.

All SAEs must be followed to resolution or stabilization.

6.2 Nonserious Adverse Events

A *nonserious adverse event* is an AE not classified as serious.

6.2.1 Nonserious Adverse Event Collection and Reporting

The collection of nonserious AE information should begin at initiation of study drug. Nonserious AE information should also be collected from the start of a placebo lead-in period or other observational period intended to establish a baseline status for the subjects.

Nonserious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious (see [Section 6.1.1](#)). Follow-up is also required for nonserious AEs that cause interruption or discontinuation of study drug and for those present at the end of study treatment as appropriate. All identified nonserious AEs must be recorded and described on the nonserious AE page of the CRF (paper or electronic).

Completion of supplemental CRFs may be requested for AEs and/or laboratory abnormalities that are reported/identified during the course of the study.

6.3 Laboratory Test Result Abnormalities

The following laboratory test result abnormalities should be captured on the nonserious AE CRF page or SAE Report Form (paper or electronic) as appropriate:

- Any laboratory test result that is clinically significant or meets the definition of an SAE
- Any laboratory test result abnormality that required the subject to have study drug discontinued or interrupted
- Any laboratory test result abnormality that required the subject to receive specific corrective therapy.

It is expected that wherever possible, the clinical rather than laboratory term would be used by the reporting investigator (eg, anemia versus low hemoglobin value).

6.4 Pregnancy

If, following initiation of the study drug, it is subsequently discovered that a study subject is pregnant or may have been pregnant at the time of study exposure, including during at least time to washout (90 days) plus one ovulatory cycle (30 days) for a total of 120 days, or plus one spermatogenesis cycle (90 days) for a total of 180 days after product administration, the investigator must immediately notify the BMS Medical Monitor/designee of this event and complete and forward a Pregnancy Surveillance Form to BMS Designee within 24 hours of awareness of the event and in accordance with SAE reporting procedures described in [Section 6.1.1](#).

In most cases, the study drug will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for subject safety).

In the rare event that the benefit of continuing study drug is thought to outweigh the risk, after consultation with BMS, the pregnant subject may continue study drug after a thorough discussion of benefits and risk with the subject

Protocol-required procedures for study discontinuation and follow-up must be performed on the subject unless contraindicated by pregnancy (eg, x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated.

The investigator must immediately notify the BMS (or designee) Medical Monitor of this event and complete and forward a Pregnancy Surveillance Form to BMS (or designee) within 24 hours of awareness of the event and in accordance with SAE reporting procedures described in [Section 6.1.1](#).

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information must be reported on the Pregnancy Surveillance Form.

Any pregnancy that occurs in a female partner of a male study participant should be reported to BMS. Information on this pregnancy will be collected on the Pregnancy Surveillance Form.

6.5 Overdose

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported as an SAE (see Section 6.1.1 for reporting details).

6.6 Potential Drug Induced Liver Injury (DILI)

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI event. All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs (see Section 6.1.1 for reporting details).

Potential drug induced liver injury is defined as:

1. AT (ALT or AST) elevation > 3 times upper limit of normal (ULN)
AND
2. Total bilirubin > 2 times ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase)
AND
3. No other immediately apparent possible causes of AT elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

6.7 Other Safety Considerations

Any significant worsening noted during interim or final physical examinations, electrocardiogram, x-ray filming, any other potential safety assessment required or not required by protocol should also be recorded as a nonserious or serious AE, as appropriate, and reported accordingly.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

8.3 Endpoints

8.3.1 Primary Endpoint(s)

8.3.1.1 Primary definition of PFS

PFS will be defined as the time, in months, from randomization to the date of the first documented tumor progression or death due to any cause. Clinical deterioration will not be considered progression. A subject who neither progresses nor dies will be censored on the date of their last tumor assessment. A subject who does not have any post-baseline tumor assessments and who has not died will be censored on the date at which they were randomized.

8.3.1.2 Secondary Definition of PFS:

PFS will be analyzed after censoring patients who either received subsequent therapy or had two or more missing tumor assessments prior to their disease progression or death. In this secondary definition, PFS will also be measured as the time in months from randomization to the date of the first documented tumor progression or death due to any cause, provided death does not occur more than 10 weeks (2 or more assessment visits) after the last tumor assessment. Clinical deterioration will not be considered progression.

The following censoring rules will be applied for this definition of PFS:

- Subjects who receive secondary anti-myeloma therapy prior to documented progression will be censored on the date of the last adequate tumor assessment prior to the initiation of the new therapy.
- Subjects who have an event (documented progression or death) > 10 weeks (2 assessment visits) after the last prior tumor assessment will be censored at the last adequate prior assessment.
- Subjects who neither receive subsequent therapy prior to progression nor have a progression event will be censored at their last adequate tumor assessment.

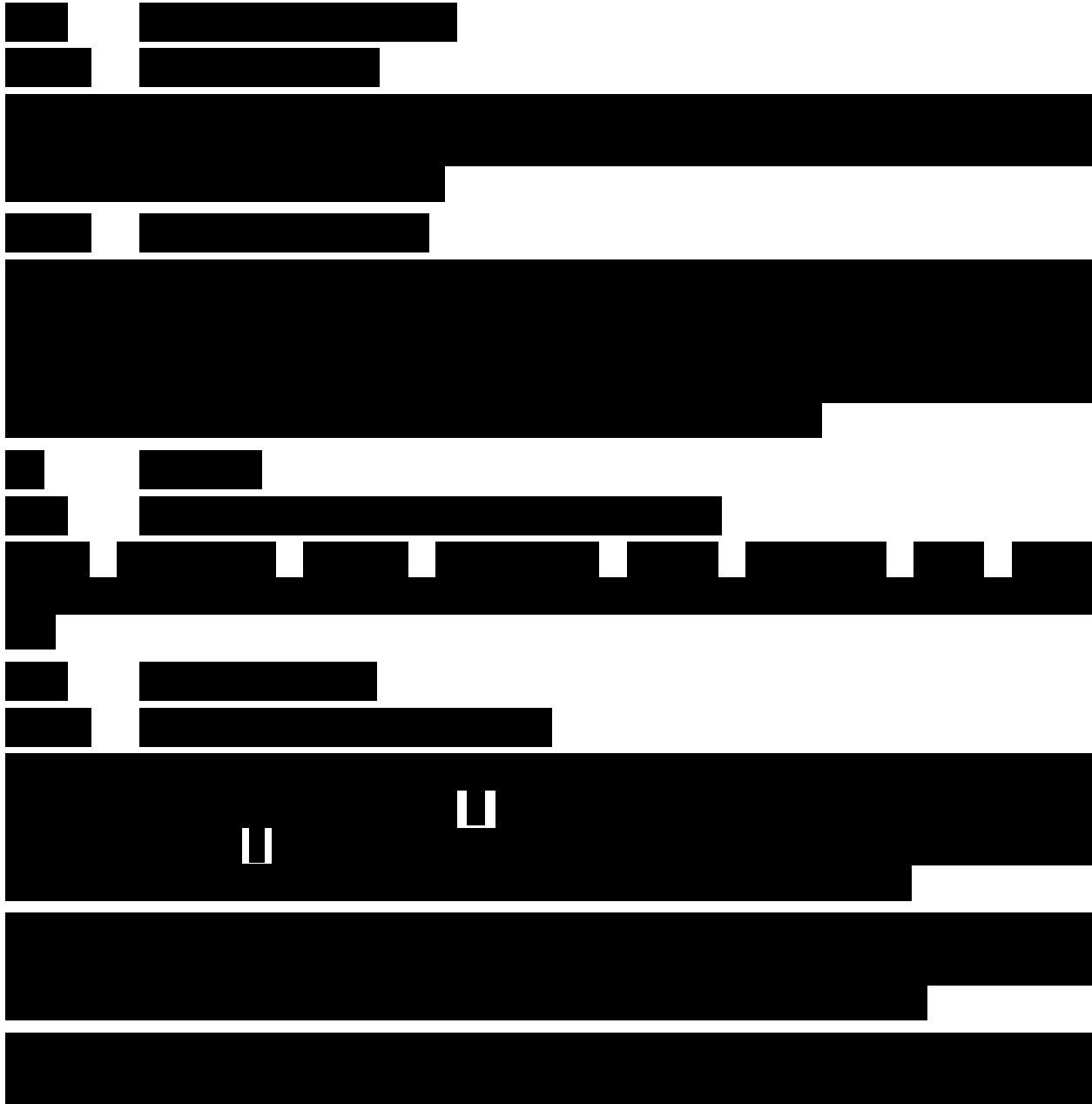
8.3.2 Secondary Endpoint(s)

8.3.2.1 Objective response rate

Objective response rate is defined as the proportion of randomized subjects who achieve a best response of partial response (PR) or better using the criteria in [Appendix 6](#).

8.3.2.2 Overall survival

Overall survival is defined as the time from randomization to the date of death from any cause. If a subject has not died, their survival time will be censored at the date of last contact (“last known alive date”). A subject will be censored at the date of randomization if they were randomized but had no follow-up.



[REDACTED]

[REDACTED]

8.4.2.2 Secondary Efficacy Analysis

Objective response rate is a secondary objective. A two-sided $\alpha = 0.2$ level Cochran-Mantel-Haenszel (CMH) test, stratified using the same factors as in PFS, will be used to compare the response rate between the treatment arms. The response rate, along with its exact two-sided 80% CI, will be computed within each treatment arm. A two-sided, 80% CI for difference of response rate between the treatment arms will also be computed. In addition, the two-sided 95% CI will also be computed.

Overall survival is another secondary objective. It will be compared between arms using a stratified group sequential log-rank test procedure with a two-sided, $\alpha = 0.2$ level. The stratification factors will be the same as those used for the analyses of PFS and tumor response. The OS function for each randomized arm will be estimated using the Kaplan-Meier product-limit method. Median and two-sided, confidence intervals for median OS will be computed by randomized arm.

8.4.3 Safety Analyses

Safety analyses will be conducted on all treated population. Adverse events and laboratory parameters will be summarized using CTCAE version 3.0. Summary tables will be presented on safety parameters for each treatment arm. Limited safety analysis will be presented on all treated subjects in the lead in phase of the study.

8.4.4 Pharmacokinetic Analyses

Summary statistics will be calculated for elotuzumab concentrations and summarized by scheduled sample collection time. This data will be combined with concentration data from other studies to conduct a population pharmacokinetic (PPK) analysis. Results of PPK will be reported separately. Anti-drug antibodies will also be assessed.

[REDACTED]

[REDACTED]

[REDACTED]

9 STUDY MANAGEMENT

9.1 Compliance

9.1.1 Compliance with the Protocol and Protocol Revisions

The study shall be conducted as described in this approved protocol. All revisions to the protocol must be discussed with, and be prepared by, BMS. The investigator should not implement any deviation or change to the protocol without prior review and documented approval/favorable opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to study subjects.

If a deviation or change to a protocol is implemented to eliminate an immediate hazard(s) prior to obtaining IRB/IEC approval/favorable opinion, as soon as possible the deviation or change will be submitted to:

- IRB/IEC for review and approval/favorable opinion
- BMS
- Regulatory Authority(ies), if required by local regulations

Documentation of approval signed by the chairperson or designee of the IRB(s)/IEC(s) must be sent to BMS.

If an amendment substantially alters the study design or increases the potential risk to the subject: (1) the consent form must be revised and submitted to the IRB(s)/IEC(s) for review and approval/favorable opinion; (2) the revised form must be used to obtain consent from subjects currently enrolled in the study if they are affected by the amendment; and (3) the new form must be used to obtain consent from new subjects prior to enrollment.

If the revision is done via an administrative letter, investigators must inform their IRB(s)/IEC(s).

9.1.2 Monitoring

BMS representatives will review data centrally to identify potential issues to determine a schedule of on-site visits for targeted review of study records.

Representatives of BMS must be allowed to visit all study site locations periodically to assess the data quality and study integrity. On site they will review study records and directly compare them with source documents, discuss the conduct of the study with the investigator, and verify that the facilities remain acceptable. CRF pages and/or electronic files may serve as the source documents: such as outcome assessments.

In addition, the study may be evaluated by BMS internal auditors and government inspectors who must be allowed access to CRFs, source documents, other study files, and study facilities. BMS audit reports will be kept confidential.

The investigator must notify BMS promptly of any inspections scheduled by regulatory authorities, and promptly forward copies of inspection reports to BMS.

9.1.2.1 Source Documentation

The Investigator is responsible for ensuring that the source data are accurate, legible, contemporaneous, original and attributable, whether the data are hand-written on paper or entered electronically. If source data are created (first entered), modified, maintained, archived, retrieved, or transmitted electronically via computerized systems (and/or any other kind of electronic devices) as part of regulated clinical trial activities, such systems must be compliant with all applicable laws and regulations governing use of electronic records and/or electronic signatures. Such systems may include, but are not limited to, electronic medical/health records (EMRs/EHRs), adverse event tracking/reporting, protocol required assessments, and/or drug accountability records).

When paper records from such systems are used in place of electronic format to perform regulated activities, such paper records should be certified copies. A certified copy consists of a copy of original information that has been verified, as indicated by a dated signature, as an exact copy having all of the same attributes and information as the original.

9.1.3 Investigational Site Training

Bristol-Myers Squibb will provide quality investigational staff training prior to study initiation. Training topics will include but are not limited to: GCP, AE reporting, study details and procedure, electronic CRFs, study documentation, informed consent, and enrollment of WOCBP.

9.2 Records

9.2.1 Records Retention

The investigator must retain all study records and source documents for the maximum period required by applicable regulations and guidelines, or institution procedures, or for the period specified by BMS, whichever is longer. The investigator must contact BMS prior to destroying any records associated with the study.

BMS will notify the investigator when the study records are no longer needed.

If the investigator withdraws from the study (eg, relocation, retirement), the records shall be transferred to a mutually agreed upon designee (eg, another investigator, IRB). Notice of such transfer will be given in writing to BMS.

9.2.2 Study Drug Records

It is the responsibility of the investigator to ensure that a current disposition record of study drug (inventoried and dispensed) is maintained at the study site to include investigational product and the following non-investigational product(s) pomalidomide and dexamethasone. Records or logs must comply with applicable regulations and guidelines and should include:

- amount received and placed in storage area
- amount currently in storage area
- label identification number or batch number
- amount dispensed to and returned by each subject, including unique subject identifiers

- amount transferred to another area/site for dispensing or storage
- non-study disposition (eg, lost, wasted)
- amount destroyed at study site, if applicable
- amount returned to BMS
- retain samples for bioavailability/bioequivalence, if applicable
- dates and initials of person responsible for Investigational Product dispensing/accountability, as per the Delegation of Authority Form.

BMS will provide forms to facilitate inventory control if the investigational site does not have an established system that meets these requirements.

9.2.3 Case Report Forms

An investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated or entered as a control in the investigation. Data that are derived from source documents and reported on the CRF must be consistent with the source documents or the discrepancies must be explained. Additional clinical information may be collected and analyzed in an effort to enhance understanding of product safety. CRFs may be requested for AEs and/or laboratory abnormalities that are reported or identified during the course of the study.

For sites using the BMS electronic data capture tool, electronic CRFs will be prepared for all data collection fields except for fields specific to SAEs and pregnancy, which will be reported on the paper or electronic SAE form and Pregnancy Surveillance form, respectively. Spaces may be left blank only in those circumstances permitted by study-specific CRF completion guidelines provided by BMS.

The confidentiality of records that could identify subjects must be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

The investigator will maintain a signature sheet to document signatures and initials of all persons authorized to make entries and/or corrections on CRFs.

The completed CRF, including any paper or electronic SAE/pregnancy CRFs, must be promptly reviewed, signed, and dated by the investigator or qualified physician who is a subinvestigator and who is delegated this task on the Delegation of Authority Form. For electronic CRFs, review and approval/signature is completed electronically through the BMS electronic data capture tool. The investigator must retain a copy of the CRFs including records of the changes and corrections.

Each individual electronically signing electronic CRFs must meet BMS training requirements and must only access the BMS electronic data capture tool using the unique user account provided by BMS. User accounts are not to be shared or reassigned to other individuals.

9.3 Clinical Study Report and Publications

A Signatory Investigator must be selected to sign the clinical study report.

For this protocol, the Signatory Investigator will be selected as appropriate based on the following criteria:

- Subject recruitment (eg, among the top quartile of enrollers)
- Involvement in trial design
- Other criteria (as determined by the study team)

The data collected during this study are confidential and proprietary to BMS. Any publications or abstracts arising from this study must adhere to the publication requirements set forth in the clinical trial agreement (CTA) governing [Study site or Investigator] participation in the study. These requirements include, but are not limited to, submitting proposed publications to BMS at the earliest practicable time prior to submission or presentation and otherwise within the time period set forth in the CTA.

10 GLOSSARY OF TERMS

Term	Definition
Complete Abstinence	<p>If one form of contraception is required, Complete Abstinence is defined as complete avoidance of heterosexual intercourse and is an acceptable form of contraception for all study drugs. Female subjects must continue to have pregnancy tests. Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence.</p> <p>If two forms of contraception is required, Complete abstinence is defined as complete avoidance of heterosexual intercourse and is an acceptable form of contraception for all study drugs. Subjects who choose complete abstinence are not required to use a second method of contraception, but female subjects must continue to have pregnancy tests. Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence.</p> <p><u>Expanded definition</u> Complete abstinence as defined as complete avoidance of heterosexual intercourse is an acceptable form of contraception for all study drugs. This also means that abstinence is the preferred and usual lifestyle of the patient. This does not mean periodic abstinence (eg, calendar, ovulation, symptothermal, profession of abstinence for entry into a clinical trial, post-ovulation methods) and withdrawal, which are not acceptable methods of contraception. Subjects who choose complete abstinence are not required to use a second method of contraception, but female subjects must continue to have pregnancy tests. Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence</p>

11 LIST OF ABBREVIATIONS

Term	Definition
ADA	Anti-Drug Antibodies
ADCC	Antibody dependent cell-mediated cytotoxicity
AE	Adverse event
BMS	Bristol-Myers Squibb
CDR	Complementary Determining Regions
°C	Celsius
CI	Confidence Interval
CMH	Cochran-Mantel-Haenszel
CMMC	Circulating Multiple Myeloma Cells
CR	Complete response
CRF	Case Report Form
CrCl	Creatinine Clearance
CS1	CD-2 subset 1
CT	Computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
DILI	Drug induced liver injury
DLT	Dose-limiting toxicity
DMC	Data monitoring committee
DVT	Deep Vein Thrombosis
EBMT	European Group for Blood and Bone Marrow Transplant
ECG	Electrocardiogram
EORTC	European Organization for Research and Treatment of Cancer
E-Pd	Elotuzumab Pomalidomide (low dose) dexamethasone
EPO	Erythropoietin
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
G-CSF	Granulocyte colony-stimulating factor
HCG	Human Chorionic Gonadotropin
HR	Hazard Ratio

Term	Definition
HRQoL	Health Related Quality of Life
HRT	Hormone replacement therapy
ICH	International Council on Harmonization
IF	Immunofixation
IHC	Immunohistochemistry
IL-2	Interleukin 2
IMiDs	Immune Modulatory Drugs
IMWG	International Myeloma Working Group
IRB/IEC	Institutional Review Board/Independent Ethics Committee
IV	Intravenous
ITT	Intent-to-treat
NK	Natural Killer
NKT	Natural Killer T-Cells
Ld	Lenalidomide (low-dose) dexamethasone
LD	Lenalidomide (high-dose) dexamethasone
LdE	Lenalidomide, (low-dose) dexamethasone, elotuzumab
LPFV	Last patient first visit
MDASI-MM	MD Anderson Symptom Inventory Multiple Myeloma Module
MGUS	Monoclonal Gammopathy of Undetermined Significance
MM	Multiple Myeloma
MR	Minor (Minimal) Response
MRD	Minimal Residual Disease
MRI	Magnetic Resonance Imaging
MTD	Maximum tolerated dose
NK	Natural Killer
NKT	Natural Killer T-cell
ORR	Objective Response Rate
OS	Overall Survival
PBMC	Peripheral blood mononuclear cells
Pd	Pomalidomide (low dose) dexamethsone

Term	Definition
PFS	Progression-free survival
PK	Pharmacokinetic
PR	Partial Response
rrMM	relapsed refractory Multiple Myeloma
SAE	Serious adverse event
sCR	Stringent complete response
sMICA	soluble major histocompatibility complex class I chain-related gene A
SLAMF7	Signaling Lymphocyte Activation Molecule family 7
SPM	Second primary malignancy
sSLAMF7	soluble SLAMF7
SMM	Smoldering Multiple Myeloma
WOCBP	Women of childbearing potential

APPENDIX 1 DEFINITION OF LINES OF THERAPY

Line of Therapy (from International Myeloma Working Group (Rajkumar, 2011)) is defined as one or more cycles of a *planned treatment program*. This may consist of one or more planned cycles of single-agent therapy or combination therapy, as well as a sequence of treatments administered in a planned manner. For example, a planned treatment approach of induction therapy followed by autologous stem cell transplantation, followed by maintenance is considered one line of therapy. Each subsequent line of therapy starts when a planned course of therapy is modified to include other treatment agents (alone or in combination) as a result of disease progression, relapse, or toxicity. A new line of therapy also starts when a planned period of observation off therapy is interrupted by a need for additional treatment for the disease.

