PROTOCOL

AN OPEN-LABEL EXTENSION STUDY OF XEN496 IN PEDIATRIC SUBJECTS WITH *KCNQ2* DEVELOPMENTAL AND EPILEPTIC ENCEPHALOPATHY

Sponsor:	Xenon Pharmaceuticals Inc. 200-3650 Gilmore Way Burnaby, BC V5G 4W8 Canada		
Study Number:	XPF-009-302		
Clinical Study Identifier:	EPIK OLE		
IND Number:	138144	**EudraCT Number:**	2020-003447-28
Compound:	Ezogabine (USAN)/Retigabine (INN)		
Version:	3.0	**Date:**	09 May 2022
Previous Versions:	• 2.0, dated 04 Apr 2022 • 1.0, dated 29 Sept 2020		

CONFIDENTIALITY STATEMENT

STATEMENT OF COMPLIANCE

The study will be carried out in accordance with the protocol, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use-Good Clinical Practice (ICH-GCP) and applicable regulatory requirements.

The protocol, informed consent form(s), recruitment materials, and all subject materials will be submitted to the ethics committee/institutional review board (EC/IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any subject is enrolled. Any amendment to the protocol will require review and approval by the EC/IRB. In addition, all changes to the consent form will be EC/IRB-approved; a determination will be made regarding whether a new consent needs to be obtained from subjects who provided consent, using a previously approved consent form.

SPONSOR APPROVAL

STUDY TITLE: An Open-label Extension Study of XEN496 in Pediatric Subjects With *KCNQ2* Developmental and Epileptic Encephalopathy

I, the undersigned, have read this protocol and agree that it contains all necessary information required to conduct the study.

SIGNATURES:

Signature Manifest

[redacted] **Revision:** 01

Title: XPF-009-302 EPIK-OLE Protocol V3.0

Effective Date: 09 May 2022

All dates and times are in Pacific Time.

XPF-009-302 EPIK-OLE Protocol V3.0

Approval

[redacted]	Meaning/Reason
	Approved
	Approved
	Approved
	Approved

INVESTIGATOR AGREEMENT

STUDY TITLE: An Open-label Extension Study of XEN496 in Pediatric Subjects With *KCNQ2* Developmental and Epileptic Encephalopathy

By signing below, I agree that:

I have read this protocol. I approve this document and I agree that it contains all necessary details for carrying out the study as described. I will conduct this study in accordance with the design and specific provisions of this protocol and will make a reasonable effort to complete the study within the time designated. [redacted] understand that the study may be terminated or enrollment suspended at any time by Xenon, with or without cause, or by me if it becomes necessary to protect the best interests of the study subjects.

I agree to conduct this study in full accordance with applicable local regulations, ethics committee/institutional review board regulations, and International Council for Harmonisation Guidelines for Good Clinical Practice.

Investigator's Signature Date

Investigator's Printed Name

COORDINATING INVESTIGATOR AGREEMENT

STUDY TITLE: An Open-label Extension Study of XEN496 in Pediatric Subjects With *KCNQ2* Developmental and Epileptic Encephalopathy

By signing below, I agree that:

I have read this protocol. I approve this document and I agree that it contains all necessary details for carrying out the study as described. I will conduct this study in accordance with the design and specific provisions of this protocol and will make a reasonable effort to complete the study within the time designated. [redacted] I understand that the study may be terminated or enrollment suspended at any time by Xenon, with or without cause, or by me if it becomes necessary to protect the best interests of the study subjects.

I agree to the assigned responsibility for the coordination of investigators at different centers participating in the multicenter trial.

I agree to conduct this study in full accordance with applicable local regulations, ethics committee/institutional review board regulations, and International Council for Harmonisation Guidelines for Good Clinical Practice.

Coordinating Investigator's Signature Date

Coordinating Investigator's Printed Name

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[redacted]

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1.1. Synopsis

Protocol Title:	An Open-label Extension Study of XEN496 in Pediatric Subjects With *KCNQ2* Developmental and Epileptic Encephalopathy
Protocol Number:	XPF-009-302
Protocol Identifier:	EPIK OLE
Phase:	Phase 3
Study Drug:	XEN496: Immediate-release, multi-particulate sprinkle capsule formulation of ezogabine (retigabine) for pediatric subjects. Placebo: Matching capsules containing inactive ingredients (used only during the double-blind transition/titration period). The capsules are meant to be opened and the contents dispersed into soft foods or liquids for oral administration [redacted]
Indication:	Treatment of seizures in pediatric subjects with *KCNQ2* developmental and epileptic encephalopathy (KCNQ2-DEE).
Study Description:	An international, multicenter, open-label extension (OLE) study to assess the long-term safety, tolerability, and efficacy of XEN496 in pediatric subjects with KCNQ2-DEE who participated in the primary efficacy and safety study (XPF-009-301).
Objectives:	**Primary Objective:** • To assess the long-term safety and tolerability of XEN496 in pediatric subjects with KCNQ2-DEE who had participated in the primary study (XPF-009-301). **Secondary Objectives:** • To evaluate the intrasubject efficacy of XEN496 in reducing seizure frequency compared to prior placebo treatment in pediatric subjects with KCNQ2-DEE who were previously randomized to receive placebo in the primary double-blind Phase 3 study (XPF-009-301). • To assess the long-term effect of XEN496 on seizure reduction in pediatric subjects treated with XEN496. • To evaluate Caregiver Global Impression of Severity (CaGI-S) and Caregiver Global Impression of Change (CaGI-C) scores in pediatric subjects with KCNQ2-DEE. • To assess neurocognitive development and behavior after dosing with XEN496 in pediatric subjects with KCNQ2-DEE. • To evaluate the investigator's global impression of the change in the subject's overall condition, assessed using the Clinical Global Impression of Change (CGI-C) scale. • To evaluate the use of rescue medication and change in background antiseizure medications (ASM).

	• To assess the impact of XEN496 on the quality of life of caregivers and subjects with KCNQ2-DEE. • To evaluate the plasma concentrations of ezogabine and *N*-acetyl metabolite of retigabine (ezogabine) (NAMR).
Study Population:	Approximately 40 pediatric subjects diagnosed with KCNQ2-DEE who participated in the primary study (XPF-009-301).

Study Duration:	Subjects will undergo:
	• Screening/Baseline period – subjects will undergo eligibility assessment at Visit 22 or early termination in the primary study (XPF-009-301).
	• Treatment period – 36 months:
	  ○ Blinded transition/titration period – 24 days.
	  ○ Open-label period – approximately 35 months.
	• Taper period – Up to 15 days.
	Subjects who discontinue or complete the study treatment will be required to taper off study drug over a period of up to 15 days.
	• Follow-up – Approximately 4 weeks after subjects have tapered off study drug.
	Total study duration per subject is estimated to be 37 months.

Study Design:	**Study Type:** Interventional. **Estimated Enrollment:** Approximately 40 subjects. **Intervention:** Single group, open-label treatment with XEN496. **Description:** This is an open-label, long-term extension study of XEN496 for the treatment of seizures in subjects with KCNQ2-DEE, that will be open to eligible subjects who participated in the primary study, XPF-009-301. The primary objective is to assess the long-term safety of XEN496. The study includes a screening/baseline visit to assess eligibility. A double-blind transition/titration period will be used to maintain blinding to the treatment allocation in the primary study (XPF-009-301). After completion of the blinded transition/titration period, subjects will continue to receive the study drug at their optimal dose for approximately 35 months. **Screening/Baseline:** Screening/baseline procedures and assessments will be conducted at Visit 22 or early termination in the primary study (XPF-009-301); procedures and assessments in addition to those required at these visits may be conducted in order to confirm eligibility for the OLE study. **Treatment Period:** ***Blinded Transition/Titration Period:*** Subjects who received XEN496 in the primary study will continue to receive XEN496 at the same dose throughout the OLE. Subjects allocated to placebo in the primary study will be required to begin a titration of XEN496 [redacted]

	[redacted] The transition/titration will be performed in a blinded manner to maintain the blind to the treatment arm from the primary study. ***Open-label Period:*** Following the transition/titration period, subjects will continue open-label treatment at their optimal dose of XEN496 for approximately 35 months. **Taper Period and End of Study:** At the end of the treatment period, subjects will be required to taper off study drug over a period of up to 15 days. Subjects who discontinue the study early will be required to enter into the taper period at that time and will be expected to complete the end of study follow-up safety monitoring schedule. Subjects will be monitored for safety for 28 days after the last dose of study drug has been administered.
Criteria for Subject Selection:	**Criteria for Inclusion:** To be eligible to participate in the study, an individual must meet all of the following criteria: 1. Subject completed participation as defined in the primary study, XPF-009-301. A subject who withdraws from the primary study due to meeting protocol-specified worsening criteria will be considered as having completed participation in the primary study. 2. The caregiver is willing and able to comply with diary completion, visit schedule, and study drug administration requirements. 3. Subject's caregiver achieved a minimum of 85% compliance with daily diary completion during both baseline and the double-blind period of the primary study. **Criteria for Exclusion:** Any subject who meets any of the following criteria will not qualify for entry into the study: 1. Any adverse event (AE) or serious adverse event (SAE) during Study XPF-009-301, which in the opinion of the investigator and sponsor's medical monitor, would preclude the subject's entry into the OLE. 2. A clinically significant condition or illness, or symptoms other than those resulting from KCNQ2-DEE, present at screening/baseline that, in the opinion of the investigator, would pose risk to the subject if s/he were to enter the study. 3. Any conditions that were specified as exclusion criteria in the primary study (XPF-009-301). 4. It is anticipated that the subject will require treatment with at least one of the disallowed medications during the study. 5. [redacted]

Treatment Allocation:	All subjects rolling over into the OLE study will receive active treatment with XEN496. Subjects will undergo a blinded transition/titration period, regardless of their treatment allocation in the primary study (XPF-009-301).
Dose Administration and Discontinuation:	**Dose Administration:** XEN496 is supplied as sprinkle capsules at 3 dose strengths of [redacted] Capsules in dose strengths of [redacted] will be dispensed when subjects complete their transition or titration period. The daily dose of XEN496 is calculated based on body weight and should be administered orally 3 times daily (TID) in equally divided doses (as supplied by the pharmacy). The entire contents of the capsules containing XEN496 [redacted] of a soft food or liquid prior to ingestion. [redacted] **Treatment Period:** ***Blinded Transition/Titration Period:*** The treatment period begins with a dose transition/titration period. Subjects who received XEN496 in the preceding study will continue to receive XEN496 at the same dose, in a blinded manner, without any further titration. Subjects allocated to placebo in the preceding study, [redacted] The following dose titration scheme is approximate. The final dose and number of capsules using the weight-based dosing are detailed in the pharmacy manual. [redacted] The investigator will be blinded during the transition/titration period. Assuming no moderate to severe treatment-related AEs occur, the subject's dose will be escalated to the next dose level during titration according to the dosing regimen. The maximum dose will not exceed [redacted]

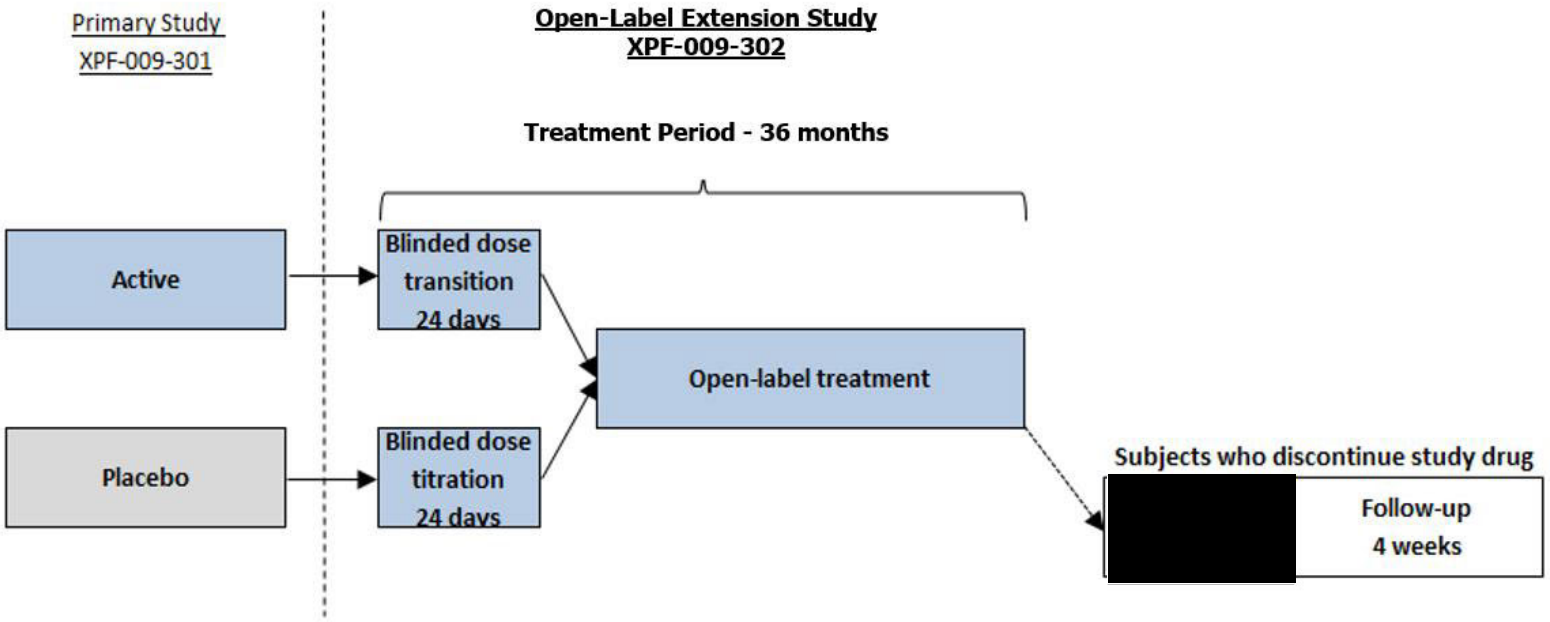
	[redacted] ***Open-label Period:*** The optimally-tolerated dose level established during the transition/titration period will be maintained throughout the duration of the open-label period unless dose adjustment is required. The investigator will assess the subject's tolerability and AE profile throughout the treatment period. [redacted] **Dose Taper Period:** Subjects who complete the study or exit the study early should have the dose reduced in a stepwise manner [redacted] that were used during titration, but in reverse order.
Outcome Measures:	**Safety Endpoints:** • Severity and frequency of AEs and SAEs; clinically significant changes in laboratory tests, vital signs, electrocardiograms (ECGs), physical and neurologic examinations, [redacted] **Key Efficacy Endpoint:** • Change in monthly countable motor seizure frequency, comparing the first 15 weeks of XEN496 treatment in the OLE study to the seizure frequency reported during treatment in the preceding primary study (XPF-009-301), among only those subjects who were randomized to the placebo arm in the primary study (XPF-009-301). **Additional Endpoints:** • Change from pre-randomization baseline in the previous study over time based on response categories (<25%, 25 to <50%, 50 to <75%, 75 to <100%, 100%), based on estimated seizure frequency every 3 months during the OLE period. • Percent change from baseline in countable motor seizure frequency, relative to pre-randomization baseline of the previous study (XPF-009-301), assessed over time every 3 months during the OLE. • Percent change from baseline in countable motor seizure frequency, relative to pre-randomization baseline of the previous study (XPF-009-301), for every 3 months based on combined data from both XPF-009-301 and the OLE, by the treatment group in the previous study.

	• Change over time in CaGI-S scores for the subject's seizures and overall condition. • Change over time in CaGI-C scores for the subject in the following domains: overall condition, seizures, behavior, alertness, motor skills, visual function, and communication. • Change over time in neurocognitive development based on the Bayley Scales of Infant and Toddler Development, Third Edition (BSID-III). • Change over time in adaptive behavior based on the Adaptive Behavior Assessment System, Third Edition (ABAS-3). • Change over time in CGI-C scores for the subject's seizures and overall condition. • Use of rescue medication. • Use of all concomitant medications including treatments used for seizure control. • Change in quality of life of subjects with KCNQ2-DEE, based on the Pediatric Quality of Life Inventory (PedsQL). • Change in quality of life of subjects with KCNQ2-DEE, based on the Pediatric Quality of Life Inventory, Family Impact Module (PedsQL-FIM). • Plasma concentrations of ezogabine and NAMR.
Statistical Considerations:	[redacted]

	[redacted]
Sample Size Determination:	Approximately 40 subjects may be included in the study based on the number of subjects who could roll over from Study XPF-009-301.

1.2. Schema

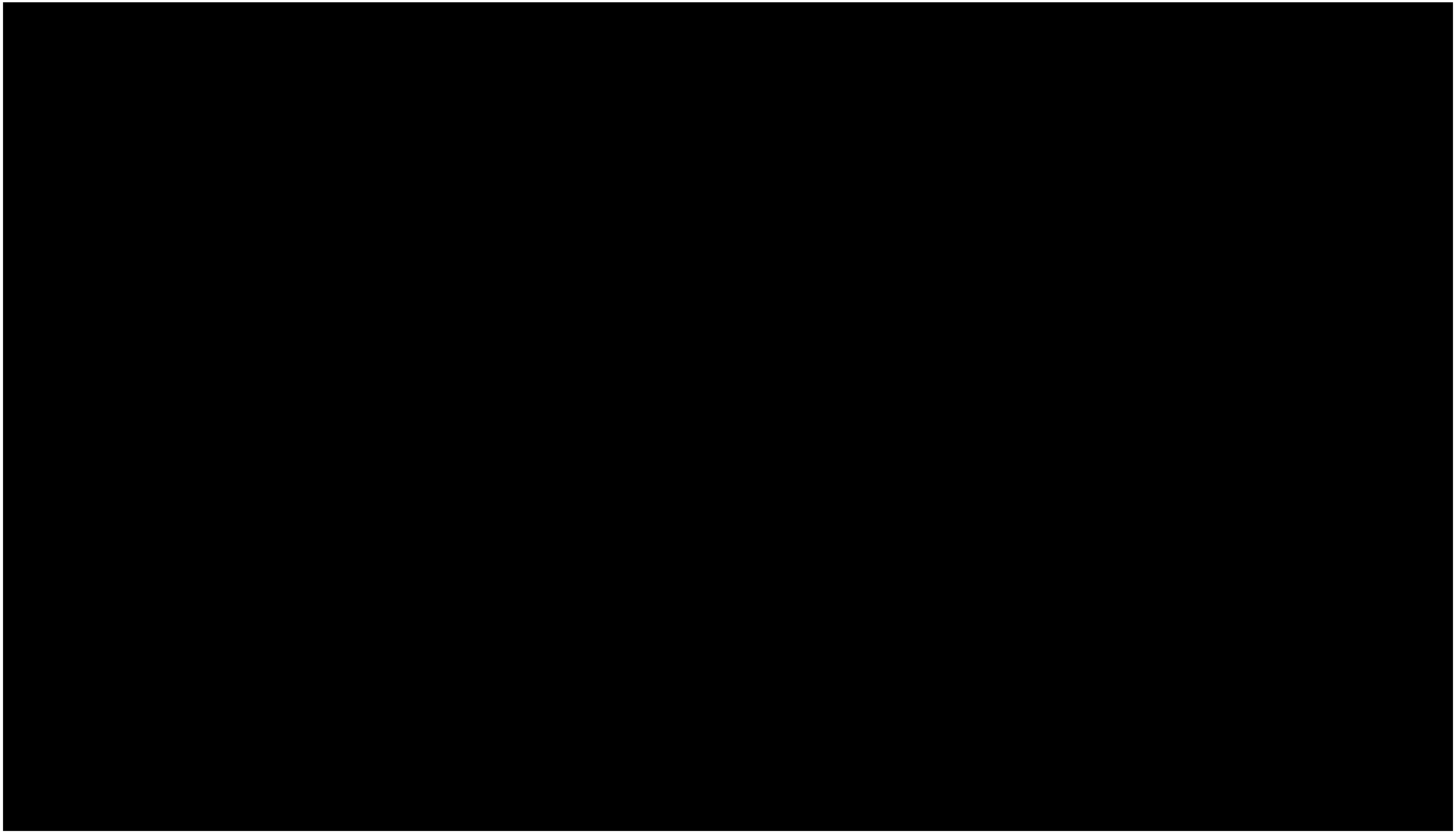
Figure 1 Study Design Schematic

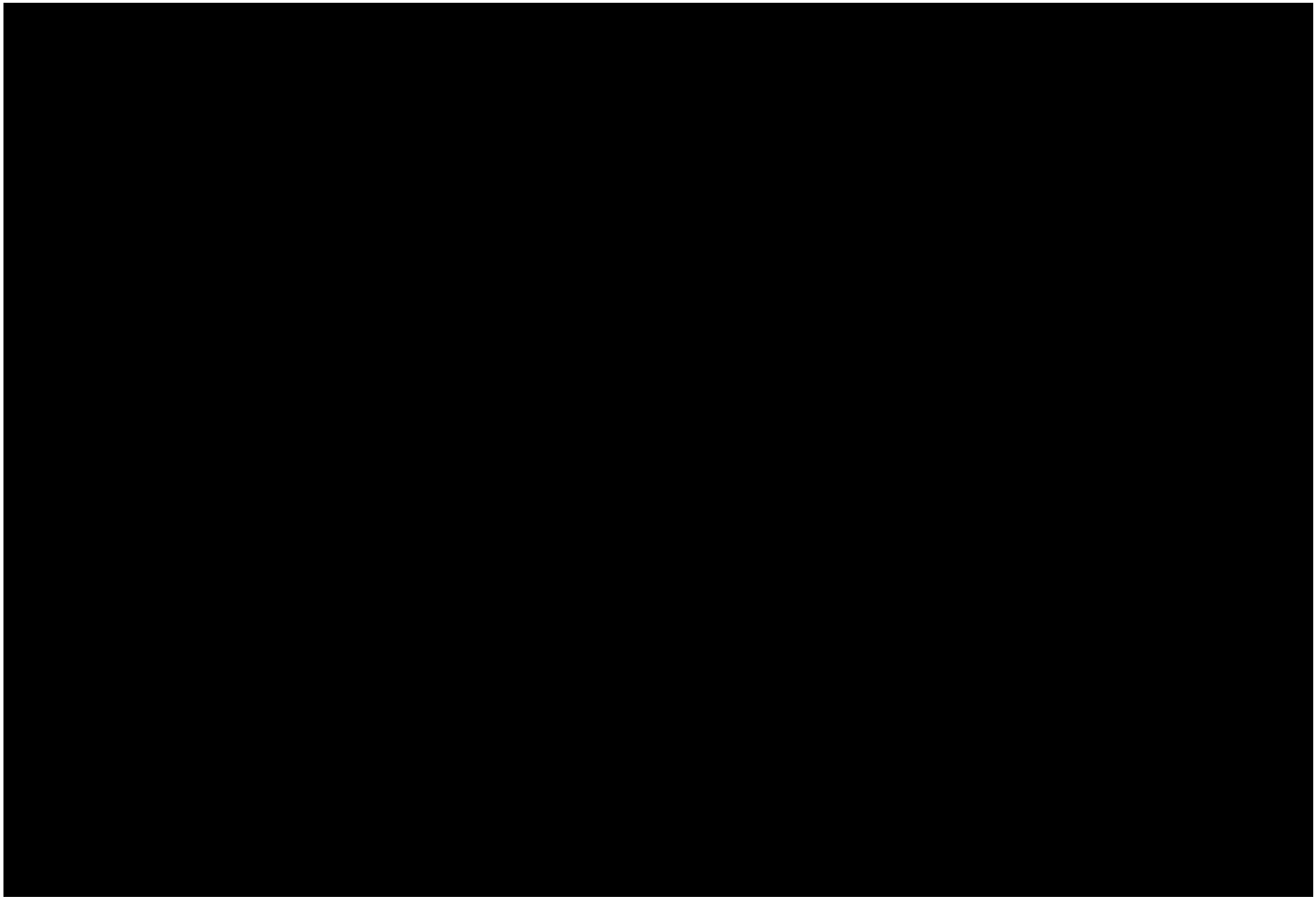


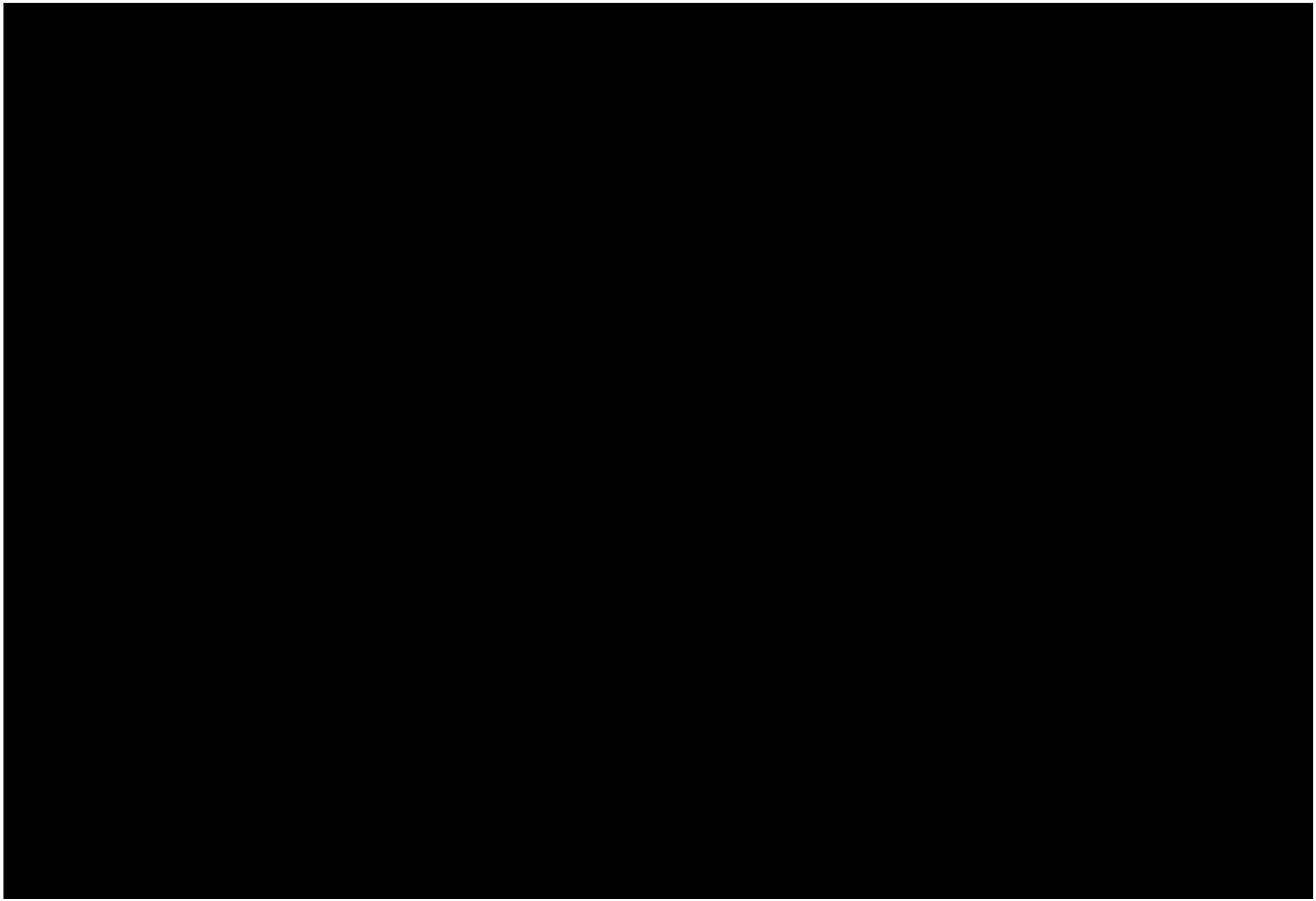
[redacted] been treated for at least 15 weeks in the open-label extension.

1.3. Schedule of Activities

The Schedule of Activities is presented in 2 tables. Table 1 includes the baseline and treatment period up to 1 year, and Table 2 includes the long-term treatment period (up to 3 years), and taper and follow-up visits.







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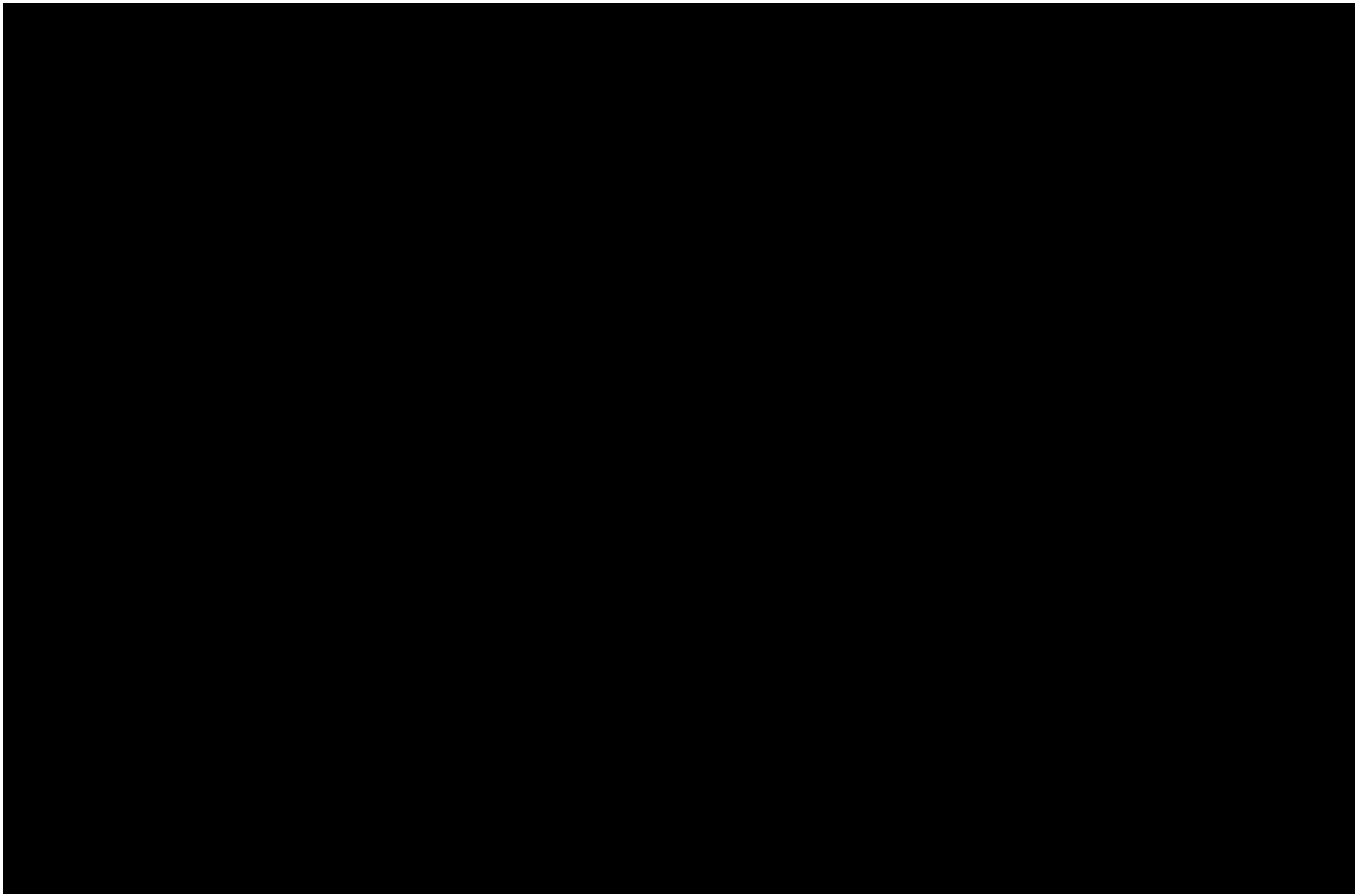

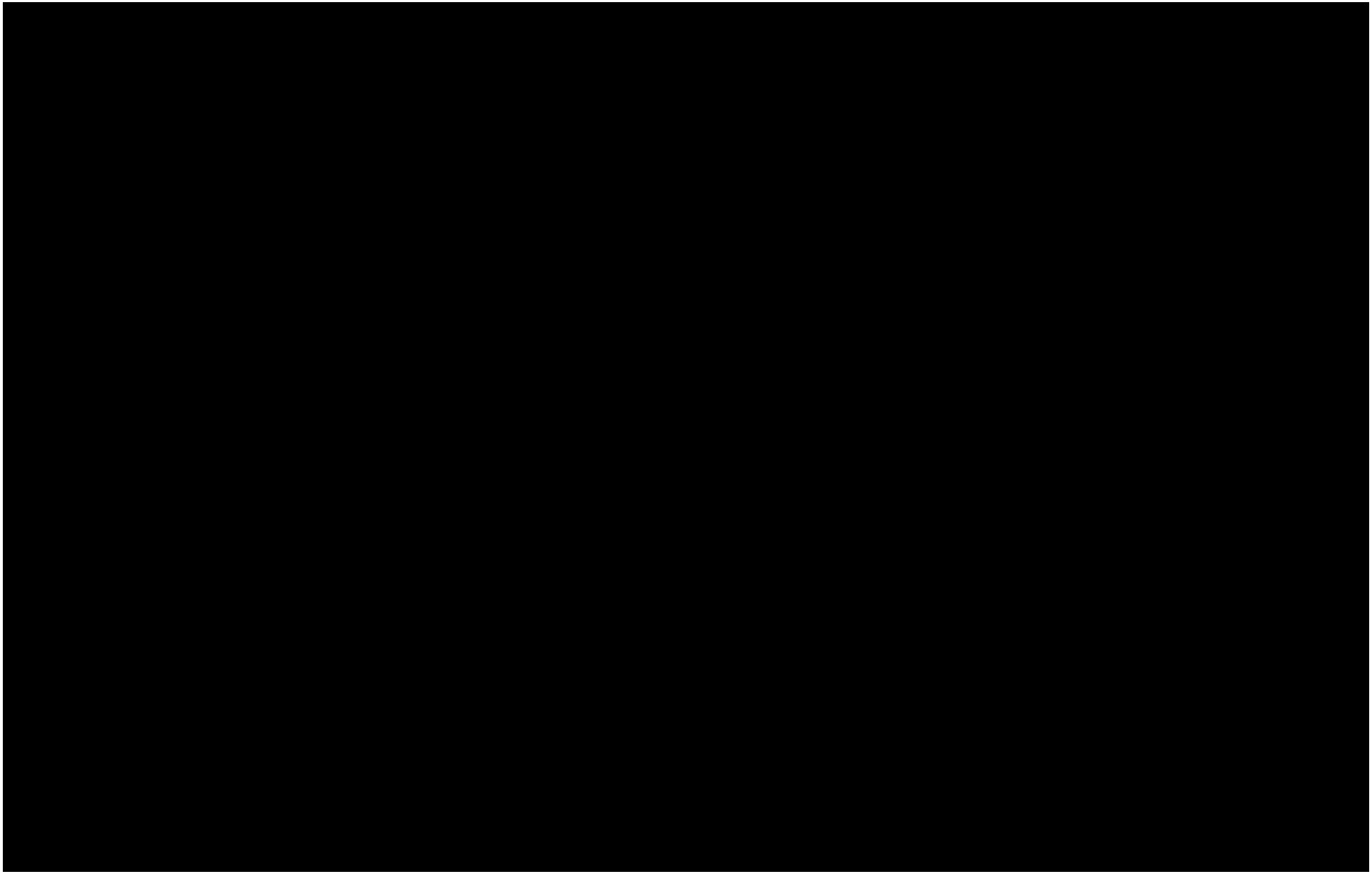

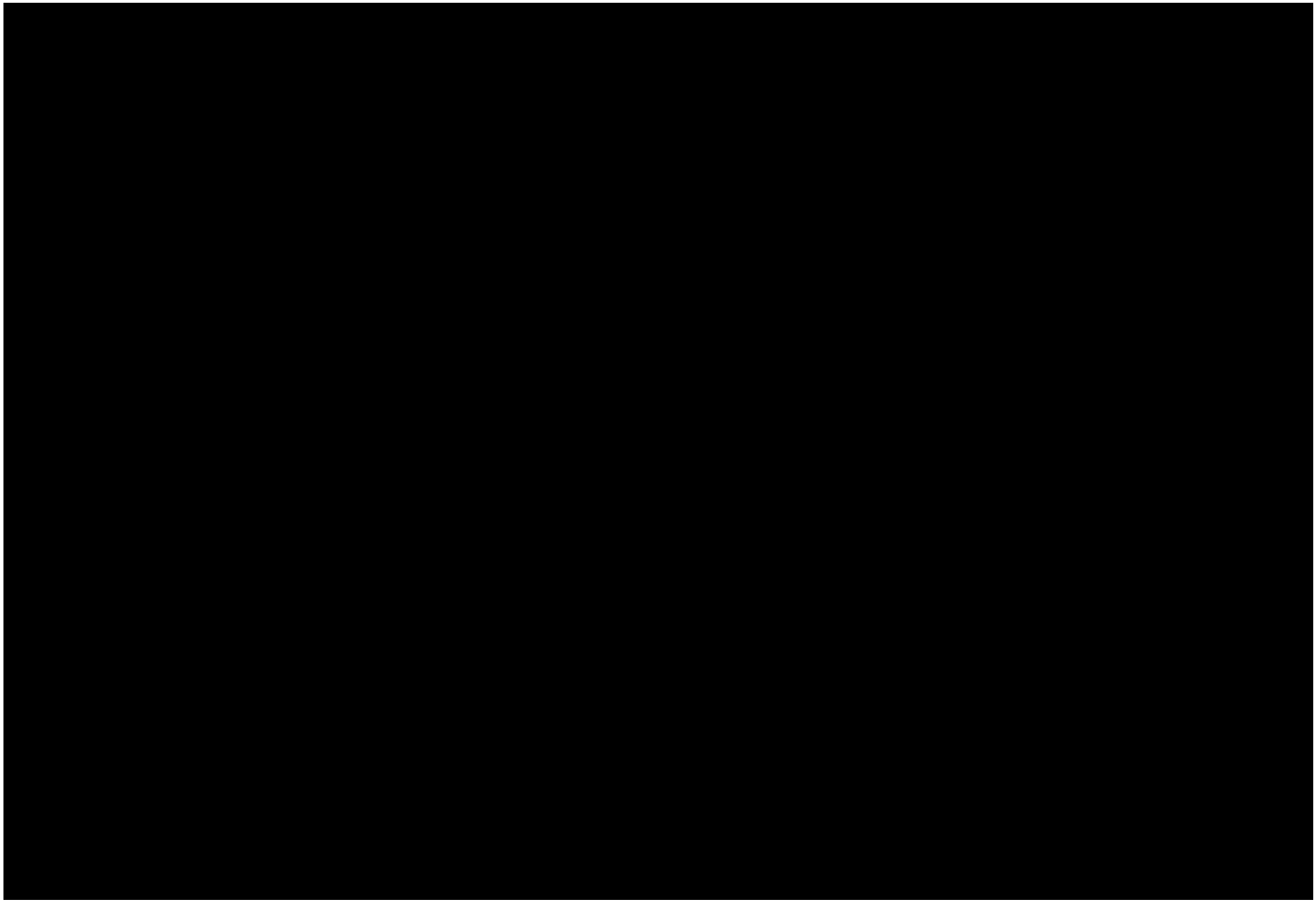

STATISTICAL ANALYSIS PLAN

Available upon request.