1 GENERAL

1.1 IDENTIFICATION OF THE CLINICAL INVESTIGATION PLAN

1.1.1 Clinical Investigation References

CLINICAL INVESTIGATION PLAN

Investigation No. LT2769-004

Date of the initial Clinical Investigation Plan: 09-APR-2024

Version of the initial Clinical Investigation Plan: 2.0

1.1.2 CIP Amendments

Amendment N#: NA Version of the Amended CIP: NA			
Section number	**Section Name**	**Changes description**	**Rationale or justifications**
NA	NA	NA	NA

TITLE: Comparison of the performance and safety of T2769 versus Hylo-Forte® in the treatment of moderate to severe Dry Eye Syndrome.

LABORATOIRES THÉA

Clinical Investigation Plan (CIP) No.:	LT2769-004
Investigational Medical Device (IMD):	T2769
Intended purpose:	Moderate to severe dry eye syndrome
Sponsor's Medical Expert:	[redacted]

1.1.3 Abbreviations and Acronyms

ADE	Adverse Device Effect
AE	Adverse Event
ALCOACCEA	Attributable, Legible, Contemporaneous, Original, Accurate, Complete, Consistent, Enduring and Available
[redacted]	[redacted]
ASADE	Anticipated Serious Adverse Device Effect
ATC	Anatomic Therapeutic Chemical
BCVA	Best Corrected Visual Acuity
CA	Competent Authority
CI	Confidence Interval
CIP	Clinical Investigational Plan
CIR	Clinical Investigation Report
[redacted]	[redacted]
CMP	Clinical Monitoring Plan
CNIL	Commission Nationale de l'Informatique et des Libertés
CRO	Contract Research Organisation
CSP	Code de la Santé Publique
DD	Device Deficiency
[redacted]	[redacted]
DED	Dry Eye Disease
DES	Dry Eye Syndrome
DMP	Data Management Plan
e-CRF	Electronic Case Report Form
EDC	Electronic Data Capture
EU	European Union
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GMP	Good Manufacturing Practice
IB	Investigator Brochure
ICF	Informed Consent Form
IEC	Independent Ethics Committee
IFU	Instructions for Use
IMD	Investigational Medical Device
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITT	Intent-To-Treat
IWRS	Interactive Web Response System
KCS	Keratoconjunctivitis Sicca
LFU	Lacrimal Functional Unit
[redacted]	[redacted]
MAR	Missing At Random

MDR	Medical Device Regulation
MedDRA	Medical Dictionary for Regulatory Activities
[redacted]	[redacted]
MMRM	Mixed Model for Repeated Measures
NA	Not Applicable
NRS	Numeric Rating Scale
OSDI	Ocular Surface Disease Index
PI	Principal Investigator
PP	Per Protocol
PT	Preferred Term
QoL	Quality of Life
Q1	First Quartile
Q3	Third Quartile
[redacted]	[redacted]
RM	Rescue Medication
RMP	Risk Management Plan
RMR	Risk Management Report
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
[redacted]	[redacted]
SDR	Source Data Review
SDV	Source Data Verification
SOC	System Organ Class
SUSAR	Suspected Unexpected Serious Adverse Reaction
TBUT	Tear Break Up Time
TEAE	Treatment Emergent Adverse Event
USADE	Unanticipated Serious Adverse Device Effect
VAS	Visual Analogue Scale

1.2 SPONSOR

Laboratoires THÉA

[redacted]

Sponsor contact: Laboratoires THÉA [redacted]

First Name - Name/function	Details
[redacted] Clinical Affairs Director	Email: [redacted]
[redacted] Medical Development Director	Email: [redacted]
[redacted] Clinical Operation Manager	Email: [redacted]
[redacted] Biometrics Manager	Email: [redacted]
[redacted] Clinical Project Leader	Email: [redacted]
[redacted] Safety Manager	Email: [redacted]
[redacted] Safety Specialist	Email: [redacted]

1.3 PRINCIPAL INVESTIGATOR AND INVESTIGATION SITE(S)

1.3.1 Investigators Details

The Sponsor will maintain an updated list of Principal Investigators (PIs), and investigation sites, separately from this CIP, throughout the duration of the clinical investigation. The definitive list will be provided with the Clinical Investigation Report (CIR).
Roles, responsibilities, and qualifications of investigators are detailed in the CIP.

1.3.2 External Organisations Details

Name and Functions	Details
[redacted]	[redacted]
[redacted]	[redacted]

STATEMENT OF THE SPONSOR

Comparison of the performance and safety of T2769 versus Hylo-Forte® in the treatment of moderate to severe Dry Eye Syndrome

The information contained in this CIP is consistent with:

- The current risk-benefit evaluation of the IMD
- The moral, ethical, and scientific principles governing clinical research as set out in the Declaration of Helsinki - October 2013, Good Clinical Practice (GCP) as described in the ISO14155 current version.

The investigator will be supplied with details of any significant or new findings, including adverse events (AEs), relating to treatment with the IMD.

SPONSOR: LABORATOIRES THÉA

Clinical Affairs Director

[redacted]

11-avr.-24

Date (dd-MMM-yyyy)

signature [redacted]

Medical Development Director

[redacted]

12-avr.-24

Date (dd-MMM-yyyy)

signature [redacted]

Biometrics Manager

[redacted]

11-avr.-24

Date (dd-MMM-yyyy)

signature [redacted]

INVESTIGATOR SIGNATURE PAGE

Comparison of the performance and safety of T2769 versus Hylo-Forte® in the treatment of moderate to severe Dry Eye Syndrome

The signature below:

- Confirms my agreement to conduct the investigation in compliance with GCP – ISO 14155 current version, Medical Device Regulation (MDR 2017/745), other applicable regulatory, and the CIP requirement(s).
- Confirms my agreement to comply with procedures for data recording/reporting.
- Confirms my agreement to permit monitoring, auditing, and regulatory inspection.
- Confirms my agreement to retain the essential documents of this clinical investigation in the investigator files until Laboratoires THÉA informs me that these documents are no longer needed (i.e. at least 10 years after the last T2769 device has been placed on the market).
- Ensure that all people assisting with the clinical investigation are adequately informed about the CIP, the IMD(s) and their trial-related duties and functions.
- Confirms that I have read this CIP and that I agree to comply with all parts or items.

All information regarding this CIP and the IMD(s) will be treated as strictly confidential.

INVESTIGATIONAL SITE

Principal Investigator

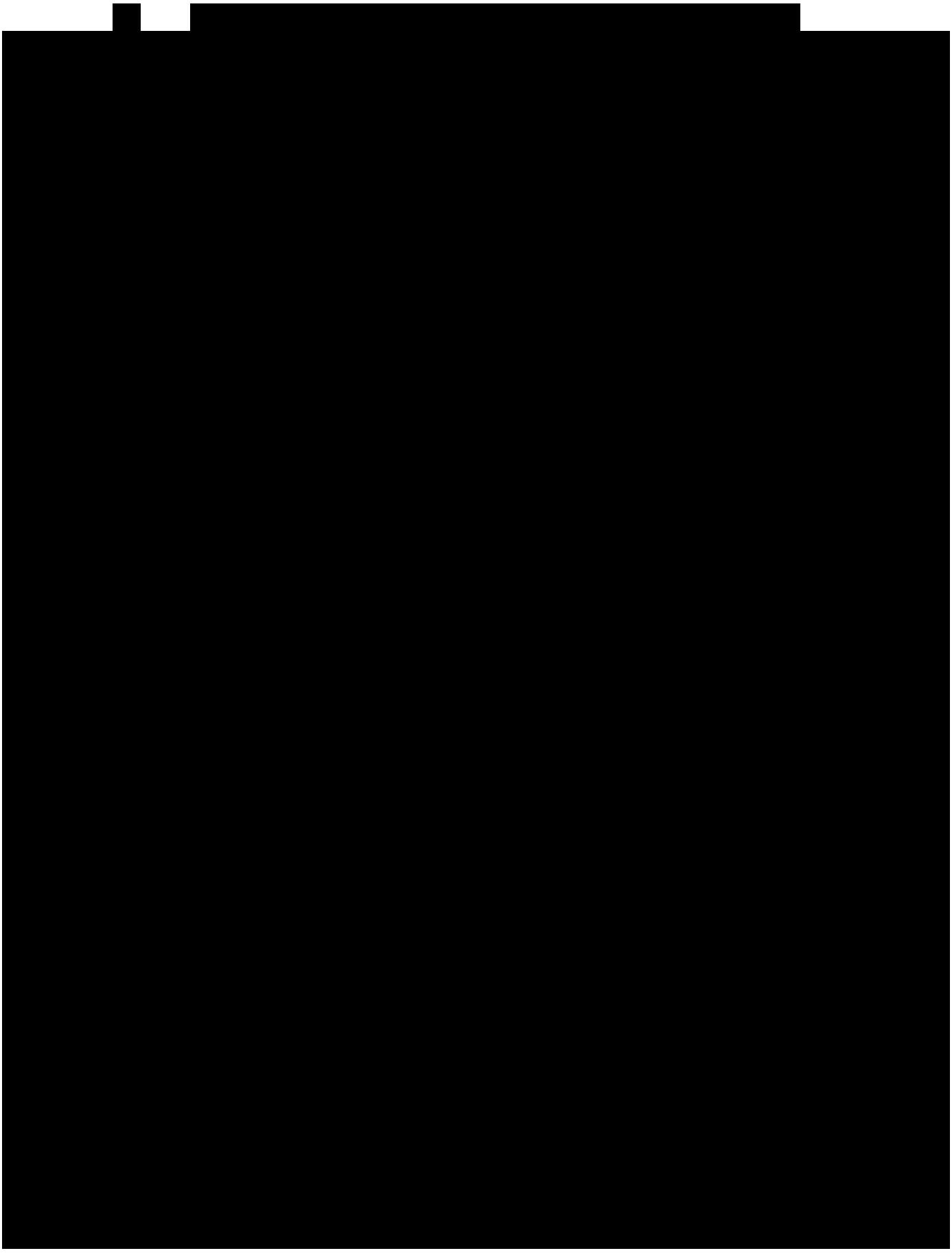
[redacted]

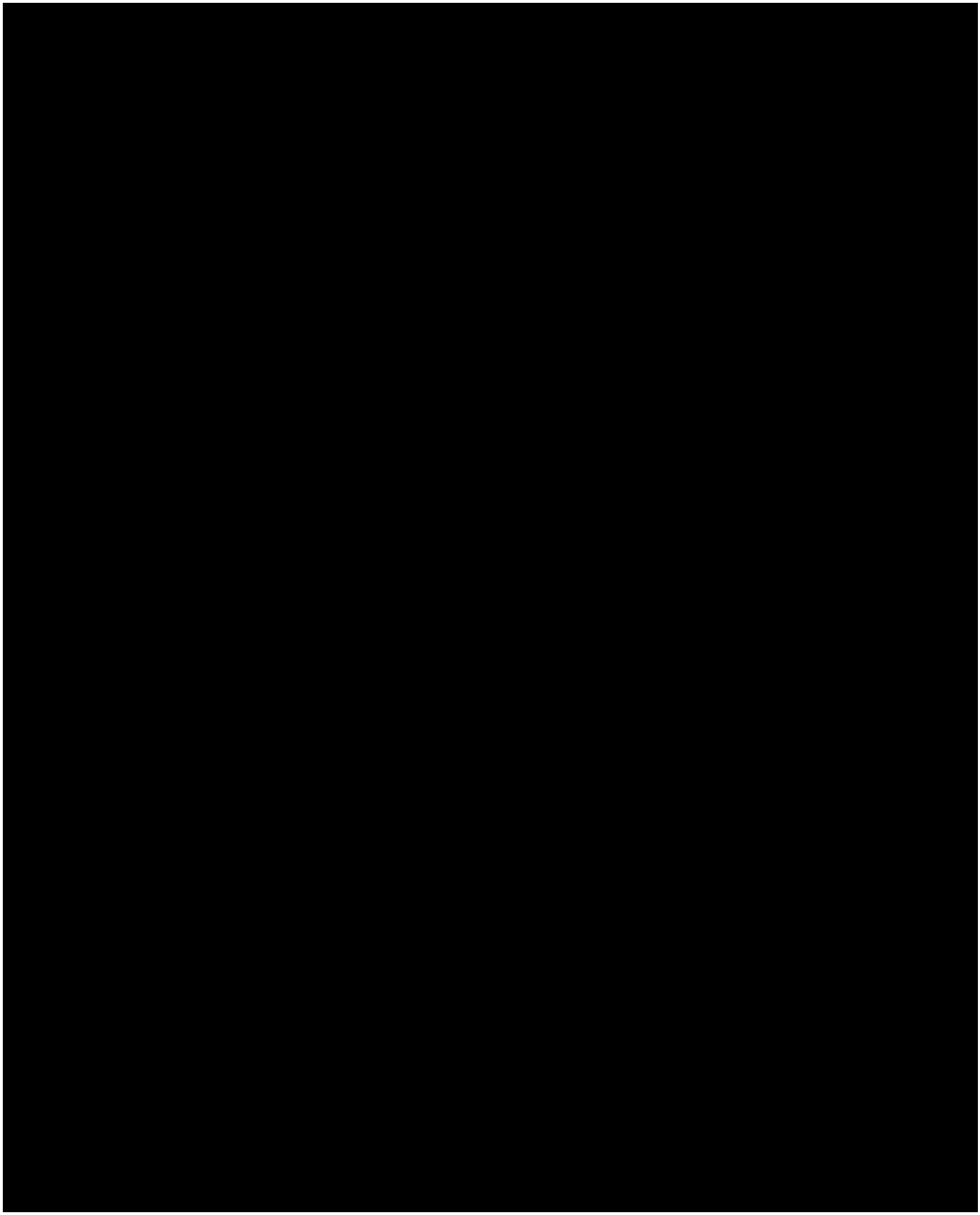
SPONSOR: LABORATOIRES THÉA

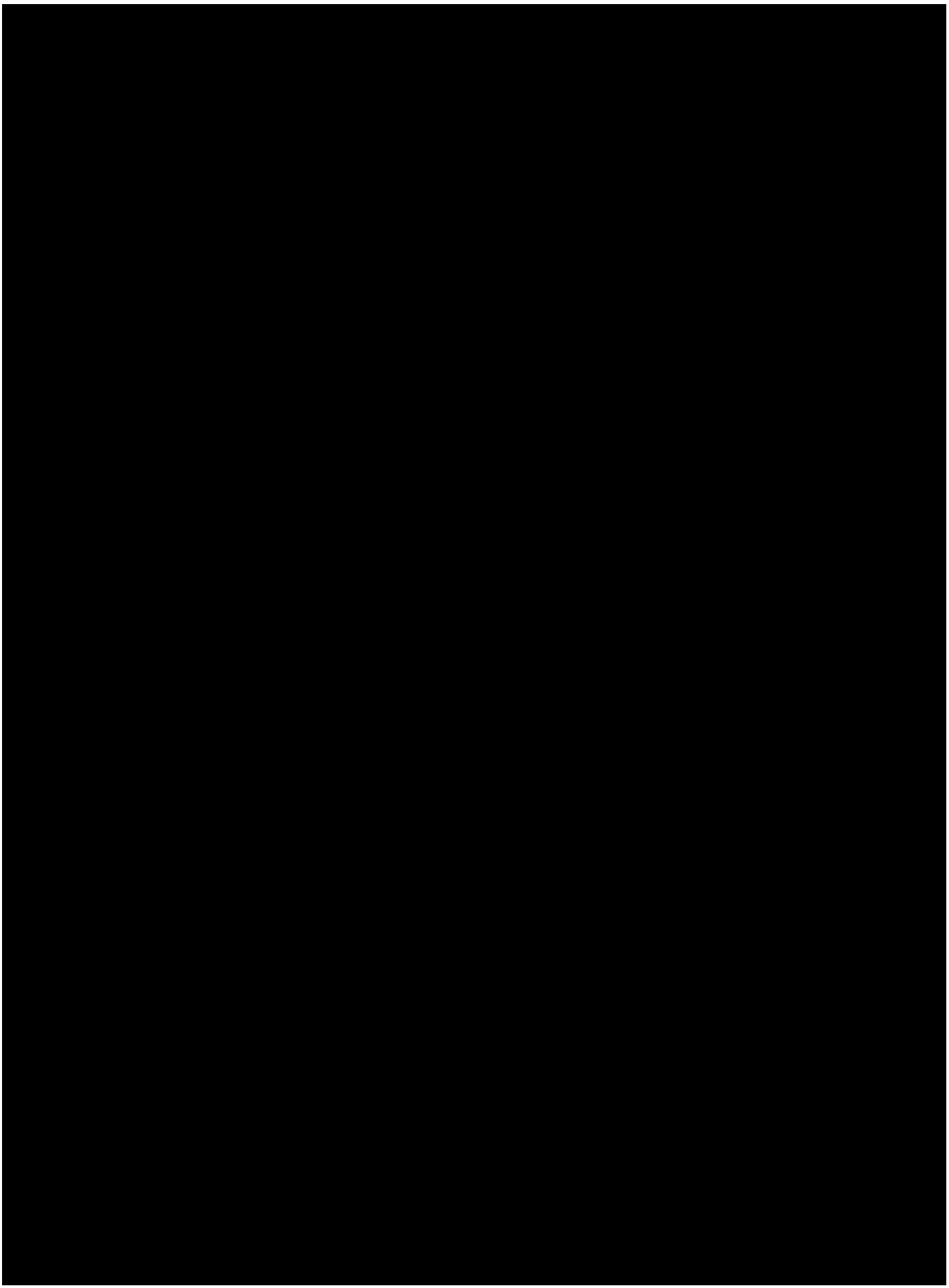
Clinical Project Leader

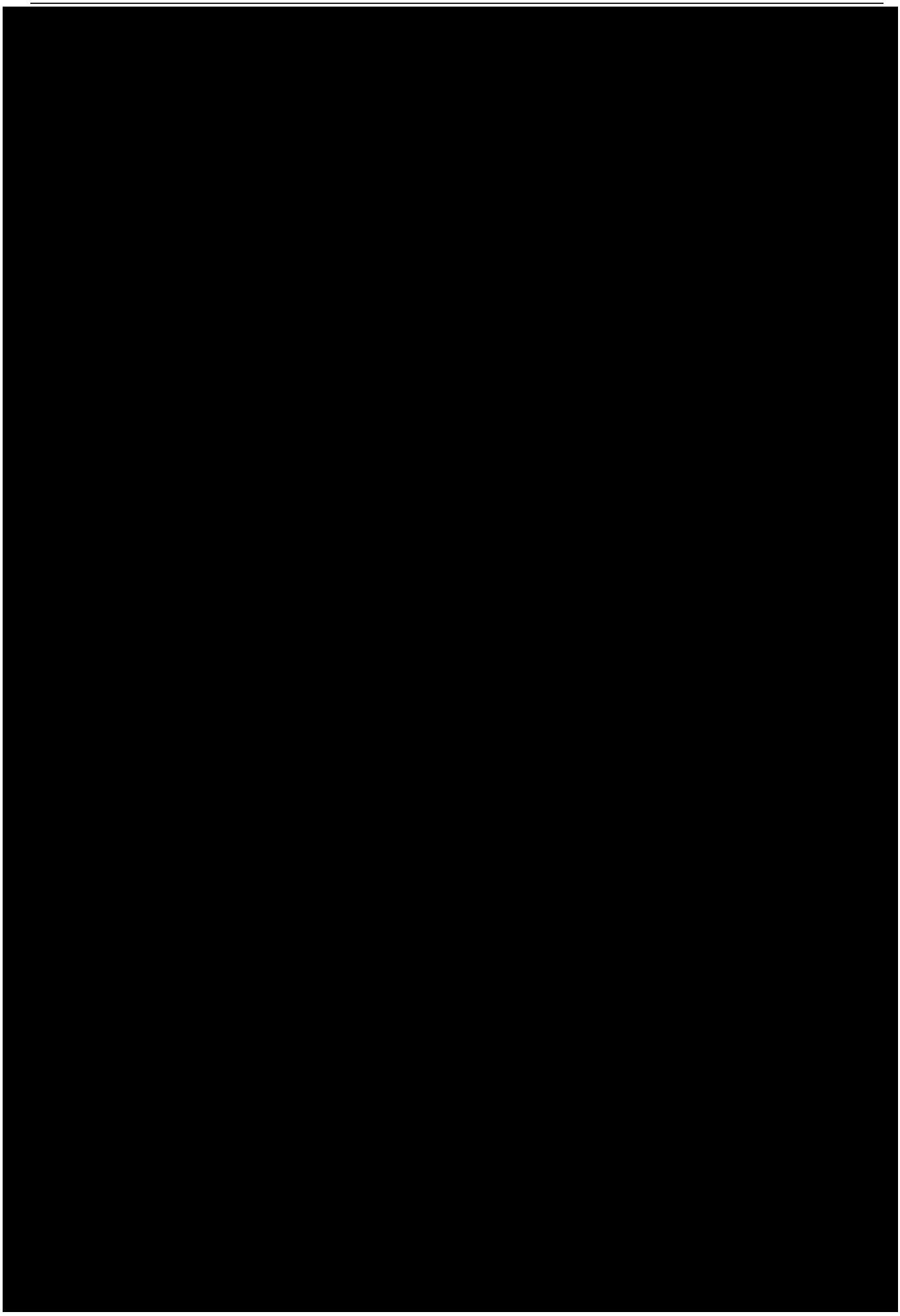
[redacted] 11-avr.-24 [redacted]

First Name - Name *date (dd-MMM-yyyy)* *signatur*

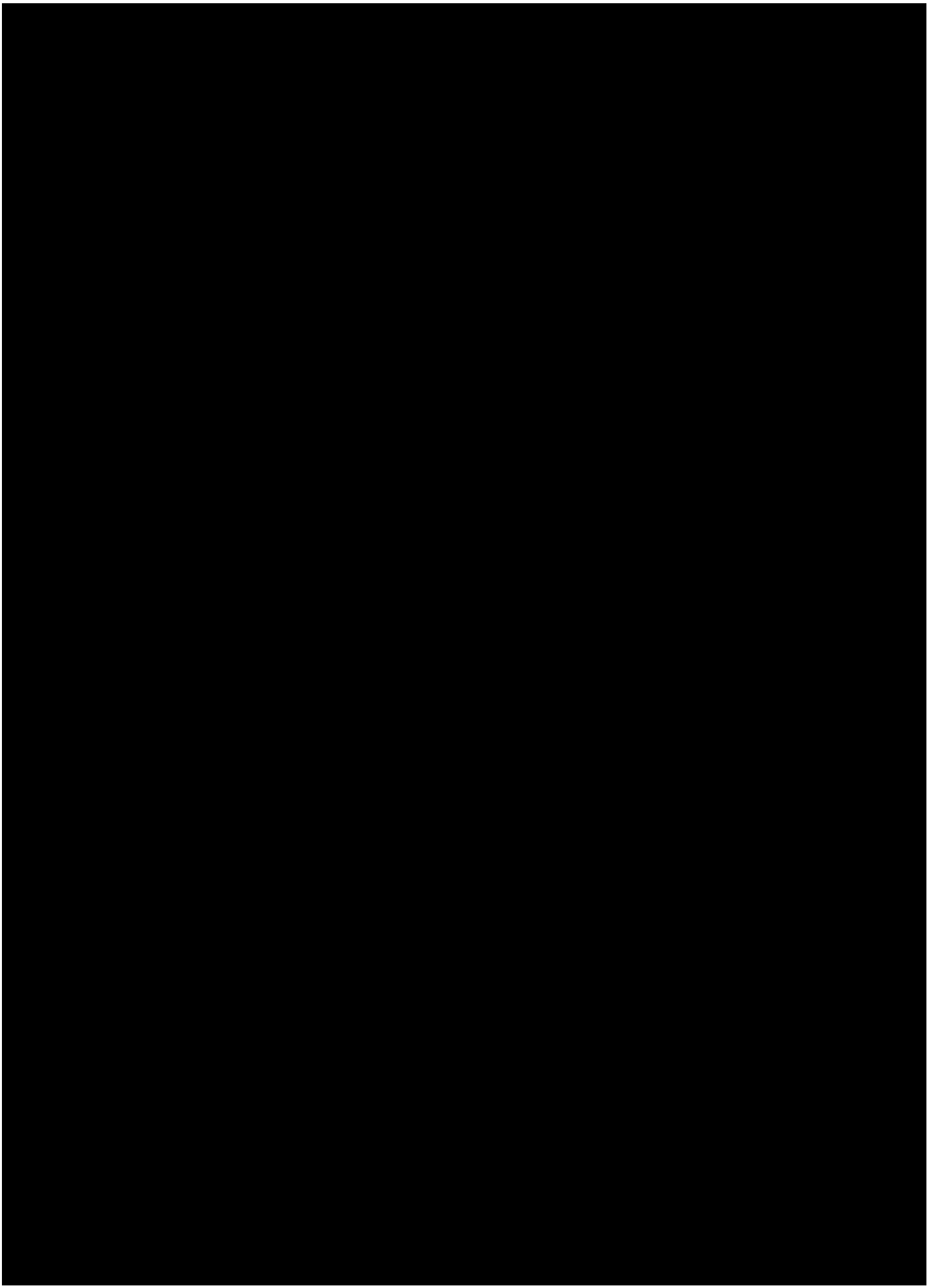


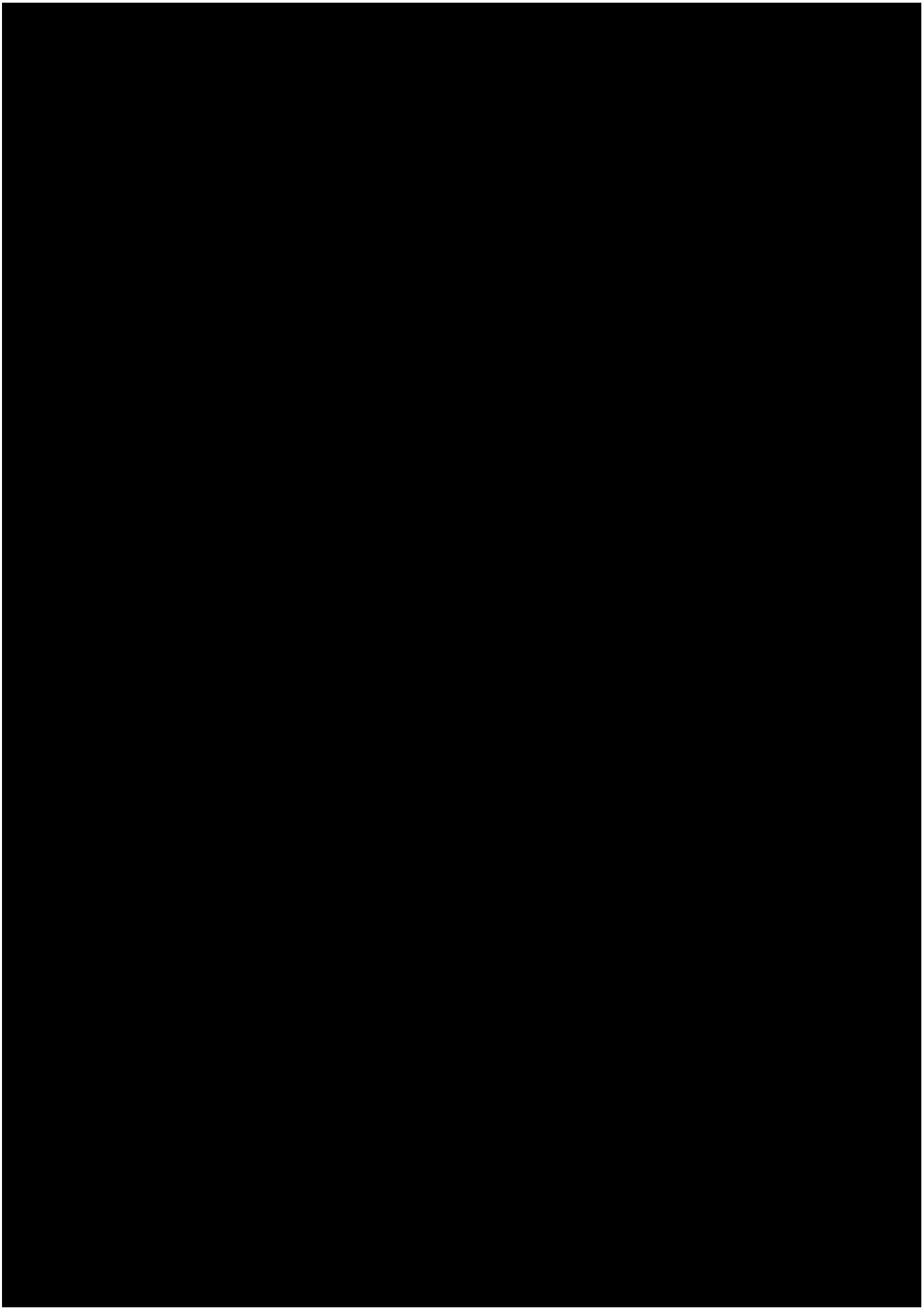


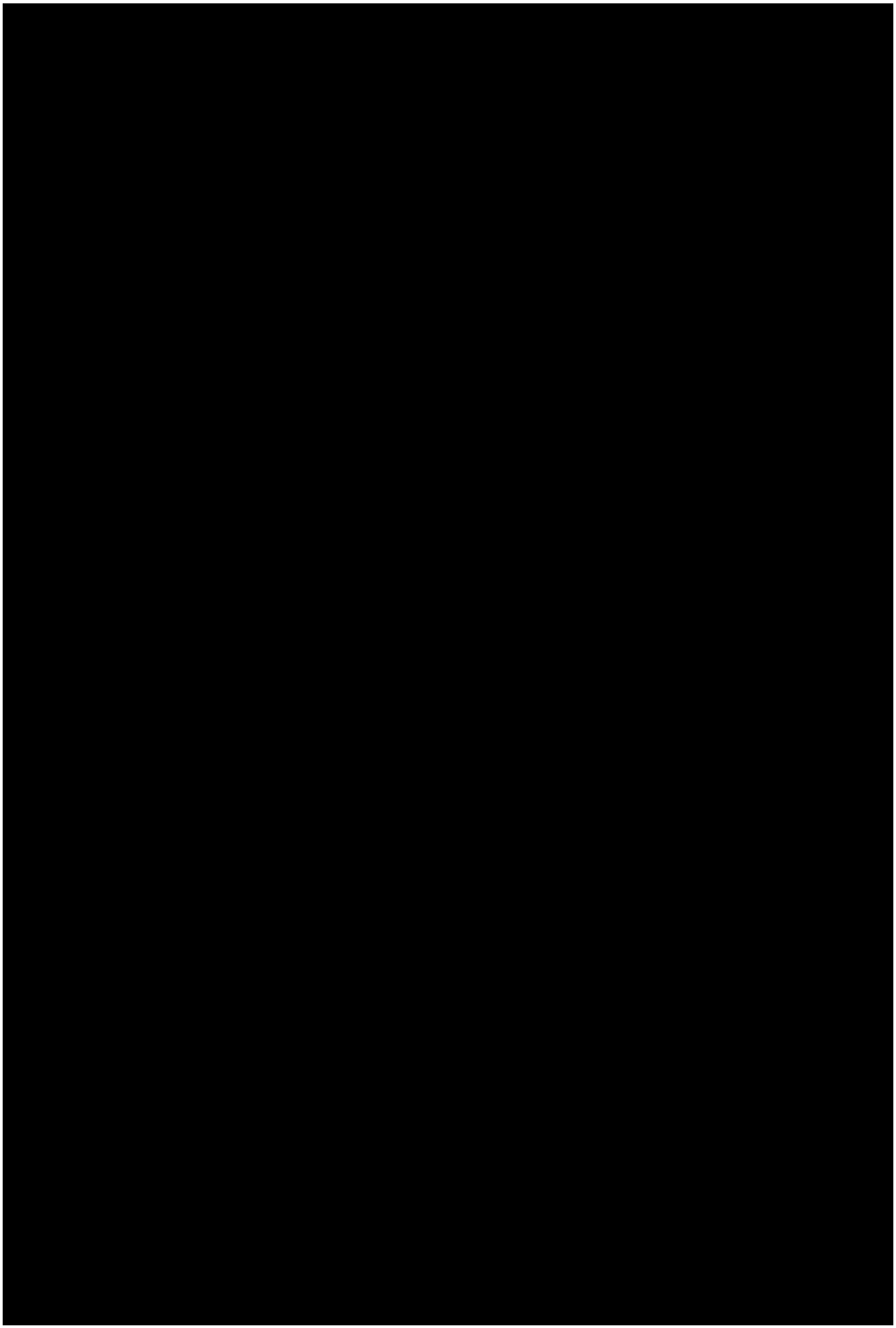


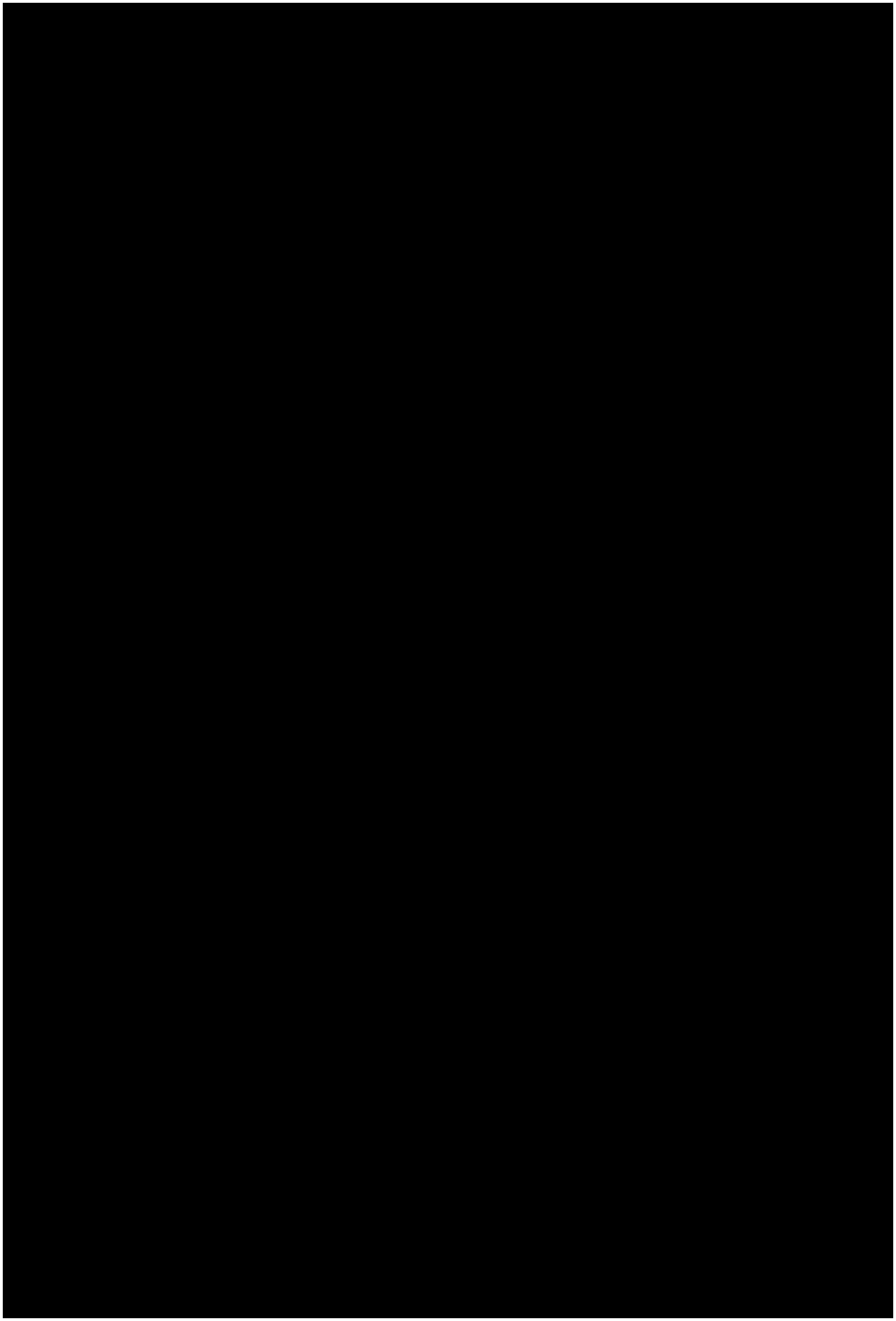


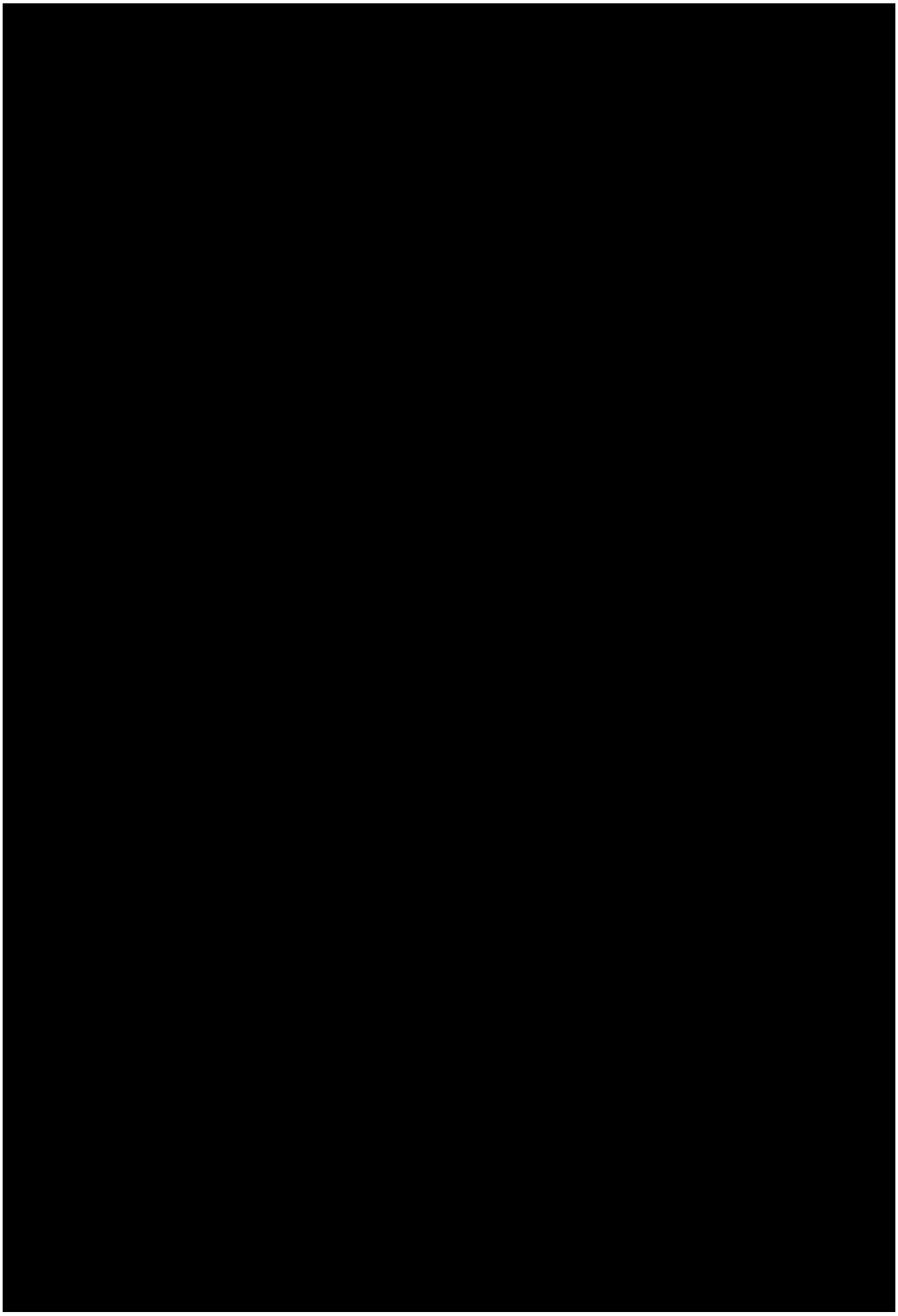
[redacted]

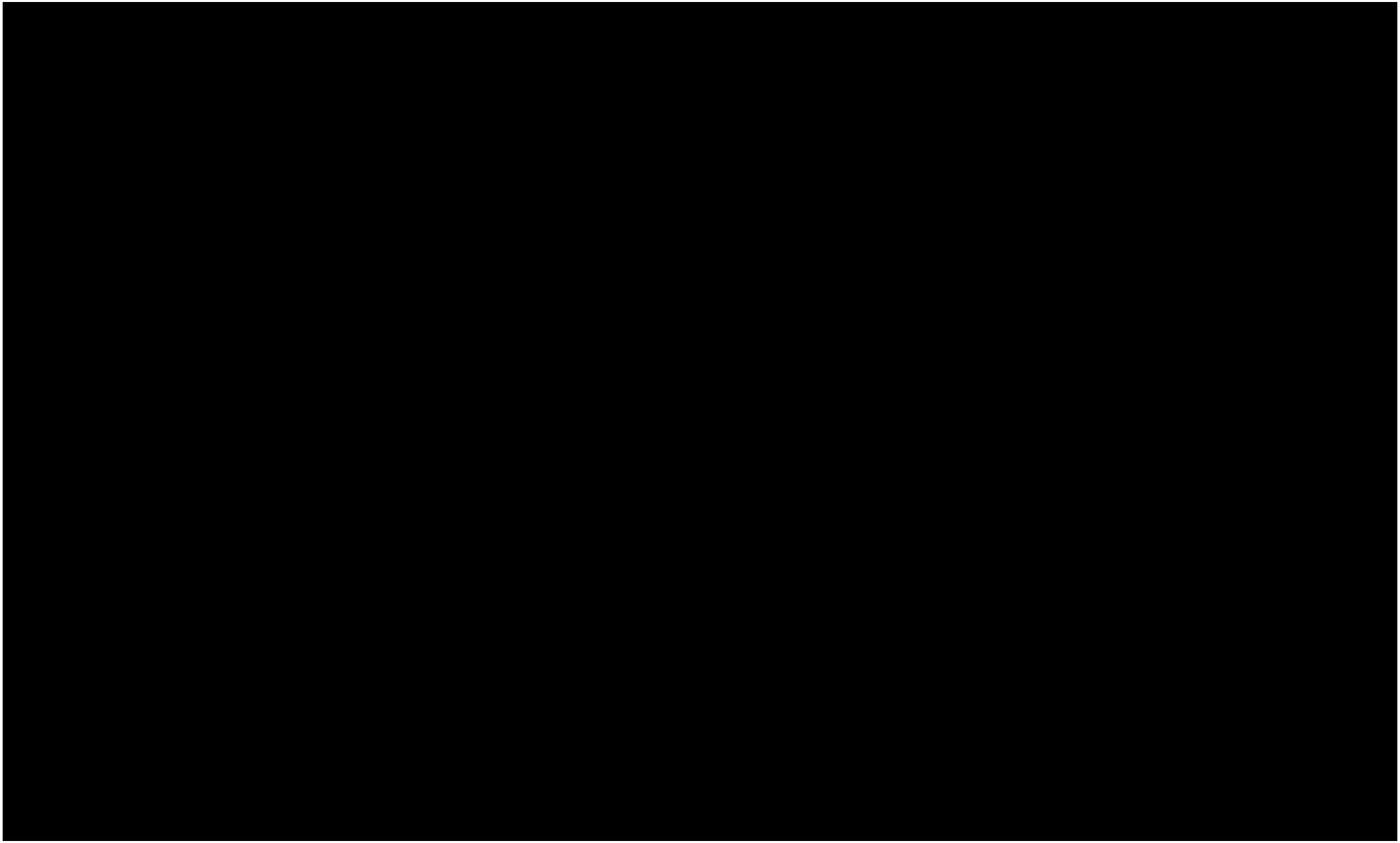












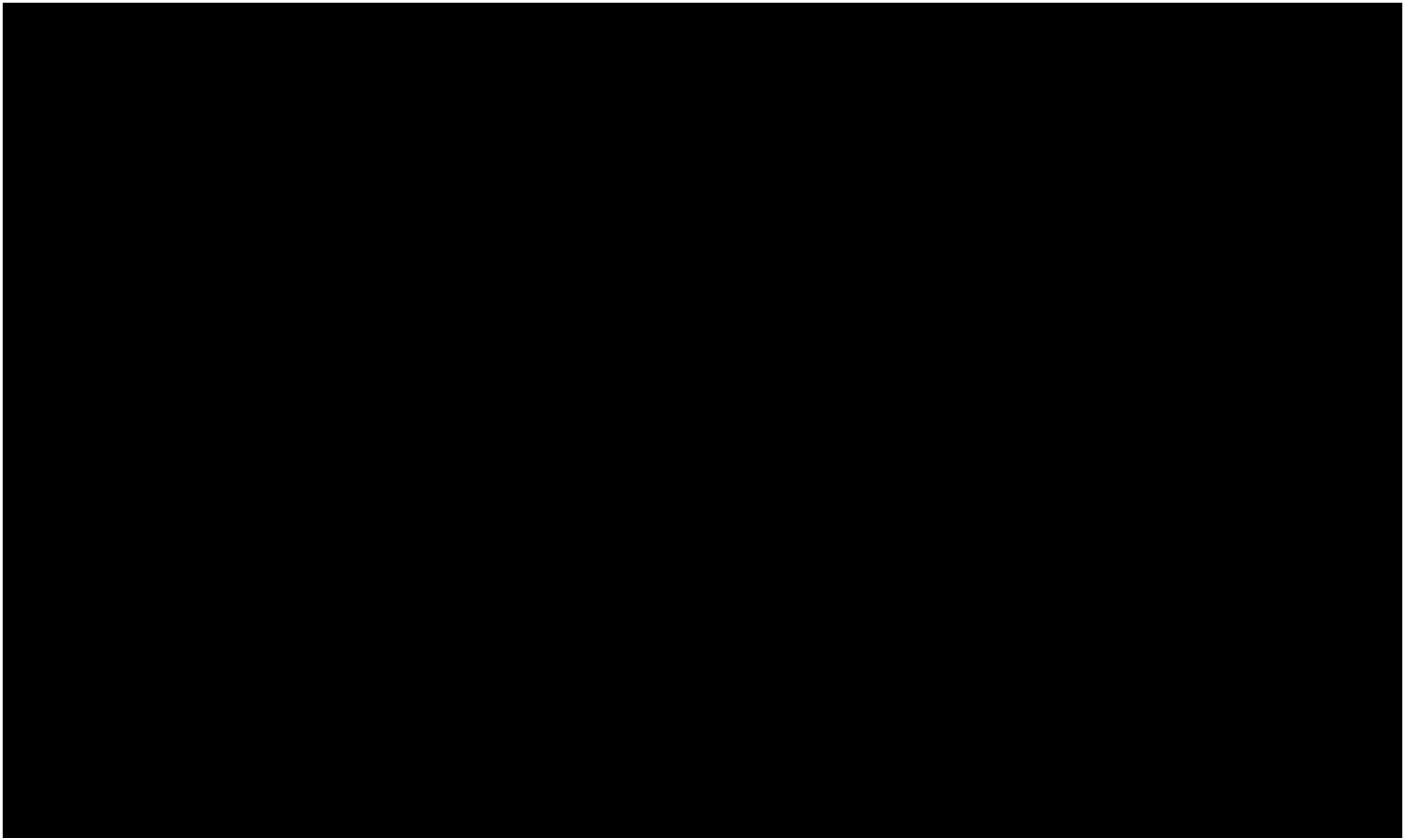
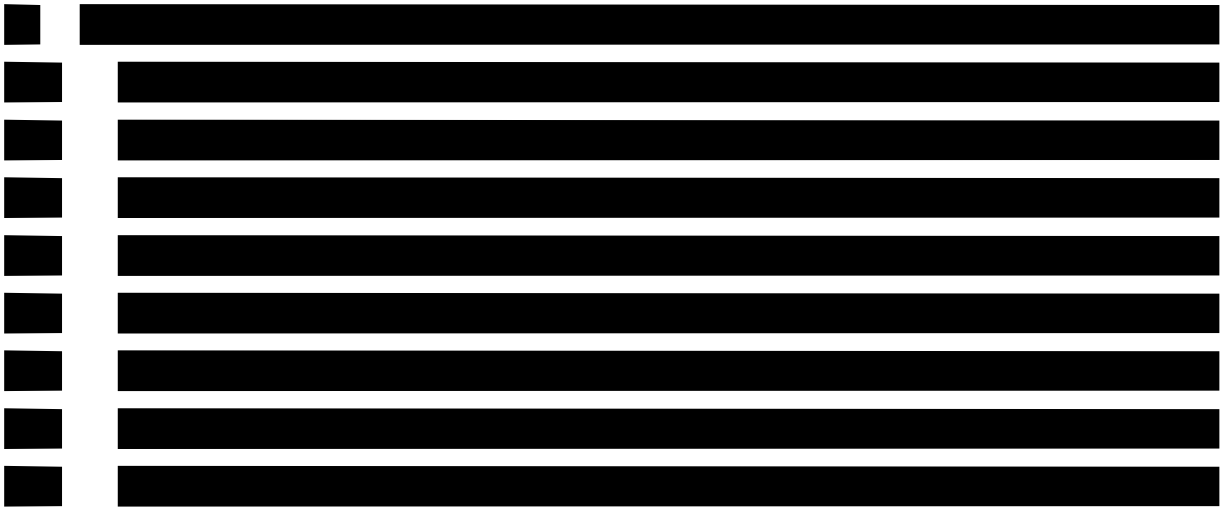


TABLE OF CONTENTS

[redacted]

[redacted]



2 IDENTIFICATION AND DESCRIPTION OF THE IMD

2.1 SUMMARY DESCRIPTION OF THE IMD AND ITS INTENDED PURPOSE

The patient will be trained for the correct instillation technique of IMD. The patient will be provided with an information on the informed consent form, on the labels on the IMD boxes and with some reminders about storage and administration in the patient diary.

Test device: T2769 (Thealoz® Total)
T2769 is a sterile, phosphate-free and pH neutral solution. It contains Trehalose, Sodium Hyaluronate (SH) and Naaga.
T2769 device is presented in the ABAK® III multi-dose bottle (10 mL).
As per Instructions for Use (IFU), T2769 is indicated for the treatment of moderate to severe dry eye syndrome.

Comparative device: Hylo Forte®
HYLO-FORTE® is a sterile, phosphate and preservative-free solution for ocular use containing sodium hyaluronate, citric acid anhydrous, sodium citrate and sorbitol. It is presented in a COMOD® multi-dose application system (10 mL).
HYLO-FORTE® is an eye drop for the intensive and therapeutic lubrication of the ocular surface in more severe and persistent dry eye sensation including treatment after surgical procedures.

2.2 DETAILS CONCERNING THE MANUFACTURER OF THE IMD

The legal manufacturer of T2769 according to the EU Medical Device Regulation (MDR) 2017/745 is Laboratoires THÉA.

[redacted]

[redacted]

2.4 PACKAGING AND LABELLING

2.4.1 Packaging

The IMD will be packaged by approved contractor in accordance with ISO 14155 current version and EU MDR 2017/745. The IMDs will be prepared according to the packaging list provided by the CRO responsible for biometry (see Section **6.1.2.1**).

T2769 is packaged in a multidose white polyethylene ABAK® III system bottle. The dispenser is already used in several currently marketed eye drops. This innovative and patented device provides eye drops through a 0.2 µm filter, preventing any bacterial contamination of the solution without the use of any preservatives:

HYLO-FORTE® is presented in a COMOD® multi-dose application system (10 mL).

The complete treatment for one patient and for the complete investigation duration will be as following:

Packaging	**Run-in treatment: Hydrabak®**	**T2769 or Hylo Forte®**	
		Visit #2 Period Visit #2 - D1 to Visit #3 - D15	Visit #3 Period Visit #3 - D15 to Visit #4 - D36
Primary (I)	1 vial	2 vials	2 vials
Final	1cardboard box	1cardboard carton	1 cardboard carton

Each patient will receive 1 preservative-free multidose bottle of Hydrabak® during the run-in period and 4 preservative-free multidose bottles of the IMD during the clinical investigation.

Hydrabak® is supplied in the ABAK® multi-dose bottle. This innovative and patented device provides eye drops through a 0.2 µm filter, preventing any bacterial contamination of the solution without the use of any preservatives.

2.4.2 Labelling

All labels will be written in the local language. The content of the labelling is in accordance with ISO 14155 current version and EU MDR 2017/745 specifications and requirements.

Each vial of run-in treatment and IMD will carry one label.

The cardboard carton of IMD will also carry a detachable label (flag label) bearing at least the CIP number and IMD kit number. This label will be torn off by the person dispensing the IMD to the patient and will be stuck in the space provided in the IMD allocation form to record the dispensing procedure.

2.5 INTENDED PURPOSE OF THE IMD IN THE PROPOSED CLINICAL INVESTIGATION

T2769 is intended to hydrate and soothe itchy, red or irritated eyes in case of moderate to severe dry eye syndrome.

2.6 THE POPULATIONS AND INDICATIONS FOR WHICH THE IMD IS INTENDED

T2769 is indicated in moderate to severe dry eye syndrome.

T2769 is suitable for adults (patients over or equal than 18 years excluding pregnant or breastfeeding women, see Sections **6.3.1** and **6.3.2**).

2.7 DESCRIPTION OF THE IMD

T2769 is an ophthalmic solution composed of trehalose (3%), sodium hyaluronate (0.15%), N-Acetyl Aspartyl Glutamic Acid Sodium salt (Naaga, 2.45%), [redacted]

The solution is supplied in the ABAK® III multi-dose bottle. This innovative and patented device provides eye drops through a 0.2 µm filter, preventing any bacterial contamination of the solution without the use of any preservatives.

The product can be used until 3 months after first opening.

Table 4 Investigational Medical Device T2769

Names of ingredients	Percentage formula (g/100 ml)	Function	Reference to standards
Trehalose dihydrate*	3.00*	Lubricating, hydrating agent	Current Eur. Ph. [2297]
N-acetyl aspartyl glutamic acid, sodium salt (NAAGA, Na)*	2.45*	Soothing agent	Internal monograph
Sodium hyaluronate**	0.15*	Lubricating, hydrating agent	Current Eur. Ph. [1472]
[redacted]			

[redacted]

* *The quantity of the ingredient (Trehalose dihydrate and Naaga Na) is adjusted as a function of its titre and water content*

** *The quantity of this ingredient is adjusted as a function of its water content*

[redacted]

The excipients of the T2769 eye-drops [redacted] are well-known and commonly used in ophthalmic formulations.

Batch number and expiry dates will be provided in the certificate of analysis and will be specified on the packaging.

2.8 STORAGE CONDITIONS AND INDICATIONS OF USE

All IMD should be stored in its original packaging, protected from light and moisture, at a temperature between 8°C and 25°C and the expiry date refers to the last day of that month as long as the packaging is intact, and it has been stored correctly.

The IMD must not be used if the vial is damaged and must not be refrigerated or frozen.

Until dispensed to the patient, products should be kept in a secure area with restricted access. The investigator, the hospital pharmacist or other personnel allowed to store and dispense IMD(s) will be responsible for ensuring that the IMD(s) are securely maintained as specified by the Sponsor and in accordance with the applicable regulatory requirements.

The IMD should not be used after the expiry date indicated on the outer cardboard box. The expiry date refers to the intact correctly stored packaging.

The product can be used until 3 months after first opening.

If significant changes and/or update on labelling, handling and storage are required during the clinical investigation, the corresponding sections will be updated by notifying or submitting to Competent Authorities (CAs) concerned accordingly. All investigators' sites will be immediately informed about any change by the Sponsor. Investigator or a delegate will inform the patient, if any.

Accordingly, the Sponsor may decide to halt temporarily the recruitment (see Section **16.1**). In any way, the reasons and the procedures for any changes will be justified and described by the Sponsor.

2.9 DESCRIPTION OF THE SPECIFIC MEDICAL OR SURGICAL PROCEDURES INVOLVED IN THE USE OF THE IMD

NA.

2.10 INVESTIGATOR BROCHURE (IB) AND INDICATION FOR USE (IFU)

All details concerning the IMD are specified in the IB and the IFU. These documents will be updated whenever necessary and all applicable versions will be provided to each investigation site throughout the clinical investigation.

At time of CIP writing, validated and applicable version are:

- For the IB: V4, MAR-2024,

- For the IFU: Ver. 9-07/2023.

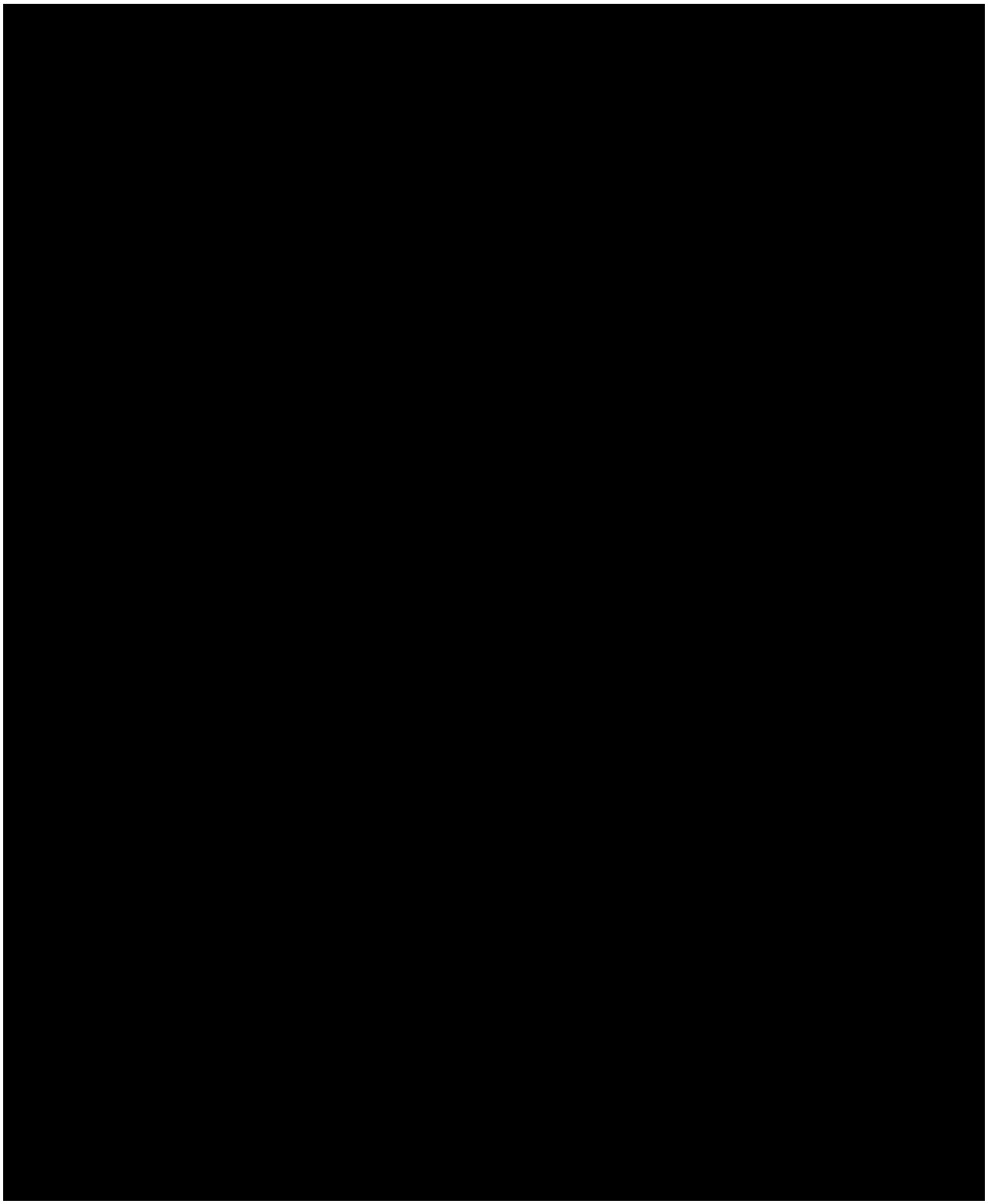
2.11 DESCRIPTION OF COMPARATIVE DEVICE

Hylo Forte® is purchased from Scope Ophthalmics. It is a sterile, phosphate and preservative-free solution for ocular use.

Packaging and labelling are provided in Sections **2.1** and **2.4**, batch number and expiry dates will be specified on the packaging.

Storage conditions are specified in Section **2.8**.

One ml of HYLO-FORTE® contains 2 mg sodium hyaluronate, citric acid anhydrous, sodium citrate, sorbitol and water for injections.



[redacted]

3.4 DESCRIPTION OF THE CLINICAL DEVELOPMENT STAGE

The investigation is defined as a post-market stage (refer to ISO 14155:2020). The clinical investigation design is confirmatory.

4 BENEFITS AND RISKS OF THE IMD, CLINICAL PROCEDURE AND CLINICAL INVESTIGATION

4.1 ANTICIPATED CLINICAL BENEFITS

[redacted]

4.3 RISKS ASSOCIATED WITH PARTICIPATION IN THE CLINICAL INVESTIGATION

Laboratoires THÉA performed a risk analysis according to the current ISO 14971 standard.

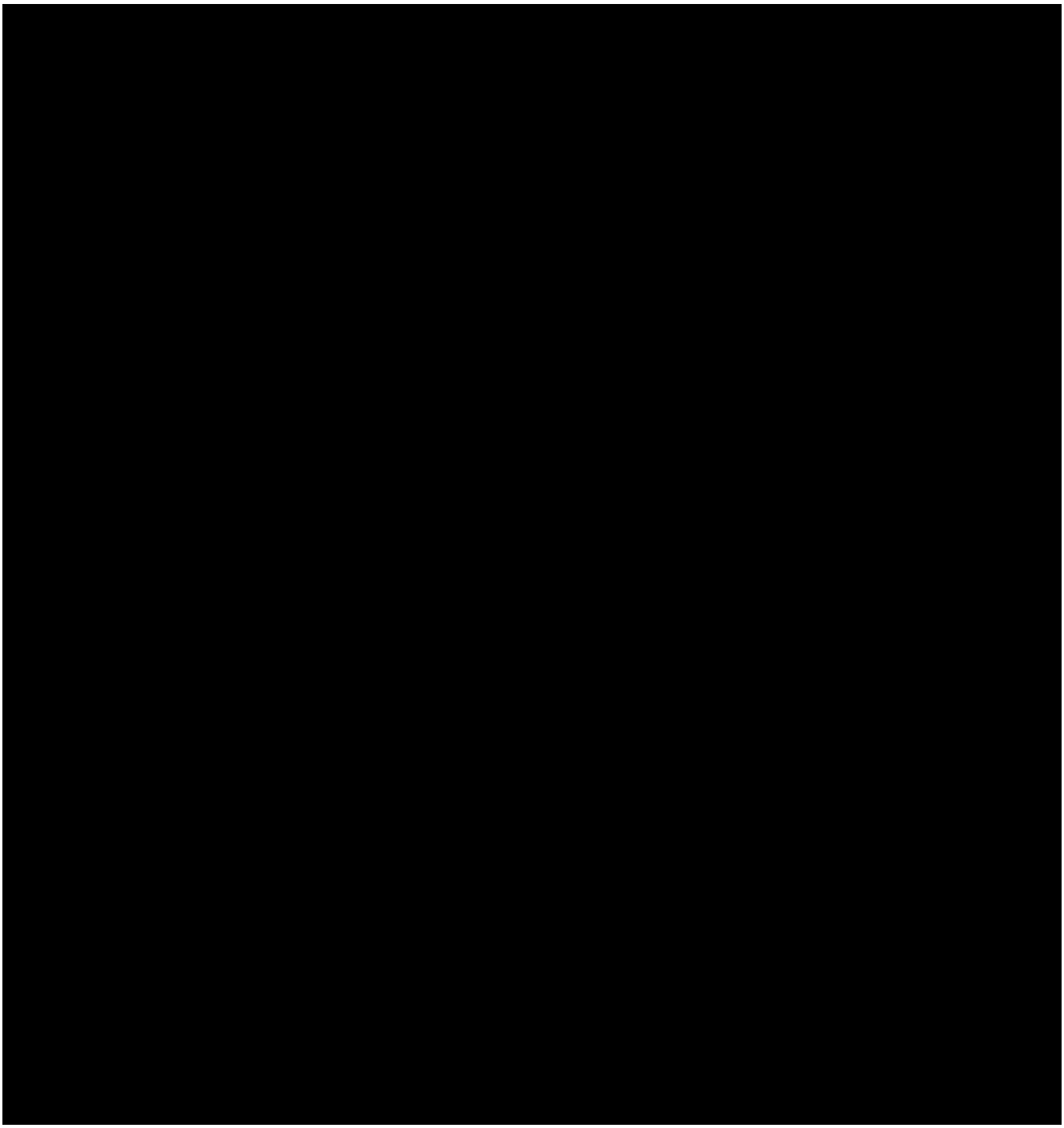
All risks identified in Laboratoires THÉA's risk analysis were mitigated. The remaining residual risks were considered to be of negligible or acceptable levels. This is fully described in the Risk Management Report (RMR). The risks mitigated to this latter risk level (acceptable) are described in section **4.5**.

All the possible warnings have been put in place in the instructions for use as well as on the secondary and primary packaging if possible.

These hazards cannot arise in the normal conditions of use.

4.4 POSSIBLE INTERACTIONS WITH CONCOMITANT MEDICAL TREATMENTS

To avoid possible interactions with a concomitant treatment, patients will be asked to wait at least 15 minutes between use of the IMD and any other eye product.



5 OBJECTIVES AND HYPOTHESES OF THE CLINICAL INVESTIGATION

5.1 CLAIMS FOR CLINICAL PERFORMANCE, EFFECTIVENESS OR SAFETY OF THE IMD

There is no claim concerning the clinical performance of THEALOZ TOTAL in the IFU. However, the following clinical performances support the claimed clinical benefits:

- THEALOZ TOTAL reduces ocular surface damages.
- THEALOZ TOTAL increases tear film stability/quantity.

As per the IFU, the claim on clinical safety is:

- THEALOZ TOTAL is well tolerated on the ocular surface.

As per the IFU, the clinical benefits of THEALOZ TOTAL are:

- THEALOZ TOTAL relieves from the symptoms of dry eyes.
- THEALOZ TOTAL soothes the eyes from itchiness and irritation.
- THEALOZ TOTAL reduces the redness of the eyes.

As per Laboratoires THÉA, other clinical benefit of THEALOZ TOTAL is improvement of (global) ocular comfort.

5.2 OBJECTIVES, PRIMARY [redacted]

The primary objective of the investigation is to demonstrate the non-inferiority of T2769 compared to Hylo-Forte® in terms of total ocular surface staining (Oxford score) in patients with moderate to severe DES.

[redacted]

5.3 SCIENTIFIC JUSTIFICATION AND CLINICAL RELEVANCE FOR EFFECT SIZES, NON-INFERIORITY MARGINS OR EQUIVALENCE LIMITS

Estimation of the standard deviation and determination of the non-inferiority limit are based upon data of previous studies and literature.

Concerning the non-inferiority limit, according to clinicians, a variation not exceeding 2 points in the total Oxford grade is considered as not clinically significant (Labetoulle et al. 2022; Chiambaretta et al. 2017; Baudouin et al. 2012).

[redacted]

[redacted]

5.5 RISKS AND ANTICIPATED ADVERSE DEVICE EFFECTS

There are no specific risks and ADE to be assessed during this clinical investigation.

6 DESIGN OF THE CLINICAL INVESTIGATION

6.1 GENERAL

6.1.1 Justification of the Investigation Design

Methodology: a 5-week, international, multicentre, randomised, investigator-masked, 2 parallel groups (T2769 versus Hylo-Forte®) investigation.

- Multicentre

The investigation will be performed in different sites in EU.
A multicentre (and multi-investigator) design will provide the possibility of recruiting the patients from a wider population than a single-centre design and of using the device in a broader range of clinical settings, thus presenting an experimental situation that is more typical of future use. In this case, the involvement of a number of investigators also gives the potential for a wider range of clinical judgments concerning the value of the therapeutic intervention. In addition, it is also a practical means of accruing sufficient patients to satisfy the investigation objective.

- Randomised

At the randomisation visit on Day 1, a patient fulfilling all eligible criteria will be randomly assigned to 1 of the 2 treatment groups (T2769 or Hylo-Forte®). Randomisation ensures the investigator remains masked to product assignment for DES treatment. It is generally considered the most reliable method for evaluating the effects of interventions.

- Choice of run-in period

Patients meeting the screening criteria will undergo a 7-10-days run-in period. During this period, all patients will substitute their current dry eye treatment with Hydrabak®, ophthalmic solution containing NaCl 0.9%. Patients will instill 1 drop in each eye, from 3 to 6 times daily. [redacted] (Baudouin et al. 2017; Chiambaretta et al. 2017; Labetoulle et al. 2018; Holland et al. 2019).

- Investigator-masked

A double-masked investigation design is not possible due to different commercial packaging between T2769 – Hylo-Forte®.

However, the identity of the IMD given to each patient will not be known for the masked investigator who is independently in charge of the ophthalmic examination.

To this aim, the masked investigator will differ from the person who will record the used/unused IMDs. The recording will be delegated either to the hospital pharmacy or to a trained collaborator (trained by the masked investigator; hereafter referred to as unmasked collaborator). Therefore, the masked investigator should not receive the returned IMDs from the patients and returned IMD must be stored in a different place from the IMD that have not yet been dispensed. Patients will also be trained to not report any information that could lead to unblinding in the diary and to the masked investigator.
If the masked investigator become unmasked, then the patient continues the clinical investigation. The patient data will be handled accordingly for the analysis.

- Choice of the comparator group

[redacted]

- Choice of the investigation population

[redacted].

- Scheme of administration

The dose regimen recommended is 1 drop in each eye, from 3 to 6 times daily.

- Choice of the treatment period

A 5-week treatment period may allow to evaluate the therapeutic effect and to observe any potential safety issues.
A period of 1 month is usually the minimum time required to demonstrate the therapeutic effect of a product.

- Choice of primary endpoint [redacted]

The primary [redacted] endpoint [redacted] of this clinical investigation (total ocular surface staining (Oxford scale), [redacted] (Jones et al. 2017; Aragona et al. 2019; Fariselli et al. 2018; Mateo Orobia et al. 2017; Nasser et al. 2018; Pinto-Bonilla et al. 2015; Chiambaretta et al. 2017; Novack et al., 2017; Wolffsohn et al., 2017; Begley et al., 2019; Nichols et al., 2021; Begley et al., 2022). Consequently, these endpoints are clinically relevant, clearly defined and assessed at specified time points in order to provide clinical evidence on the efficacy [redacted] of T2769 in its intended use (i.e., improvement of the ocular signs and symptoms in DED patients).

- Symptom assessment

Ocular symptoms (except symptoms immediately after drop instillation, not assessed at inclusion) as well as AEs will be assessed at all investigation visits.

[redacted]

6.1.2 Description of the Measures to be Taken to Minimize or Avoid Bias

6.1.2.1 *Randomisation*

The use of randomisation attempts to mitigate accidental bias (such as selection bias), promoting comparability of the study groups and serves as a basis for statistical inference for quantitative evaluation of the treatment effect.

The randomisation code list stratified by site and lists of IMDs kit numbers for the packaging is generated by the CRO responsible for biometry. Patients will be randomised on a 1:1 basis to T2769 or Hylo-Forte® respectively.

Randomisation list(s) and lists of IMD numbers for the packaging are to be kept securely by the editor according to their procedures.

The IMD packaging list is to be kept by the company responsible for manufacturing and labelling of the treatment kits.

The randomisation and the IMD kit number will be allocated to the patients according to randomisation list using an Interactive Response Technology (IRT).

Randomisation will occur at Randomisation Visit (Visit #2 - D1) after all procedures have been performed and eligibility for the clinical investigation confirmed. The patient who meets the eligibility criteria will be randomly assigned to treatment and associated to a randomisation number.

6.1.2.2 *Concealment of Allocation*

Concealment of allocation will be ensured using an IRT system to perform IMD kit number allocation so that it’s not possible for the investigators to know the allocation sequence in advance.

6.1.2.3 *Masking and Code Breaking*

Serious biases may occur in a clinical investigation including investigator bias (which may arise due to knowledge by the investigator of treatment allocated to a particular patient), evaluator bias and placebo effects. To protect an investigation against these potential biases, masking will be used.

This will be an investigator-masked clinical investigation.

The **masked investigator** will remain masked to the IMD (T2769 – Hylo-Forte®). He/she will not receive the returned IMD from the patients.

The following-up and the number of returned IMDs will be recorded by **unmasked collaborator** throughout the clinical investigation.

The **unmasked collaborator** will also be in charge of incidents reporting as it may include information that could lead to unblinding.

Masking will be achieved by coding the interventions, providing each product unit with identical cardboard box and by identifying it by an IMD kit number.

The code should not be broken except:

- in case of medical emergency (where knowledge of the IMD received would affect the treatment of the emergency),
- or when it is a regulatory requirement (*e.g.*, for serious incident).

The investigator is responsible for accessing the IRT System to obtain the name of the IMD received by the patient.

If an emergency code breaking becomes necessary, the investigator should notify the Sponsor.

When a code is broken, the date, time and reason must be recorded in the patient's Source and in any associated AE report. The identity of the IMD should not be disclosed in these documents.

The incident form must be completed by unmasked staff. Further to a serious incident assessment by the Global Drug Safety & Medical Information Department, the code might be broken for reporting purposes. The relevant Laboratoires THÉA, Contract Research Organization (CRO), masked investigator and masked staff remain unaware of the identification of the IMD as per the above-mentioned process.

The overall randomisation list will be broken for data analysis after database lock.

6.1.2.4 *Management of potential confounding factors*

NA

6.1.2.5 *Dispensing*

IMD will be dispensed by the masked collaborator and/or pharmacist or authorised person delegated by the investigator and according to the local regulations. Each dispensing of IMDs will be recorded in the appropriate documentation.

During the whole investigation treatment period, the **masked investigator and/or delegate** will remain masked to the IMD (T2769 – Hylo-Forte®). He/she will not receive the returned IMD from the patients.

All information regarding the use of the IMDs will be contained in the package given to patients.

The IMDs must be dispensed only to patients in accordance with the CIP and the randomisation.

As soon as the patient has signed the Informed Consent, he/she will receive a patient number in the Electronic Case Report Form (e-CRF).

Once all screening criteria have been checked, the patient will receive a box including Run-in Hydrabak® treatment for the run-in period.

At the randomisation visit (Visit #2 - D1), once inclusion and exclusion criteria have been checked and once the patient is eligible, the randomisation will be performed and the IRT will provide the IMD kit number allocated to the patient.

At the other visit (Visit #3 - D15) with dispensation, the IRT will provide the IMD kit number allocated to the patient.

Two dispensations will be performed as follows:

- At randomisation (Visit #2 - D1): one box containing enough bottles for the treatment period Day 1 to Day 15 ± 1 day will be provided by the investigator (or delegate) or pharmacist with the number assigned by the IRT.

- At Visit #3 - D15: one box containing enough bottles for the treatment period Day 15± 1 day to Day 36 ± 3 days will be provided by the investigator (or delegate) or pharmacist with the number assigned by the IRT.

The site team member will instruct patient on the method of instilling the doses and will train his / her patient to not disclose the IMD characteristics neither during the visit not when reporting / discussing AE / Device Deficiency (DD). If the IMD is dispensed by a masked investigator, he must not open the IMD kit in order to avoid unblinding. [redacted]

6.1.2.6 *Primary Performance Endpoint*

The primary performance endpoint is the change from baseline[a] (D1) in total ocular surface staining grade according to Oxford 0-15 grading scheme[b] at D36 in the study eye[c].

It is the most commonly used endpoint in clinical trials with DED patients. It is performed to detect ocular damage surface, which is considered as a hallmark sign of DED.

As per literature, 1 month is a standard approach, commonly considered enough to assess a product performance in dry eye. In addition, in the previous clinical investigation on T2769 conducted by Laboratoires THÉA (CIR LT2769-001/17E1044), the improvement was rapidly observed after 14 days of treatment (see Section **3.3**).

Thus, the change from baseline (D1) in total ocular surface staining grade according to Oxford 0-15 grading scheme[b] (corneal staining by fluorescein and conjunctival staining by fluorescein with a yellow filter at D36 in the study eye[c]) was set as the primary performance endpoint to evaluate the performance of the treatment.

Different ocular surface staining scales have been developed and despite common usage, a universally accepted “gold standard” grading scale does not exist for corneal and conjunctival staining. This investigation will use the Oxford scale, a widely used and standardised grading scale. International regulatory agencies such as the Food and Drug Administration (FDA) rely on corneal and conjunctival staining measurement as a primary endpoint in clinical trials of commercially registered dry eye treatments (Begley et al. 2019).

[a]baseline is defined as the assessment at randomisation visit before the first IMD instillation. Missing value at randomisation visit will not be replaced.

[b]the analysis will be performed following original oxford scale [redacted]

[c]defined in the statistical considerations section (see Section 7.2).

[redacted]

[redacted]

6.1.2.8 *Safety Endpoints*

The following safety [redacted] endpoints will be assessed:

- Treatment-Emergent Adverse Events (TEAEs) by System Organ Class and Preferred Term (separately for ocular and systemic TEAE).

[redacted]

[redacted]

[redacted]

6.1.5 Methods and Timing for Assessing, Recording, and Analysing Variables

Four visits are scheduled during the course of the clinical investigation as presented below:

Visit#1 (Screening Visit): Day 1-10 to Day 1-7 (Run-in Period)

Visit#2 – D1 (Randomisation Visit): Day 1

Visit#3 – D15: Day 15 (±1 day)

Visit#4 – D36 (Final Visit): Day 36 (±3 days) or Premature Discontinuation Visit.

Visits should be performed at the same hour (±2 hours) in the morning.

[redacted]

6.1.5.1 *Screening Period*

Visit#1: Screening Visit (Day 1-10 to /Day 1-7)

Visit#1 will consist of the following procedures and examinations by the investigator or authorised delegate who will perform the ophthalmologic examination during all the visits and according to the following order in each eye.

By the masked investigator or authorised delegate (according to local requirements, the investigator may delegate tasks to collaborator).

- Information for the patient and signature of the informed consent (can be done before this visit, see Section **13**).
- Demography
- History of the dry eye
- Questioning about ocular and systemic medical, and surgical history (other than dry eye)
- Questioning about previous and concomitant ocular and non-ocular treatments
- Urine pregnancy testing (if applicable)
- Measurement of far BCVA*
- Slit lamp examination*
- Verification of inclusion and exclusion criteria
- Status of the patient (start of run-in period or not)
- Run-in treatment dispensation
- Patient diary dispensation.
- The following instructions will be given to the patient:

The next visit must be scheduled within 7 to 10 days later at the same hour, in the morning (± 2 hours).

Site staff must remind the patients:

- how to complete the patient diary,
- to bring the patient diary back at Visit #2,
- how to instil Hydrabak® and to respect the posology of 1 drop in each eye, from 3 to 6 times daily,
- that no preservative-free artificial tears (Hydrabak®) must be instilled for at least 6 hours before Visit#2,
- to bring back used preservative-free artificial tears (Hydrabak®) for compliance check at Visit#2.

The run-in period duration will be calculated based on the start and end dates of Hydrabak®. The start and end dates of run-in period will be the start date of Hydrabak® and the end of run-in period will be the end date of Hydrabak®.

*Ophthalmological examinations and assessments MUST be performed by the SAME masked investigator for all the visits and using the same slit lamp.

6.1.5.2 *Treatment Period*

Visit#2: Randomisation Visit (Day 1)

Visit#2 will consist of the following procedures and examinations by the investigator or authorised delegate who will perform the ophthalmologic examination during all the visits and according to the following order in each eye.

By the masked investigator or authorised delegate, the same as the screening visit (according to local requirements, the investigator may delegate tasks to collaborator).

- Questioning about previous and concomitant ocular and non-ocular treatments
- OSDI Questionnaire
- DEAL questionnaire
- Ocular discomfort (VAS)
- Questioning about dry eye related ocular symptoms within the last 48 hours
- Measurement of Far BCVA*
- Tear Sampling for IL6 and IL8 concentration assessment**
- Slit lamp examination* for measuring:
  - Measurement of conjunctival hyperaemia* [redacted]
  - [redacted] Oxford 0-15 grading scheme* (corneal staining by fluorescein and conjunctival staining by fluorescein with yellow filter),
  - TBUT*
- Schirmer test* (without anaesthesia)
- AE reporting
- Verification of inclusion and exclusion criteria
- Randomisation (IRT system)
- IMD dispensation
- Questioning about Run-in treatment compliance
- Check of the patient diary completion with the patient
- Status of the patient (Screen failure or randomised)

By the unmasked collaborator:

- Incidents reporting

The next visit must be scheduled 15 days after Visit #2 (±1 day) at the same hour (± 2 hours).
Site staff must remind the patients:

- how to complete the patient diary,
- to not report any information that could lead to unblinding in the diary,
- to not report any information that could lead to unblinding to the masked investigator,
- to bring the patient diary back at Visit #3,
- how to instil IMD and to respect posology of 1 drop in each eye, from 3 to 6 times daily,
- that no IMD must be instilled for at least 2 hours before Visit#3.

*Ophthalmological examinations and assessments MUST be performed by the SAME masked investigator for all the visits and using the same slit lamp.

**It's necessary to wait at least 15 minutes after tear sampling to perform the next ophthalmic assessment.

Visit#3: Day 15 (± 1 day)

Visit#3 will consist of the following procedures and examinations by the investigator or authorised delegate who will perform the ophthalmologic examination during all the visits and according to the following order in each eye.

By the masked investigator or authorised delegate (the same as the screening visit) (according to local requirements, the investigator may delegate tasks to collaborator).

- Questioning about previous and concomitant ocular and non-ocular treatments
- OSDI Questionnaire
- DEAL questionnaire
- Ocular discomfort (VAS)
- Questioning about ocular symptoms immediately after drop instillation,
- Questioning about dry eye related ocular symptoms within the last 48 hours
- Assessment of global performance by the patient
- Assessment of the ocular tolerance by the patient
- Measurement of Far BCVA*
- Tear Sampling for IL6 and IL8 concentration assessment**
- Slit lamp examination* for measuring:
    - Measurement of conjunctival hyperaemia* [redacted]
    - [redacted] Oxford 0-15 grading scheme* (corneal and conjunctival staining by fluorescein with yellow filter)
    - TBUT*
- Schirmer test* (without anaesthesia)
- AE reporting
- Assessment of the ocular tolerance by the investigator
- Assessment of the performance by the investigator
- IMD dispensation
- Questioning about IMD compliance
- Check of the patient diary completion with the patient

*Ophthalmological examinations and assessments MUST be performed by the SAME masked investigator for all the visits and using the same slit lamp.

**It's necessary to wait at least 15 minutes after tear sampling to perform the next ophthalmic assessment.

By the unmasked collaborator:

- Recording the number of returned used and unused IMD in source document (the accountability is expected for the quantity of bottles) and transfer this information to masked investigator for compliance assessment.
- Incidents reporting

The next visit must be scheduled 36 days after Visit #2 (±3 days) at the same hour (± 2 hours).

Site staff must remind the patients:

- how to complete the patient diary,
- to not report any information that could lead to unblinding in the diary,
- to not report any information that could lead to unblinding to the masked investigator,
- to bring the patient diary back at Visit #4.
- how to instil IMD and to respect the posology of 1 drop in each eye, from 3 to 6 times daily,
- that no IMD must be instilled for at least 2 hours before Visit#4.

Visit#4: Day 36 (± 3 days)

Visit#4 will consist of the following procedures and examinations by the investigator or authorised delegate who will perform the ophthalmologic examination during all the visits and according to the following order in each eye.

By the masked investigator or authorised delegate (the same as the screening visit) (according to local requirements, the investigator may delegate tasks to collaborator).

- Questioning about previous and concomitant ocular and non-ocular treatments
- OSDI Questionnaire
- DEAL questionnaire
- Ocular discomfort (VAS)
- Questioning about ocular symptoms immediately after drop instillation,
- Questioning about dry eye related ocular symptoms within the last 48 hours
- Assessment of global performance by the patient
- Assessment of the ocular tolerance by the patient
- Measurement of far BCVA*
- Tear Sampling for IL6 and IL8 concentration assessment**
- Slit lamp examination* for measuring:
  - Measurement of conjunctival hyperaemia* [redacted]
  - [redacted] Oxford 0-15 grading scheme* (corneal and conjunctival staining by fluorescein with yellow filter)
  - TBUT*
- Schirmer test* (without anaesthesia)
- Urine pregnancy testing
- AE reporting

*Ophthalmological examinations and assessments MUST be performed by the SAME masked investigator for all the visits and using the same slit lamp.

**It's necessary to wait at least 15 minutes after tear sampling to perform the next ophthalmic assessment.

- Assessment of the ocular tolerance by the investigator
- Assessment of the performance by the investigator
- Questioning about IMD compliance
- Check of the patient diary completion with the patient

By the unmasked collaborator:

- Recording the number of returned used and unused IMD in document source (the accountability is expected for the quantity of bottles) and transfer this information to masked investigator for compliance assessment.
- Incidents reporting

6.1.5.3 *Additional/Optional Visit(s) during the clinical investigation*

NA

6.1.5.4 *Premature Discontinuation Visit during the clinical investigation*

A patient who prematurely discontinues from the clinical investigation should have, if possible, a Premature Discontinuation Visit. This last site visit should take place as soon as possible after the patient stops taking IMD. All follow-up procedures and examinations scheduled to be performed at the final visit should be performed at the patient's premature discontinuation visit.

If the patient is tested COVID-19 positive during the course of the clinical investigation, the patient has to inform the investigator. Either the patient may continue the clinical investigation when he/she can follow the CIP requirements safely and in accordance with the national/regional recommendations or the patient may be withdrawn from the clinical investigation.

6.1.5.5 *Additional Follow-Up Visit(s) (after the end of the treatment)*

NA

6.1.5.6 *Adaptive Follow-Up of Patients Prematurely Withdrawn due to an Exceptional Circumstance (e.g. COVID-19 pandemic)*

The benefit/risk ratio will be evaluated both by the Sponsor at global level (regulatory requirement) and by the investigator regarding the situation and local regulatory requirements in his/her country/region and in his/her own investigational site.

If the patient withdrew from the investigation due to an exceptional circumstance, and if an onsite visit was not authorised, a premature discontinuation visit by phone is required.

- **Premature discontinuation phone call**

- Check the IMD compliance with the patient.
- Instruct the subject to stop the IMD and keep used and unused IMD for later return.
- Ensure the continuity of artificial tears medication as per routine clinical practice.
- Collect AE/Serious Adverse Event (SAE), incidents and any changes in concomitant treatments.

- Plan a safety onsite visit 4 weeks later (±7 days) and ensure that the patient understands all recommendations.
- Record the phone call and all information collected in the patient medical record.

– **Safety Follow-up visit on site**

During the onsite follow-up visit done 4 weeks (±7 days) after the premature discontinuation phone call, the following procedures are required:

- Ensure that dry eye is well controlled.
- Check the IMD compliance with the patient.
- Record the number of the returned used and unused IMD (by the authorised unmasked delegate).
- Check that the patient had stopped the IMD and takes the new treatment, collect start and end dates of these medications.
- Collect AE/SAE, incidents and any changes in treatments.
- Record the visit and all information collected in the patient medical record.

If a safety onsite visit is still not possible, the follow-up will be done by phone or online video consultation and the patient is asked to return the used and unused investigation products later, when the situation improves or the pickup of the IMD directly from the patient will be organised. The compliance will be checked with the number of the returned used and unused IMD.

6.1.6 Equipment to be used for Assessing the Clinical Investigation Variables and Arrangements for Monitoring Maintenance and Calibration

A slit lamp will be used to measure the total ocular surface staining grade according to [redacted] Oxford 0-15 grading scheme.
During the Site Qualification Visit and the Site Initiation Visit, the site must prove that he has a maintenance certificate for the slit lamp. During the clinical investigation, the monitor should verify that the maintenance is performed (cf. manufacturer guidelines).
During the clinical investigation, the same slit lamp must be used for the same patient at each visit.

6.1.7 Procedures for the Replacement of Patients

The number of screened patients will be followed to obtain 74 randomised patients.

A screen-failed patient (i.e. patient who consent to participate in the clinical investigation and undergo Visit#1 but not subsequently randomised) may be rescreened one time.

Randomised patients who withdraw will not be replaced by another patient. The patient number and associated randomisation number of the withdrawn patient must not be reassigned to a different patient.

6.1.8 Investigation Sites

Patients will be enrolled in approximately 4 investigational sites in EU.

The Sponsor will maintain an updated list of PIs and investigation sites, separately from this CIP, throughout the duration of the clinical investigation. The definitive list will be provided with the CIR.

6.1.9 Definition of Completion of the Clinical Investigation

The clinical investigation completion is defined with the last visit of the last patient.

In the case of early termination of the clinical investigation (see Section **16.2**), the date of the early termination shall be deemed to be the date of the clinical investigation completion.

6.2 IMD(S) AND COMPARATOR(S)

6.2.1 Description of the Exposure to the IMD

IMD will be administered by the patient every day from D1 until Visit 4 (included), one drop in each eye 3 to 6 times daily into the lower conjunctival sac of each eye.

No IMD instillation must be done at least 2 hours before Visit#3 and 4. However, the first instillation can be done any time after the patient has completed the randomisation visit.

There will be two treatment groups:

• T2769 (test device)

• Hylo-Forte® (comparative device)

A detailed description of T2769 and of Hylo-Forte® is available in Section **0**.

6.2.2 List of any Other Medical Device or Medication to be Used during the Clinical Investigation

6.2.2.1 *Run-in Treatment*

Once all screening criteria have been checked, the patient will receive a box containing 1 bottle of Hydrabak® treatment for the run-in period between Day-10/Day-7 to Day 1. The patient will instil 1 drop in each eye 3 to 6 times daily.

6.2.2.2 *Auxiliary Products*

An auxiliary product is defined as a product used for the needs of a clinical investigation as described in the CIP, but not as an IMD.

Fluorescein [redacted] a small amount (micro instillation) of fluorescein will be applied in the upper bulbar conjunctiva of each eye by the investigator at visits 2, 3 and 4 to perform the slit lamp examination: TBUT and corneal/conjunctival staining with Oxford 0-15 grading scheme. Conjunctival staining is assessed with a yellow filter.

Yellow filter: it is used for the assessment of the conjunctival staining with fluorescein. The filter is placed between the slit lamp objective and the patient eye to enhance contrast.

Petri dishes and inoculation loops: they are used to perform the fluorescein micro instillation. Some drops of fluorescein are put in a petri dish and a small amount of fluorescein is collected with an inoculation loop.

Schirmer-Plus: while the patient looks upwards, the lower lid will be drawn gently downwards and temporally. The rounded bent end of a sterile Schirmer test strip will be hooked in the lower conjunctival sac over the temporal one-third of the lower eyelid margin. After five minutes, the moistened paper is removed and the length of the tear absorption on the strip will be measured (in millimeters).

Urine pregnancy test: each childbearing potential woman will perform a urine pregnancy test at Visit#1 and Visit#4.

6.2.3 Number of IMD to be Used, Together with a Justification

During the clinical investigation, each patient will receive 1 bottle of Hydrabak® and the IMD (4 bottles of T2769 or Hylo-Forte®) to cover run-in and active treatment period.

6.3 PATIENTS

6.3.1 Inclusion Criteria

- *At screening visit*

1.1. Informed consent signed and dated (obtained prior to initiating any procedures).

1.2. Patient aged ≥18 years old.

1.3. Persistence of dry eye syndrome, despite artificial tears use in the previous month prior to the screening visit.

[redacted]

6.3.2 Exclusion Criteria

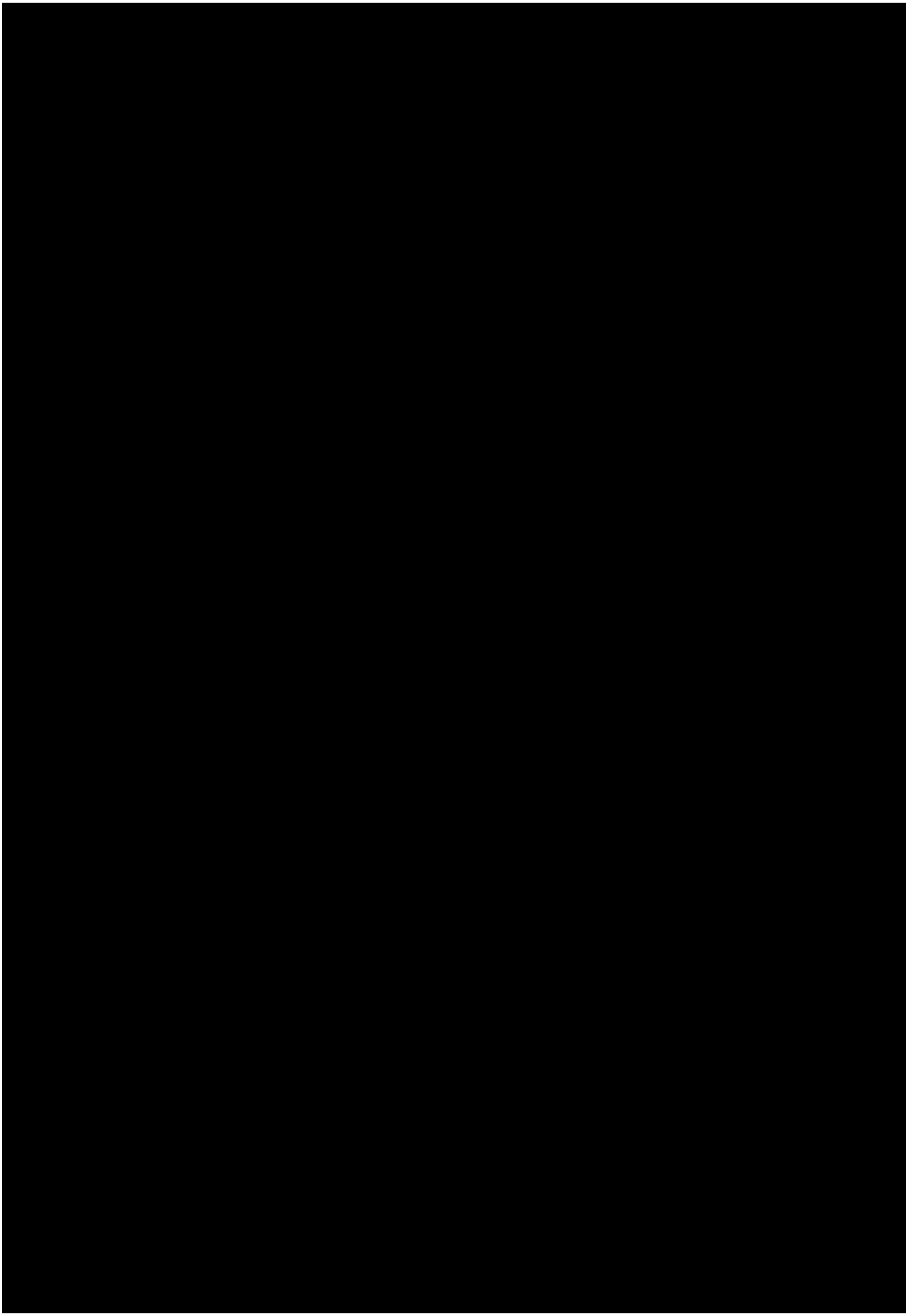
Patient will NOT be eligible if ONE OR MORE of the following criteria is met at both screening and randomisation visits.

<u>Ophthalmic Exclusion Criteria in AT LEAST ONE EYE</u> [2.1]

2.1.1 Far best-corrected visual acuity (BCVA) ≥+0.7 LogMar (e.g., ≤0.2 in decimal value or ≤20/100 Snellen equivalent or ≤50 (ETDRS).

Patient with previous or current ophthalmic condition as defined in the following table:

[redacted]



[redacted]

6.3.3 Criteria and Procedures for Treatment/Investigation Withdrawal or Discontinuation

There are no pre-defined criteria for temporary or permanent treatment discontinuation apart from those listed below.

The patient may voluntarily withdraw from the clinical investigation at any time without penalty and for any reason without prejudice to his/her future medical care (Declaration of Helsinki).

The patient must be withdrawn from the clinical investigation if, in the opinion of the investigator, there is any situation or condition which puts the patient at significant risk, especially in case of:

- Any safety reason(s)/AEs necessitating discontinuation from the investigation,
- Any abnormality with IMD,
- Lack of performance: if the patient or the investigator does not feel that the IMD has sufficiently controlled the pathology/has adequately relieved his/her symptoms,
- Patient compliance,
- Patient's request,
- Any exceptional circumstance (e.g., COVID-19 pandemic),
- Other reasons.

If a patient has received a prohibited medication, the investigator may withdraw the patient from the clinical investigation if it can interfere with the patient safety or data integrity. If no risk is identified, the patient may continue the clinical investigation. This will be recorded as a protocol deviation and managed accordingly. The Sponsor may also make the decision to withdraw a patient if a risk is suspected.

If a patient prematurely stops the IMD or should/wants to prematurely withdraw from the clinical investigation for any reason, the investigator (or delegated assessor) must make every effort to perform all the evaluations described for the Final Visit (Visit#4) as soon as possible.

The investigator (or delegated assessor if physician) will prescribe the best appropriate treatment to the patient.

Additionally, Sponsor can terminate the clinical investigation per reasons discussed in Section **16.2**.

In all cases, the reason(s) for withdrawal, must be recorded on the patient files (source documentation) and the primary reason, must be recorded on the e-CRF.

The patient discontinued for AE(s) will be followed-up after discontinuation until the event is resolved or considered medically stable by the investigator.

If a patient is lost-to-follow-up, the investigator must do his/her best to contact the patient initially by phone, then by letter, and finally by certified mail. If no response is obtained from the patient, the investigator is encouraged to contact one of the patient's relatives or his/her general practitioner. The evidence of these contacts must be recorded in the patient files.

Screen failures are defined as patient who consent to participate in the clinical investigation and undergo Visit#1 but are not subsequently randomised in the clinical investigation.

If a patient is screen-failed, all reasons of screen-failure must be documented in the Source document. The screen-failed patient may be rescreened one time.

The Procedures for the replacement of patients is described in section **6.1.7**.

Adaptive follow-up in the case of an **exceptional circumstance (e.g. COVID-19 pandemic)** is described in section **0.0**

6.3.4 Point of Enrolment

The point of enrolment corresponds to the time at which a patient signs and dates his/her consent form. Patients are to be enrolled at about 4 investigational sites in EU.

6.3.5 Point of Randomisation

The point of randomisation corresponds to the time at which a patient is assigned with a randomisation number. This randomisation number will be allocated when all Inclusion / Exclusion criteria are verified.

6.3.6 Total Expected Duration of the Clinical Investigation

This investigation is planned to start in August 2024 and to be completed in April 2025.

6.3.7 Expected Duration of each Patient's Participation

The treatment period for each patient is 36 ± 3 days for a total maximum investigation duration of 49 days (maximum days comprising the run-in, treatment period).

6.3.8 Number of Patients Required to be Randomised in the Clinical Investigation

It is planned to randomise 74 patients in order to have 68 evaluable patients (34 per group) for the FAS analysis.

Evaluable patients will be defined as randomised patients having received at least one dose of IMD and with at least one performance endpoint post-randomisation visit.

6.3.9 Estimated Time Needed to Select this Number (*i.e.* enrolment period)

The enrolment period is estimated at about 6 months.

[redacted]

6.3.11 Information on Vulnerable, Pregnant, and Breastfeeding Population

This clinical investigation will not be conducted in vulnerable populations as children, pregnant or breastfeeding women. A urine pregnancy testing will be performed at Visit#1 and Visit#4 (See Section **15)**.

6.4 PROCEDURES

[redacted]

Some procedures must be performed by the same masked investigator or the same authorized assessor/delegate throughout the clinical investigation (Far BCVA, Slit Lamp Examination, Schirmer test, tolerance/performance assessment by investigator).

6.4.1 Description of all the Clinical-Investigation-Related Procedures that Patients Undergo during the Clinical Investigation.

6.4.1.1 *Demographics and Screening Characteristics*

The following characteristics will be collected:

- Age (in years),
- Sex,
- Previous and concomitant ocular and non-ocular medications,
- Result of the urinary pregnancy test (only for women of childbearing potential),
- History of the investigated disease,
- Ocular medical and surgical history with relevant diagnosis other than the investigated disease,
- Systemic medical and surgical history with relevant diagnosis

6.4.1.2 *Performance Measures*

6.4.1.2.1 *Ocular Surface Disease Index (OSDI) Questionnaire*

The OSDI questionnaire (Schiffman et al., 2000; Miller et al., 2010) must be completed by the patient at the beginning of a visit before medical history information is collected or any investigation assessments are performed. The total OSDI score range on a scale from 0 to 100 [redacted]

[redacted]

6.4.1.2.3 *Ocular discomfort (VAS)*

Ocular discomfort (global evaluation for both eyes) will be assessed by the patient at D1, D15 and D36 visits according to the following:

"Please mark a vertical line (not a cross) on the horizontal line, indicating your level of ocular discomfort due to ocular dryness within the last 48 hours". VAS will be a 100 mm line: 0 mm = No discomfort, 100 mm = Maximal discomfort.

0	100
No discomfort	Maximal discomfort

6.4.1.2.4 *Dry eye related ocular symptoms throughout the day within the last 48 hours*

Patient will be asked: "How do you judge the severity of the following ocular symptoms throughout the day within the last 48 hours, excluding the symptoms you felt immediately after instillation?"

The severity of the following ocular symptoms will be assessed: burning/irritation, stinging/eye pain, light sensitivity, itching/pruritus, eye dryness feeling, tearing, foreign body sensation as follows:

0 = Absent

1 = Mild, present but not disturbing

2 = Moderate, disturbing, but not limiting with daily activities

3 = Severe, very distressing and interfering with daily activities

The ocular symptoms will be assessed in global for both eyes at D1, D15 and D36 visits. The value at D1 will be the baseline value.

6.4.1.2.5 *Slit lamp examination*

- Conjunctival hyperaemia

The level of severity of conjunctival hyperaemia will be scored [redacted] in each eye and at D1, D15 and D36 visits (see Section **19.4**).

- Tear Break-Up Time (TBUT)

The tear film stability will be measured 3 times after the instillation of fluorescein. TBUT will be rapidly assessed and expressed in seconds. The sum of the 3 measures will also be expressed in seconds. TBUT will be measured in each eye and at D1, D15 and D36 visits.

- Ocular surface staining ([redacted] Oxford scale)

The total ocular staining grade using [redacted] Oxford 0-15 grading scheme will be assessed at D1, D15 and D36 visits by staining in corneal area by fluorescein and conjunctival areas (temporal and nasal) by fluorescein with a yellow filter.

Cornea and conjunctiva staining is represented by punctate dots on a series of panels (A-E). Staining ranges form 0-5 for each zone and from 0-15 for the total exposed inter-palpebral

conjunctiva and cornea. The dots are ordered on the log scale ([redacted] Oxford scale) (see Section **19.5)**.

The score for each area will be recorded for each eye. The global score (sum of score reported for each area: corneal + conjunctival) will be used for statistical analysis. The statistical analysis will be performed following original oxford scale [redacted]

TBUT and ocular surface staining will be assessed after micro instillation of fluorescein. Some drops of fluorescein are put in a petri dish and a small amount of fluorescein is collected with an inoculation loop and then applied to the upper bulbar conjunctiva. This process will be detailed in a specific guide provided to investigation sites.

A slit lamp examination will also be performed at Visit #1 (Screening visit) for evaluation of the prohibited ophthalmic conditions in order to verify the ocular eligibility.

6.4.1.2.6 *Schirmer Test*

The Schirmer test will be performed without anaesthesia (Test I). The test should be done **without touching directly the strip with the finger** to avoid contamination of skin lipids.

The strip should be placed in the temporal part to avoid any contact with the cornea. The patient should keep the eyes closed. Values should be measured just at the end of the 5 minutes.

The Schirmer test will be measured in mm/5 min in each eye and at D1, D15 and D36 visits.

6.4.1.2.7 *Performance Assessment by the investigator*

The investigator must answer to the following question at the end of the patient examination at D15 and D36:

“Do you consider the IMD performance as:

- Very satisfactory
- Satisfactory
- Not very satisfactory
- Unsatisfactory”

6.4.1.2.8 *Global performance by patient*

The global performance is assessed by the patient using a vocal NRS scale. The investigator must ask the following question in local language:

“In a scale from 0 to 10, where 0 is COMPLETELY UNSATISFIED and 10 is COMPLETELY SATISFIED, indicate the number which corresponds the best to your overall satisfaction with the efficacy of the study product in treating your dry eye” (see Section **19.7)**.

The patient must answer the question verbally.

6.4.1.2.9 *Tear level of inflammatory cytokines (IL-6 and IL-8)*

A tear sampling of at least 5 µL will be performed at D1, D15 and D36 in the study eye using a method which is defined in a specific guide. The sample will be analysed by central laboratory in order to assess the level of inflammatory cytokines in tears. The Tear sampling will be done after answer to patients’ questionnaires and before ocular examinations.

To prevent the tear sampling from interfering with other ocular assessments, it will be required to wait at least 15 minutes after the sampling is performed to continue with the next ocular assessment.

6.4.1.3 *Safety measures*

6.4.1.3.1 *Adverse Events*

Ocular and systemic AEs will be collected by the investigator (or authorised assessor/delegate) at each visit. In case of appearance of a new clinically significant sign or symptom, it should be reported as an AE. In case of clinically significant worsening of a pre-existing sign or symptom, it should be reported as an AE.

The handling of AEs is detailed in Section 0.

6.4.1.3.2 *Incidents*

Incidents will be collected by the unmasked investigator (or authorised assessor/delegate) at D1, D15 and D36 visits.

6.4.1.3.3 *Ocular Symptoms immediately after drop instillation*

The severity of ocular symptoms immediately after drop instillation will be assessed by the patient.

“Since the last visit, have you felt any unusual ocular sensation immediately after drop instillation(s)?

The following symptoms will be evaluated:

- Burning/Irritation
- Stinging/Eye Pain
- Itching/pruritus
- Eye dryness feeling
- Foreign body sensation
-

Severity will be assessed based on a 4-point scale:

0 = Absent,
1 = Mild - Present but not disturbing,
2 = Moderate - Disturbing
3 = Severe - Very disturbing.

The translation of these terms will be provided to the site.

6.4.1.3.4 *Visual Acuity*

Far BCVA will be assessed in each eye at each visit using the same chart (for example a Snellen chart) throughout the clinical investigation. It can be expressed using units as /10, decimal notation, MAR, logMAR, ETDRS or Snellen notation. It will be analysed after conversion in LogMar. (see Section **19.6)**.

6.4.1.3.5 *Ocular Tolerance Assessment by the investigator*

The investigator must answer to the following question in local language:

"How do you consider the IMD ocular tolerance?

- Very satisfactory
- Satisfactory
- Not very satisfactory
- Unsatisfactory"

6.4.1.3.6 *Ocular Tolerance Assessment by the Patient*

The investigator must ask the patient the following question in local language:

"How do you consider the study treatment ocular tolerance?

- Very satisfactory
- Satisfactory
- Not very satisfactory
- Unsatisfactory"

6.4.1.3.7 *Treatment Compliance Evaluation*

Patient will return all investigational products (IMDs and Hydrabak®), whether used or unused.

For Hydrabak® and IMD *(*T2769 or Hylo-Forte®), the patient will also have to report information about his/her compliance on a paper patient diary during the run-in and the treatment period. Each day the patient will enter the date and number of instillations* per day. Moreover, it will be asked to add the date and hour of last instillation before the beginning of each visit.

In addition*,* compliance will be assessed by questioning the patient during the visit (*e.g.* if there was any treatment interruption or missed instillation), by checking on paper patient diary and by cross-checking with IMD accountability information provided by unmasked collaborator.

** one instillation = 1 drop in each eye*

6.4.1.4 *Prior and Concomitant Therapy*

At screening visit, patient will be asked what treatment he/she has taken within the last 3 months; this will be recorded on the patient medical record and on the e-CRF documenting product details, dose and treatment duration.

Concomitant treatment means any medications or non-medicinal therapies given concurrently with the IMD. Any other local or systemic treatment necessary for the patient's welfare has also to be recorded on the patient medical record and on the e-CRF documenting product details, dose and treatment duration. In case of premature discontinuation, the new treatment for dry eye with the start date and dosing must also be collected.

6.4.1.5 *Permitted Treatments*

Auxiliary products are permitted (see Section **0).** Systemic medication not listed in **Table 2** are permitted **ONLY** if there has been no modification of the dosage in the month preceding the inclusion visit and if no modification is planned throughout the duration of the study.

6.4.1.6 *Prohibited Prior and Concomitant Medications or Treatments*

6.4.1.6.1 *Rescue Medications (RMs)*

NA.

6.4.1.6.2 *Prohibited Treatments other than Rescue Medications (RMs)*

Prohibited treatments as well as prohibited modifications during the clinical investigation are presented in the summary in the exclusion criteria and in **Table 2**.

6.4.2 Description of those Activities Performed by Sponsor Representatives (excluding monitoring)

Laboratoires THÉA through CROs is responsible for selecting the investigator(s). Each investigator should be qualified by training and experience and should have adequate resources to properly conduct the clinical investigation.

Laboratoires THÉA /representatives of Laboratoires THÉA will remind the investigator upon his/her responsibilities and procedures for ensuring adequate and correct documentation.

Laboratoires THÉA will inform the investigator, directly or through CRO in charge of monitoring, prior to the commencement of the clinical investigation of all relevant chemical, toxicological and clinical information required for the proper planning and conduct of the clinical investigation and will update this as often as may be necessary during the course of the clinical investigation. However, this obligation shall not require Laboratoires THÉA to provide information which is already available in published material or of which the investigator could reasonably be expected to have knowledge in view of his/her professional training.

Laboratoires THÉA or CROs will nominate a suitably trained person or persons to monitor the clinical investigation and to liaise with the investigator.

Laboratoires THÉA/representatives of Laboratoires THÉA, will also be responsible for complying with the local regulations applicable to clinical investigation.

6.4.3 Any Known or Foreseeable Factors that may Compromise the Outcome of the Clinical Investigation or the Interpretation of Results

The population will be selected according to the inclusion and exclusion criteria to have a homogenous population.

A run-in period with Hydrabak® is scheduled to have patient with the same treatment at the baseline visit.

6.4.4 Methods for Addressing these Factors in the Clinical Investigation

To not compromise the outcome of the clinical investigation, the patient will be randomly assigned to 1 of the 2 treatment groups during the randomisation visit.

6.4.5 Description of the Follow-Up Period

NA

6.4.6 Appropriate Specific Medical Care Address after the Clinical Investigation

NA

6.4.7 Recommended Follow-Up Address after the Clinical Investigation

NA

6.4.8 Final Disposition or Potential Future Use of Samples obtained from Patients Address

All biological samples (tear samplings) that have already been collected may be retained and analysed at a later date, per local regulations (e.g. for potential post study genomic analysis).

[redacted]

6.5.1 Source Documents

Each participating investigational site will maintain appropriate medical and research records in compliance with GCP (ISO 14155 current version) and any other regulatory and institutional requirements for the protection of patient's confidentiality.

Source data are all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical investigation necessary for the reconstruction and evaluation of the clinical investigation. Source data are contained in source documents.

Source documents are any original documents, data and records. These may include, but are not limited to, patient medical records, hospital charts if any, clinic charts, laboratory notes, patient's questionnaires, patient's diaries if any, the investigator's files, pharmacy dispensing records and recorded data from automated instruments.

Some specific medical data gathered during routine medical practice visits prior to the participation can be used in screening visit and before informed consent form on the patient best care interest.

All following patient's assessments will be collected via a paper diary and paper questionnaire and will be considered as source data:

- Run-in treatment compliance: number of instillations/day
- IMD compliance: number of instillations/day
- OSDI questionnaire
- DEAL questionnaire
- VAS

The following information should be entered into the patient's medical record:

- Patient's name, date of birth, gender
- Patient's contact information
- The date the patient entered the clinical investigation and patient's number
- The study title and/or the clinical investigation number
- A statement that informed consent was obtained (including the date) and patient's card was provided to the patient; data protection consent or other country and local patient privacy required documentation for this investigation have been obtained (including the date)
- Date of all patient's visits
- Investigated disease history:
    - Diagnosis of DES for each eye
    - Date of onset of the diagnosis in each eye (months/year)
    - Previous use of artificial tears
- Ocular and systemic medical and surgery history (other than dry eye)

For systemic medical history, the information could be collected via patient interview. For ophthalmic medical history of referred patient's, a letter from the referring ophthalmologist is strongly recommended.

- Prior and concomitant medications (list all prescription and non-prescription medications being taken at the time of enrolment and within 3 months before screening visit). At each subsequent visit, changes to the list of medications should be recorded.
- Name/initials and signature of the persons who perform assessments
- Visual acuity values (standard BCVA value with used chart name)
- Slit-lamp examination results with score of ocular signs, conjunctival hyperaemia, corneal staining by fluorescein and conjunctival staining by fluorescein with a yellow filter and TBUT
- Shirmer test results for both eyes
- Occurrence and status of any AEs
- Occurrence and status of any incident
- Review of inclusion/exclusion criteria and patient's status (confirmation of patient eligibility or not, reason for screen failure if applicable)
- Ocular tolerance and performance assessment by Investigator
- Tolerance and performance assessment by the patient
- Information on diary dispensation to the patient and instructions correctly provided
- Information on Run-in treatment dispensation, instruction for use and kit number provided to patient
- Information on IMD dispensation, including kit number assignment with IRT notification
- Run-in treatment compliance collected by reviewing patient's diary and interview and checked against returned kit
- IMD compliance collected by reviewing patient's diary and interview and checked against returned IMD
- Information on used/unused IMD by patient, assessed by unmasked collaborator
- The date of the patient exited the clinical investigation and a notation as to whether the patient completed the clinical investigation or reason for discontinuation**.**

6.5.2 Source Data Verification

One of the primary responsibilities of monitoring is the Source Data Review (SDR) to check quality of source, review CIP compliance, ensure the critical processes and source documentation are adequate, to ascertain Investigator involvement and appropriate delegation and assess compliance to other areas (e;g; SOPs, GCP, ISO 14155 current version). This will require direct access to all source documents, any original documents, data and records of each patient.

It will be verified that informed consent documentation is filed for all screened patients whether or not they were randomised into the clinical investigation and that the information is listed in the source documents.

Source Data Verification (SDV) will be recorded in e-CRF and SAE/pregnancy related documents, consisting in a comparison of the source documentation and other records relevant to the clinical investigation/ with the e-CRF. This will require direct access to all source documents, any original documents, data, and records of each patient.

The SDV will ensure the data are Attributable, Legible, Contemporaneous, Original, Accurate, Complete, Consistent, Enduring and Available (ALCOACCEA guiding principles).

Source Data Monitoring combines:

- ✓ Site Monitor review of the source data for a patient in order to confirm that the site is compliant with ICH GCP, ISO 14155 current version and the CIP.
- ✓ Evaluation of the conformity of the data presented in e-CRF, or other Sponsor-provided documents, with the available Source Data.

SDR can be done alone, but SDV cannot be done without prior SDR, since validating data transcription is not useful if CIP and GCP, ISO 14155 current version compliance have not been confirmed first.

6.5.3 Case Report Forms

The patients will be monitored throughout the clinical investigation and all results of evaluations will be recorded in an e-CRF.

The e-CRF completion guidelines will be provided and introduced to the investigation staff before the start of the clinical investigation.

The investigator and authorised delegate(s) will have secured access to enter the data in the appropriate sections of the e-CRF and to IRT.

The e-CRF must be completed for each patient screened in the clinical investigation, including screening failure patients. It should be completed as soon as possible after the patient visit.

The investigator is required to prepare and maintain adequate and accurate ocular and systemic history designed to record all observations and other data pertinent to the investigation for each patient.

The investigator is responsible for ensuring that data are properly recorded on each patient's e-CRF and related documents.

The investigator will be responsible for the punctuality, completeness, consistency and accuracy of e-CRF. E-CRF and source data will be retained by the investigator for data verification at each scheduled monitoring visit.

The principal investigator or delegate(s) should personally electronically validate and sign e-CRFs to ensure that the observations and findings are correctly and completely recorded on the e-CRFs.

All information recorded on the e-CRFs for this clinical investigation must be consistent with the patients' source documentation (i.e., medical records).

A copy of completed e-CRFs pages and incident forms will be stored in the investigator's archives for at least 10 years after the last T2769 device has been placed on the market.

7 STATISTICAL DESIGN AND ANALYSIS

The Statistical Analysis Plan (SAP) will provide, before locking the database and breaking the blind, detailed methods for the analyses outlined below.

Any changes from the planned analyses will be described and justified in the final CIR.

7.1 ANALYSIS POPULATION AND PROCEDURES

The following analysis sets will be considered:

- **Safety set:**

All enrolled patients, having received at least one dose of IMD. Patients will be analysed according to the treatment received.
Safety set will be the primary population for safety analysis.

- **Intent-to-Treat (ITT) set:**

All randomised patients. Patients will be analysed according to the treatment they were assigned to at randomisation.

- **Full Analysis Set (FAS):**

All randomised patients having received at least one dose of IMD, with at least one baseline and one post-randomisation performance assessment. Patients will be analysed according to the treatment they were assigned to at randomisation.

- **Per protocol (PP) set:**

Subset of the FAS including patients without any major CIP violations likely to seriously affect the primary outcome of the study. Patients will be analysed according to the treatment received.

[redacted]

The FAS will be the primary population for performance analysis. The PP set will be considered as the secondary population and will be used for sensitivity analyses of the primary [redacted] performance endpoint[redacted]

7.2 STATISTICAL ANALYSIS

Statistical descriptions will be performed by treatment groups. For disposition and demography description will also be presented overall.

Variables recorded for each eye will be described separately for the study eye and for the contralateral eye (if applicable).

Baseline is defined as the assessment at D1 visit before the first IMD instillation. Missing values at randomisation visit will not be replaced.

For endpoints defined as change from baseline, the descriptive statistics by visit (Screening, D1, D15 and D36) and the change from baseline at D15 and D36 will be presented. [redacted]

[redacted]

Disposition, demographics, exposure, history of dry eye, medical/surgical history (by System Organ Class [SOC] and PT separately for ocular and systemic history), will be summarised by treatment group and overall, for the FAS, PP set and Safety set [redacted] Disposition and demographics will also be presented for the ITT. Previous and concomitant ocular/non-ocular treatments will be listed.

7.2.1 Performance Analyses

Primary [redacted] performance endpoint will be primarily analysed on the FAS. Sensitivity analysis of the primary [redacted] performance endpoint will be performed on the PP.

The detailed analysis methods for primary and each secondary performance variables will be discussed further in the SAP.

Primary performance endpoint

The primary performance endpoint is the change from baseline (D1) in total ocular surface staining grade according to Oxford 0-15 grading scheme at D36 in the study eye. The analysis will be performed following original Oxford scale [redacted]

The inferential analyses of the primary performance endpoint will aim to assess the non-inferiority of T2769 to Hylo-Forte®. The hypothesis of non-inferiority will be tested by calculating the bilateral 95% CI around the difference between groups (T2769 – Hylo-Forte®) in mean change from baseline in the total ocular surface staining (Oxford score) to D36 in the study eye. If the upper bound is no higher than +2 points, it will be concluded that the null hypothesis can be rejected and that the performance of T2769 is non-inferior to that of Hylo-Forte®.

The non-inferiority will be primarily tested using a Mixed Model for Repeated Measures (MMRM) approach. The model will include treatment and scheduled visit time points (D15 and D36) as fixed factors, patient as random factor, and baseline total ocular surface staining (Oxford score) as continuous covariate Treatment by scheduled visit time point and baseline total ocular surface staining (Oxford score) by scheduled visit time point will be included as an interaction term in the model.

[redacted]

[redacted]

Descriptive tables will also be produced presenting data for total ocular surface staining values and change from baseline at each visit.

[redacted]

7.2.2 Safety Analyses

Safety endpoints will be analysed on the Safety set.

Ocular and systemic adverse events (AEs)

Ocular and systemic AE reported during the investigation will be coded using the Medical Dictionary for Regulatory Activities (MedDRA dictionary).

Summary tables will be performed on Treatment-Emergent AEs (TEAEs).

Ocular and systemic TEAEs will be analysed separately on the basis of the localisation and System Organ Class (SOC).

TEAEs are AEs that occurred after the first IMP instillation. For the AEs that occurred the day of the first IMP instillation, a question on the eCRF will establish the timing compared to the first instillation. .
Separate descriptions of ocular (for both, study and contralateral eye together) and systemic TEAEs will be performed by treatment group:

- An overall summary of the number and percentage of patients experiencing at least one AE, SAE, IMD-related AE, IMD-related SAE and AE leading to premature investigation IMD discontinuation.
- Number and percentage of patients experiencing at least one AE, as well as the number of AEs, by SOC and Preferred Term (PT). The summaries will be performed for AEs leading to premature IMD discontinuation.
- Number and percentage of patients with AEs, by SOC, PT and severity.

• Number and percentage of patients with AEs, by SOC, PT and relationship to IMD.

Documented list of individual data concerning TEAEs will be performed.

[redacted]

7.3 ANALYTICAL PROCEDURES

Quantitative variables (Continuous data) will be summarised in summary tables indicating the number of non-missing/missing observations (n), mean, SD, median, first quartile (Q1), third quartile (Q3), minimum and maximum, and 95% Confidence Interval (CI) of the mean/median.

Qualitative variables (Categorical data) will be summarised in summary tables indicating the number of non-missing/missing observations (n), count and percentage of each modality, and 95% CI.

[redacted]

7.5 SAMPLE SIZE CALCULATION AND JUSTIFICATION

The sample size is driven by the statistical hypothesis on the primary objective: to demonstrate the non-inferiority of T2769 compared to Hylo-Forte® in terms of the change from baseline (D1) in total ocular surface staining score assessed on Oxford 0-15 scale, in the study eye at the D36 visit.

[redacted]

7.6 RATIONALE FOR THE NUMBER OF PROCEDURES TO BE PERFORMED BY A SINGLE USER AS PART OF THE LEARNING CURVE AND HOW THESE DATA ARE TO BE ANALYSED

[redacted]

7.8 INTERIM ANALYSIS, CRITERIA FOR THE TERMINATION OF THE CLINICAL INVESTIGATION ON STATISTICAL GROUNDS

NA.

7.9 MANAGEMENT OF BIAS AND, WHEN RANDOMISATION, MATCHING OR BLINDING ARE APPLIED, PLAN FOR ASSESSMENT OF SUCCESS THEREOF.

The use of randomisation attempts to mitigate accidental bias (such as selection bias), promoting comparability of the study groups and serves as a basis for statistical inference for quantitative evaluation of the treatment effect.

Masking will be achieved by providing each product unit with identical cardboard box and by identifying it by an IMD kit number.

7.10 MANAGEMENT OF POTENTIAL CONFOUNDING FACTORS

Baseline value will be included in all MMRM models (if applicable) as covariate.

Other covariates will be explored and detailed in the SAP.

[redacted]

7.12 SPECIFICATION OF SUBGROUPS

NA.

[redacted]

7.15 PROCEDURES FOR REPORTING ANY DEVIATION(S) FROM THE ORIGINAL STATISTICAL PLAN

Any changes from the planned analyses will be described and justified in the SAP and the final CIR.

[redacted]

7.17 DEFINE A STRATEGY FOR POOLING DATA, IF APPLICABLE.

NA.

8 DATA MANAGEMENT

8.1 METHODS FOR DATA ENTRY AND COLLECTION

Each participating site will maintain appropriate medical and research records for this clinical investigation in compliance with GCP - ISO 14155:2020 sections 3.47, 3.48 and 7.8.1 and any other regulatory and institutional requirements for the protection of patient's confidentiality.

Data will be reported in an electronic data capture (EDC) system for collection of electronic Case Report Forms. CRO is responsible for the set-up and maintenance of the EDC. The EDC will be compliant with FDA 21 CFR Part 11 and EU Annex 11.

The eCRFs will be completed by the PI or delegates within the investigational sites. Entries in the eCRF shall be made complete, correct and in a timely manner.

8.2 PROCEDURES USED FOR DATA REVIEW, DATABASE CLEANING, AND ISSUING AND RESOLVING DATA QUERIES

Data Management activities will be performed by Laboratoires THÉA Data Manager and/or the CRO in charge of Data Management and will be defined in the Data Management Plan (DMP).

- Management of queries

The sponsor or representative will ensure that the reported data are consistent and complete.

Data clarifications requests, also called queries or edit checks, will be generated in the EDC by a data manager or the site's CRA.

The CRAs affected to the site can open queries for source data verification mismatch, deviation verification, safety clarifications, and when data inconsistencies are detected. The CRAs will follow and close the queries that they posted.

The Data management department will create queries based on the data validation plan as detailed in the DMP. The purpose of the clarifications will be, but not limited to, data completion request, data inconsistencies, verification of possible deviations, clarification requests on safety events. The Data management team will follow and close the queries that they posted.

The investigational sites will have to answer directly in the EDC by giving a comment and making the necessary corrections to the reported data until the query is considered as resolved by the query creator or affiliate.

No self-evident corrections will be made by the sponsor.

- Coding of events

Diagnosis for AEs and medical and surgical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA). Whodrug Anatomic Therapeutic Chemical (ATC) code will be used for previous and concomitant treatment coding. Versioning will be specified in the DMP.

- Management of external data
    - The clinical database and the IRT database will be periodically reconciled to ensure that the information reported in both databases are matching.
    - The results of the Tear level of inflammatory cytokines will be sent by the central laboratory to the data management department and included in the clinical database. The clinical and laboratory databases will be reconciled as detailed in the DMP.

The investigator will cooperate with Laboratoires THÉA and any person nominated by Laboratoires THÉA to monitor or supervise the conduct of the investigation.

The investigator and authorised delegate(s) will ensure that proper data for the clinical investigation are collected and accurately documented in the appropriate sections of eCRFs.

8.3 PROCEDURES FOR VERIFICATION, VALIDATION AND SECURING OF ELECTRONIC CLINICAL DATA SYSTEMS

Laboratoire Théa will verify that the EDC provider is able to demonstrate the validity and security of the electronic tools used during the study. If necessary, security tests will be performed.

The access to the electronic data systems will be individual and protected by a personalized password.

All data entry and modifications will be stored in an audit's trail indicating who performed the action and when.

8.4 PROCEDURES TO MAINTAIN AND PROTECT PATIENT PRIVACY

Laboratoires THÉA, as Sponsor of the clinical investigation, acting as data controller and is committed to protecting the privacy and security of personal data processed for the purposes of the clinical investigation under the conditions define below:

- **Compliance with the General Data Protection Regulation (GDPR) and other applicable law or regulation:**

Laboratoires THÉA is committed to comply with the Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (hereinafter the General Data Protection Regulation "GDPR") and any other applicable law or regulation related to the protection of personal data.

It is specified that for the clinical investigation, Laboratoires THÉA also comply with the applicable guidelines of the French supervisory authority ("Commission Nationale de l'Informatique et des Libertés" hereinafter the "CNIL") as defined in the deliberation n°2019-153 of 3 May 2019 of the CNIL, also called the "MR-001".

- **Data subjects information on the processing of their personal data**

The data subjects namely the patients and the investigator, including the personnel working with the investigator, are informed of the collection and processing of their personal data for the realisation of the clinical investigation.

In particular, the patients are informed by the investigator during the delivery of the Informed Consent Form (ICF) where all the mandatory information of Article 13 of the GDPR are provided.

- **Data subjects exercise of their rights on their data**

The data subjects, namely the patients and the investigator, including the personnel working with the investigator, have the right, under the conditions and within the limits provided by the regulations, to access, rectify, delete or determine guidelines as to the use of their personal data after their death, as well as the right to oppose or request the limitation of processing.

In addition, and according with article L1111-7 of the French Public Health Code, the patients can access to their personal data by asking to the investigator.

For all requests concerning the rights of the patients regarding their personal data, they are advised to contact the investigator who will in turn contact Laboratoires THÉA. Otherwise, Laboratoires THÉA named a Data Protection Officer who can be contacted by the patients.

The data patients, namely the patients and the investigator, including the personnel working with the investigator, have the right to bring a complaint with the supervisory authority, namely the CNIL in France and/or local equivalent of CNIL.

8.5 METHODS FOR DATABASE LOCKING AT THE START OF THE ANALYSIS AND STORAGE UPON COMPLETION OF THE CLINICAL INVESTIGATION

The database lock consists in the removal or changing of user access for database to prevent any further changes to the data. The database lock enables data collected to be used for formal analysis or submission to a regulatory authority. Database lock occurs following the conduct of the clinical investigation.

Database will be locked when all data will be entered and clean. Data Management CRO coordinates the activities around Database Lock, including completing the Database Lock Checklist, managing Database Lock Form, and ensuring archival activities are complete.

8.6 CONFIDENTIALITY

All information concerning the product as well as any matter concerning the operation of the Sponsor, such as clinical indications for the IMD, its formula, methods of manufacture and other scientific data relating to it, that have been provided by the Sponsor and are unpublished, are confidential and must remain the sole property of the Sponsor. The investigator will agree to use the information only for the purposes of carrying out this clinical investigation and for no other purpose unless prior written permission from the Sponsor is obtained.

Laboratoires THÉA has full ownership of the original e-CRFs completed as part of the clinical investigation.

8.7 DATA RETENTION PROCEDURES AND SPECIFIED RETENTION PRIOD

The investigator must retain the patient identification codes for at least 10 years after the last T2769 device has been placed on the market. Patient files and other source data must be kept for the maximum period of time permitted by the hospital, institution or private practice, but not less than 10 years after the last T2769 device has been placed on the market, to meet the Sponsor local regulatory requirements. The investigator must produce investigation documentation or supply copies thereof to Sponsor, its designee or to CAs upon request, while ensuring patient confidentiality at all times.

8.8 OTHER ASPECTS OF CLINICAL QUALITY ASSURANCE

8.8.1 Monitoring/Data Audits

Laboratoires THÉA/representatives of Laboratoires THÉA shall be permitted to audit any proposed investigational site prior to commencement and during the course of the clinical investigation to ensure that the investigational site is suitable and has the suitable facilities, staff and capacity for the conduct of the clinical investigation.

The e-CRFs should be available for review by the clinical monitor or auditor or national regulatory inspectors. The investigator is required to give access to all source documents and investigation data, all relevant documentation to the clinical investigation, site facilities and

materials/equipments used in the clinical investigation. Laboratoires THÉA and CROs will not require the investigator or any member of their staff to take any action or be a party to any action which is contrary to the laws of the country in which the clinical investigation is being carried out or to medical ethics.

8.8.2 On-site Audits/Regulatory Inspection

CAs, Independent Ethics Committees/ Institutional Review Boards (IECs/IRBs), and/or Laboratoires THÉA's Clinical Quality Assurance Group may carry out on-site audits and/or on-site audit inspections. Direct access to source data will be required for these inspections and audits; they will be carried out giving due consideration to data protection and medical confidentiality. The investigator assures the Sponsor of the necessary support at all times.

The clinical investigation may be subjected to auditing by representatives of the Sponsor and/or to inspection(s) by authorized representatives of local and/or foreign CAs. In case of an audit or inspection, the investigator will be informed in advance. The investigator must inform the Sponsor as soon as he/she receives the notification of inspection.

9 APPROVAL OF THE CLINICAL INVESTIGATION AND AMENDMENTS

Prior to starting the clinical investigation, the CIP and other relevant documents will be submitted and approved by the IEC/IRB and/or CAs, in accordance with regional/local regulatory requirements. The Sponsor must ensure that all ethical and legal requirements have been met before the first patient is enrolled in the clinical investigation.

Full compliance with this CIP must be sought. To alter the CIP, amendments must be written, approved by the appropriate personnel, and by IEC/IRB/CAs prior to implementation.

All amendments will be distributed to all CIP recipients, with appropriate instructions.

By signing the CIP, the investigator confirms that he/she agrees to perform the clinical investigation as outlined in the CIP.

The CIP is the binding document for the investigator, the Sponsor and its designee; modifications are only valid if agreed upon by the Sponsor and its designee. Modifications must be documented in a signed amended CIP.

The Sponsor will promptly report the following for review or information to the Ethics Committee(s) and the CA for:

- Substantial CIP modifications
- Administrative changes
- Deviations to the CIP implemented to eliminate immediate hazards to the trial patients
- New information that may affect adversely the safety of the patients or the conduct of the clinical investigation. The IEC and the CA must be informed and approve all CIP amendments, in accordance with local legal requirements before implementation. Amendments must be evaluated to determine whether formal approval must be sought and whether the informed consent document should also be revised.

The written signed approval of the CIP amendment must contain specific identification of the document (*e.g.*, the investigator's name and the CIP title and number).

10 DEVIATIONS FROM CIP

The investigator will conduct the clinical investigation in accordance with this CIP, all relevant local laws, regulations or guidelines and in accordance with the principles of GCP – ISO 14155 current version. The investigator should not initiate the clinical investigation before:

- The CIP is signed;
- Written approval from the appropriate IEC and Clinical Trial Authorization from CA are received;
- The site is initiated by Laboratoires THÉA or the CRO designated by Laboratoires THÉA.

During the clinical investigation, in case of important deviations observed in an investigational site, (such as deviations related to inclusion and/or exclusion criteria, deviations that may put a patient at risk), the Sponsor could decide to stop the enrolment in this site.

At the end of the clinical investigation, CIP deviations will be reviewed and classified as minor or major during a blind data review meeting that will be held before database lock. The exclusion of patients from the analysis sets (see details of analysis sets in section **0**) will be discussed during the blind data review meeting.

11 IMD ACCOUNTABILITY

11.1 DESCRIPTION OF THE PROCEDURES FOR THE ACCOUNTABILITY OF IMD

Patients will return used and unused IMDs to the site at D15 and D36 visits.

The unmasked collaborator or pharmacist counts the number of IMDs remaining in the returned pack, completes and validates the "Treatment Tracking Form" (used, not used, not returned IMD) and the Drug Accountability Module and Return Form in IWRS (if applicable).

The masked investigator will remain masked to the IMD. He/she will not retrieve the product from any patient. IMD returned by patient will have to be stored in a different place from the ones that have not yet been dispensed.

All IMDs will be retained for inspection by the study monitor. The monitor will, upon completion of drug count and validation of the return section of the "Treatment Tracking Form", collect used/unused/broken containers of the supplied investigational products and these will be returned as instructed by Laboratoires THÉA.

11.2 PROCEDURES AND PARTICULAR MATERIALS AND INSTRUCTIONS FOR THE SAFE RETURN OF IMD, INCLUDING THOSE THAT ARE POTENTIALLY HAZARDOUS

The IMD used and unused will be returned to the depot in France for destruction.

This return will be prepared by the site team with the help of monitor. The return request will be sent to the packaging/labelling CRO. At receipt, the packaging/labelling CRO has to confirm the Good Receipt to the site team and monitor.

All details regarding return of used and unused IMD will be recorded in the Drug accountability return module in IRT (if applicable).

The return will be stored in the depot in waiting the authorization of destruction by the Sponsor.

12 STATEMENTS OF COMPLIANCE

This clinical investigation will be conducted in accordance with the ethical principles of the Declaration of Helsinki of October 2013, with GCP as described in the International Standards ISO 14155 current version and with the local regulations.

Prior to commencement of the clinical investigation, the Sponsor or his legal representative in the community must submit a valid application, with the same version of the documentation, to the IEC and the CA (see Section **9**).

Before the clinical investigation starts, the clinical monitor must ensure that all relevant documents are available and that IEC/IRB/CAs authorisation(s) and approval(s) have been obtained. Only then, arrangements for shipment of the clinical supplies can be made and recruitment can begin.

The Sponsor or his legal representative will report any amendments (see Section **9**) and safety-related events (see Sections **14.5** and **14.6**) according to the local regulations.

The Sponsor will notify each IEC/IRB/CAs concerned of the end of a clinical investigation in all countries in which the clinical investigation has been conducted. That notification will be made within 15 days from the end of the clinical investigation in the last country in which the clinical investigation has been conducted/in accordance with the local regulations.

If the clinical investigation has terminated prematurely, the reason for the termination must be given (see Section **16**).

When a temporarily halted clinical investigation is resumed the Sponsor will inform all involved investigators and must notify IEC/IRB/CA concerned through the EU portal and/or another way within 15 days from the restart of the temporarily halted clinical investigation in all country concerned.

The Sponsor will take out reasonable third-party liability insurance cover in accordance with all local legal requirements. The civil liability of the investigator, the persons instructed by him/her and the hospital, practice or institute in which they are employed and the liability of the Sponsor with respect to financial loss due to personal injury and other damage that may arise as a result of the carrying out of this clinical investigation are governed by the applicable law.

The Sponsor will arrange for patients participating in this clinical investigation to be insured against financial loss due to personal injury caused by the products being tested or by medical steps taken in the course of the clinical investigation.

When required, a hospital specific indemnity agreement and/or an investigator specific agreement will be used.

13 INFORMED CONSENT PROCESS

In obtaining and documenting informed consent, the investigator must comply with the applicable regulatory requirement(s) and adhere to the International Standards ISO 14155 on GCP for medical devices and the requirements in the Declaration of Helsinki – October 2013.

Prior to any investigation-related activity or any discontinuation of current medication, the investigator must give the patient oral and written information about the aims, methods, anticipated benefits, potential risks and inconveniences of the clinical investigation. The measures taken to safeguard the patient's privacy and the protection of personnel data should also be described in the informed consent. The patients must be informed about their right to

abstain from participating in the clinical investigation and to withdraw their consent at any time without affecting their medical care.

Before informed consent may be obtained, the investigator should provide the patient ample time and opportunity to inquire about details of the clinical investigation and to decide whether or not to participate in the clinical investigation. All questions about the clinical investigation should be answered to the satisfaction of the patient. The patient must be given the opportunity to ask questions and have reasonable time for reflection before giving his/her informed consent.

Written informed consent must be obtained prior to initiation of any investigational procedures or any discontinuation of current medication. No measures whatsoever described in the CIP shall be undertaken without such consent indicating that the patient has been given both verbal and written information about the investigation and the IMD.

If the patient is illiterate, oral information regarding the investigation will be provided to the patient using the ICF. A witness will be present during the entire informed consent discussion. The witness will personally sign and date the ICF to confirm that the information was accurately explained to the patient, and apparently understood, and that consent was freely given.

The ICF is signed and personally dated by the patient or by a patient's legally acceptable representative and by the investigator designee responsible for obtaining the ICF (as per ISO14155 and local regulations).

Once signed, the original ICF is filed in the Investigator Site Binder and a copy is provided to the patient (according to the local regulations).

As soon as the patient has signed the Informed Consent, he/she will receive a patient number.

The information/consent form may be revised during the clinical investigation whenever important new information becomes available. The amended ICF will be submitted for approval to the IEC and/or CAs as appropriate (see Section **9**). Once approved, informed consent of the already enrolled patients will be documented as described above i.e., in the same way as the initial informed consent.

14 ADVERSE EVENTS, AND INCIDENTS

14.1 DEFINITION OF ADVERSE EVENT (AE)

Adverse Event (AE): Any untoward medical occurrence, unintended disease or injury or untoward clinical signs (including abnormal laboratory finding) in subjects, users or other persons whether or not related to the IMD.

NOTE:

- This definition includes events related to the IMD or the comparator
- This definition includes events related to the procedures involved
- For users or other persons, this definition is restricted to events related to the use of the IMD or comparator.

NOTE:

- Adverse event is an incident.

.**Treatment-Emergent AE (TEAE)**: AE that occurs or that worsens in severity after at least one dose of IMD has been administered/applied.

14.2 DEFINITION OF INCIDENT/FIELD SAFETY CORRECTIVE ACTION

Incident: any malfunction or deterioration in the characteristics or performance of a device made available on the market, including use-error due to ergonomic features, as well as any inadequacy in the information supplied by the manufacturer and any undesirable side-effect.

Field safety corrective action: corrective action taken by a manufacturer for technical or medical reasons to prevent or reduce the risk of a serious incident in relation to a device made available on the market.

14.3 DEFINITION OF A SERIOUS INCIDENT

Serious incident: any incident that directly or indirectly led, might have led or might lead to any of the following:

- the death of a patient, user or other person,
- the temporary or permanent serious deterioration of a patient's, user's or other person's state of health,
- a serious public health threat: an event which could result in imminent risk of death, serious deterioration in a person's state of health, or serious illness, that may require prompt remedial action, and that may cause significant morbidity or mortality in humans, or that is unusual or unexpected for the given place and time.

14.4 DEFINITION OF A SERIOUS ADVERSE EVENT (SAE)

A **Serious Adverse Event (SAE)** is an AE that:

- Led to death
- Led to serious deterioration in the health of the subject, that either resulted in
  - ✓ A life-threatening illness or injury, or
  - ✓ A permanent impairment of a body structure or a body function, or
  - ✓ In-patient or prolonged hospitalization, or
  - ✓ Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function or
  - ✓ Chronic disease
- Led to foetal distress, foetal death or a congenital abnormality or birth defect.

NOTE: Planned hospitalization for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered a SAE.

14.4.1 Definition of the Severity of an Adverse Event

The intensity of each AE must be assessed by the investigator using one of the following categories, and recorded in the e-CRF and incident form [redacted]

1 = MILD: Event results in mild or transient discomfort, not requiring intervention or treatment and does not interfere with the patient daily activities;

2 = MODERATE: Event results in sufficient discomfort, may require an additional treatment, but does not interfere with the patient's daily activities;

3 = SEVERE: Event results in significant symptoms, may require an additional treatment, or a modification of this treatment (or hospitalisation) and may interfere with the patient's daily activities.

Caution: The term "severe" is used to describe the intensity (severity) of the event. This means it is not the same as "serious" used to describe the seriousness of SAE which is based on patient event outcome or action criteria usually associated with events that pose a threat to a patient's life or functioning (see Section **14.4** for having the definition of a SAE).

14.4.2 Causality Relatedness to the IMD

The investigator will assess the causality/relationship between the IMD and the AE and record that assessment in the e-CRF and incident form based on the following definitions (only one answer possible):

Each AE will be classified according to four different levels of causality:

1. Not related
2. Possible
3. Probable
4. Causal relationship

The sponsor and the investigators will use the following definitions to assess the relationship of the adverse event to the investigational device or the investigation procedures.

1. Not related: Relationship to the device or procedures can be excluded when:

- the event has no temporal relationship with the use of the device or investigation procedures;
- the adverse event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible;
- the discontinuation of medical device application or the reduction of the level of activation/exposure - when clinically feasible - and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the adverse event;
- the event involves a body-site or an organ that cannot be affected by the device or procedures;
- the adverse event can be attributed to another cause (e.g. an underlying or concurrent illness/ clinical condition, an effect of another device, drug, treatment or other risk factors);

In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the adverse event.

2. Possible: The relationship with the use of the investigational device or the relationship with procedures, is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases where relatedness cannot be assessed, or no information has been obtained should also be classified as possible.

3. Probable: The relationship with the use of the investigational device or the relationship with procedures, seems relevant and/or the event cannot be reasonably explained by another cause.

4. Causal relationship: the adverse event is associated with the investigational device or with procedures beyond reasonable doubt when:

- the event is a known side effect of the product category the device belongs to or of similar devices and procedures;
- the event has a temporal relationship with investigational device use/application or procedures;
- the event involves a body-site or organ that
  - the investigational device or procedures are applied to;
  - the investigational device or procedures have an effect on;
- the adverse event follows a known response pattern to the medical device (if the response pattern is previously known);
- the discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the adverse event (when clinically feasible);
- other possible causes (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out;
- harm to the subject is due to error in use;

In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the adverse event.

The sponsor and the investigators will distinguish between the adverse events related to the investigational device and those related to the procedures (any procedure specific to the clinical investigation). An adverse event can be related both to procedures and the investigational device.

Complications caused by concomitant treatments, not imposed by the clinical investigation plan, are considered not related. If routine procedures are not imposed by the clinical investigation plan, complications caused by them are also considered not related.

In some particular cases the event may not be adequately assessed because information is insufficient or contradictory and/or the data cannot be verified or supplemented. The sponsor and the investigators will make the maximum effort to define and categorize the event and avoid these situations. Where an investigator assessment is not available and/or the sponsor remains uncertain about classifying the adverse event, the sponsor should not exclude the relatedness; the event should be classified as “possible” and the reporting is not delayed.

Particular attention shall be given to the causality evaluation of unanticipated serious adverse events. The occurrence of unanticipated events related could suggest that the clinical investigation places subjects at increased risk of harm than was to be expected beforehand.

14.5 RECORDING AES

AEs recording and reporting will extend from signing of informed consent until the final visit. If the investigator is aware of an AE occurring within one month after final investigation visit and that he/she considers there is a causal relationship with the IMD, the AE should be recorded in the e-CRF. An incident form must also be recorded by the unmasked collaborator.

The investigator shall:

a) Record all AEs, regardless of the relationship to IMD and seriousness, in the e-CRF together with an assessment. For each AE, a corresponding incident form must also be recorded by the masked collaborator.

b) Supply the Sponsor, upon Sponsor's request, with any additional information related to the safety reporting of a particular event.

All AE reports should contain: a brief description of the event (diagnosis, localisation …), date and time of onset (if needed), duration (hours or days), intensity of symptoms (severity), treatment required, relationship with IMD and CIP procedure, action taken with the IMD, outcome, date and time of resolution and whether the event is classified as serious.

If there is a worsening of a medical condition that was present before starting the clinical investigation, this should be considered as a new AE and a complete evaluation should be recorded.

14.6 REPORTING OF INCIDENT

Reporting by the investigator to the sponsor

If the investigator or masked collaborator observe any incident, the unmasked collaborator must report to Laboratoires THÉA **within 24 hours of being aware of it using the incident form** by email to [redacted]

If the incident is an AE, the investigator or authorised delegated person must also complete the e-CFR page.

Laboratoires THÉA must:

- review all incidents, determine and document in writing whether they meet serious incident criteria for reporting to competent authorities; in case of disagreement between the Sponsor and the PI(s), the Sponsor shall communicate both opinions to concerned parties.

- report to regulatory authorities/IEC/investigators, within the required time period, **any serious incident.**

Once made aware of any serious incident, Laboratoires THÉA will take the appropriate decision to maintain the security/safety of patients by considering field safety corrective action. Any field safety corrective action taken by Laboratoires THEA will be reported to competent authorities.

Reporting by Laboratoires THEA to Competent Authorities/Ethics Committees

Laboratoires THEA must report to the National CAs where the clinical investigation has commenced:

- in the context of vigilance
    - a serious incident, that has a causal relationship or that the causal relationship is reasonable possible with the investigational device; or a field safety corrective action, must be reported not later than 15 days
        - notwithstanding related to a serious public health threat must be reported immediately or not later than 2 days

  - notwithstanding related to death or an unanticipated serious deterioration in the person state of health must be reported immediately or not later than 10 days.
- in the context of clinical investigation
  - a SAE/device deficiency that might have led to a SAE that has a causal relationship with the investigational procedure: which indicates an imminent risk of death, serious injury or serious illness and that requires action for other patients, users or other persons or a new finding to it: must be reported immediately, but not later than 2 calendar days after.
  - any other SAE/device deficiency that might have led to a SAE that has a causal relationship with the investigational procedure: must be reported immediately, but not later than 7 calendar days following the date of awareness by the sponsor of the new reportable event or of new information in relation with an already reported event.

14.7 FOLLOW-UP OF PATIENT AFTER AE

The investigator is responsible for ensuring the follow-up of any patient who experiences an AE during the clinical investigation.

All AEs experienced by a patient, irrespective of the suspected causality, will be monitored until the event has resolved, any abnormal laboratory values have returned to baseline or stabilised at a level acceptable to the investigator and Medical Expert, until there is a satisfactory explanation for the changes observed.

In case of SAE, the investigator or an appropriate qualified physician must re-examine the patient at regular intervals until the event has resolved or stabilised at a level acceptable to the investigator and Medical Expert and/or until completion of the “Last Patient Last Visit”.

Further follow up information will be reported to Laboratoires THÉA.

14.8 MANAGEMENT OF PREGNANCY

In case of the investigator or an appropriate qualified physician is informed that a patient becomes pregnant while taking IMDs, she will be immediately withdrawn from the clinical investigation and she will be followed until the outcome of the birth is available.

A communication will be sent by the investigator to Laboratoires THÉA as soon as he/she has knowledge of the normal outcome. Conversely, if the outcome of the pregnancy meets the criteria of SAE (*e.g* spontaneous or therapeutic abortion, stillbirth, neonatal death, congenital abnormality, birth defect), the investigator should follow the procedure for reporting of AE/incident.

Handling of a pregnancy occurring throughout the investigation follows the same reporting procedure as per an AE/incident notification.

Upon medically confirmed pregnancy during the clinical investigation the investigator must:

- Report immediately (**maximum 24 hours**) the pregnancy status to Laboratoires THÉA by sending the incident form to [redacted] The investigator must also complete the corresponding AE e-CRF page.
- Discontinue the IMD
- Perform / ensure assessment until delivery of a thorough investigation of the fetus

- Remain responsible for any medical advice he/she might sought thus making appropriate decision upon pregnancy
- Report to Laboratoires THÉA Follow-Up data / update(s) using the incident form.

14.9 LIST OF FORESEEABLE AES TOGETHER WITH THEIR LIKELY INCIDENCE, MITIGATION OR TREATMENT

According to the IMD leaflets, the following side effects are known: rare possibility of mild eye irritation and ocular redness.

When you use eye drops, you might experience disturbing symptoms such as burning sensation, stinging sensation, foreign body sensation in the eye and blurred vision for a short time.

14.10 LIST OF NON-REPORTABLE ADVERSE EVENTS

NA.

14.11 INFORMATION REGARDING THE IDMC

NA.

15 VULNERABLE POPULATION

This clinical investigation will not be conducted in children, or in any other vulnerable populations.

If the patient is not capable of giving consent, the written consent of the patient’s legal representative will be required before participation in the clinical investigation (see section **13**).

16 SUSPENSION OR PREMATURE TERMINATION OF THE CLINICAL INVESTIGATION

16.1 TEMPORARY HALT OF THE CLINICAL INVESTIGATION

The Sponsor may suspend the clinical investigation for any safety, ethical or administrative reason at any time. The investigator, IEC or CA may suspend or prematurely terminate participation at the investigational sites for which they are responsible.

As required by the Clinical Trials legislation, in the case of temporary halt of the clinical investigation:

- The Sponsor shall notify each country in which that clinical investigation has been temporarily halted within 15 days from the temporary halt of the clinical investigation with a justification.
- For safety concerns, the Sponsor shall notify all the country(ies) in which that clinical investigation is being conducted thereof within 24 hours.
- For an exceptional circumstance (e.g. COVID-19 pandemic), the Sponsor will follow the CAs’ recommendations.

In case of restart after temporarily halted study, a notification will be made to the CA. In case of temporarily halt on safety grounds, this notification should be submitted as a substantial modification.

The communication of the relevant information should take place via the respective national procedures applicable to clinical investigations (until EU portal is fully functional).

16.2 EARLY TERMINATION OF THE CLINICAL INVESTIGATION

The Sponsor or the investigator has the right to terminate the clinical investigation for any safety, ethical or administrative reason at any time. As far as possible, this should occur after mutual consultation.

As required by the Clinical Trials legislation, in the case of early termination of the clinical investigation:

- The Sponsor shall notify each country in which that clinical investigation has been temporarily halted within 15 days from the temporary halt of the clinical investigation with a justification.
- For safety concerns, the Sponsor shall notify all the country(ies) in which that clinical investigation is being conducted thereof within 24 hours.

The communication of the relevant information should take place via the respective national procedures applicable to clinical investigations (until EU portal is fully functional).

The investigator, IEC or CA may prematurely terminate participation at the investigational sites for which they are responsible.

Should the clinical investigation be terminated prematurely, all investigational materials (IMDs, completed, partially completed, etc.) must be returned to the Sponsor or the Sponsor's representative as if the clinical investigation had been completed.

Laboratoires THÉA shall have the right to terminate the clinical investigation at any time on written notice to the investigator. Without in any way limiting this right, Laboratoires THÉA would normally only terminate the clinical investigation in the following circumstances:

- Occurrence of
  - new events related to the conduct of an investigation or the development of an IMD likely to affect the safety of patients, such as:
    - a SAE which could be associated with the investigation procedures and which could modify the conduct of the clinical investigation,
    - a significant hazard to the patient population such as lack of performance of an IMD used for the treatment of a life-threatening disease,
    - a major safety finding from a newly completed animal study/investigation (such as carcinogenicity),
  - a temporary halt of an investigation for safety reasons if the clinical investigation is conducted with the same IMDs in another country by the same Sponsor.
- If severe and/or serious AEs with the IMD in human or animal studies should indicate discontinuation of the clinical investigation.
- If Laboratoires THÉA should wish to discontinue the clinical investigation for commercial reasons.
- If Laboratoires THÉA had reasons to believe that the clinical investigation could not be satisfactorily completed, including, but not limited to, the reason that inadequate numbers of patients could be enrolled or insufficient investigational sites found within the necessary time.

16.3 REQUIREMENTS FOR PATIENT FOLLOW-UP AND CONTINUED CARE

In the case of temporary halt or early termination of the clinical investigation, the requirements for patient follow-up will depend on the circumstance of the temporary halt or early termination:

- For reasons not affecting the benefit-risk balance, according to the Sponsor recommendations, the investigator could decide if the patient may continue the clinical investigation as planned or if the patient should be withdrawn from the clinical investigation.
- For reasons of a change of the benefit-risk balance, the patient should be withdrawn from the clinical investigation and the IMD must be discontinued.
- For an exceptional reason (e.g. COVID-19 pandemic), each investigator has to decide whether the patient continued the clinical investigation when able to follow the CIP requirements safely or to withdraw the patient from the clinical investigation, based on his/her assessment of the benefit/risk ratio regarding the COVID-19 pandemic situation in his/her country/region and own investigational site, in accordance with the national/regional recommendations.

This concerns all patients still on-going in the clinical investigation at the time of temporary halt or early termination.

If a patient is prematurely stopping the IMD or should prematurely withdraw from the clinical investigation, the investigator must perform at least one premature discontinuation visit followed by one/several follow-up visits as decided by the Sponsor and according to the circumstances.
If possible and depending the circumstance, the premature discontinuation visit will be realized on site and the follow-visit(s) could be performed by phone.
If it is not possible, the premature discontinuation visit will be performed by phone-call and/or online video consultation. In this case and if current circumstances are favorable, at least one of follow-up safety visit should be performed onsite.
During the premature discontinuation visit/phone-call, the investigator has to:

- Collect AE/incident,
- Check the IMD compliance,
- Check the number of returned used and unused IMD,
- Instruct the patient to stop or to continue the IMD (depending on the reason as described above),
- Ensure the continuity of investigational disease medication (if appropriate),
- Perform evaluations described for the premature investigation discontinuation/final visit if possible (onsite visit),
- Prescribe to the patient the best appropriate treatment if needed,
- Collect information on concomitant medications changes.

If some follow-up visit(s) are required or if the premature discontinuation visit could not be realized on site, the investigator will have to schedule these phone-calls/visits. During this/these visit(s), the investigator has to:

- Collect AE/incident,
- Collect information on concomitant medications changes,
- Check the IMD compliance, if applicable,
- Check the number of returned used and unused IMD, if applicable,
- Perform evaluations described for the premature investigation discontinuation/final visit if not done at the premature discontinuation visit,

- Prescribe to the patient the best appropriate treatment if needed.

In any case, the requirements for patient follow-up will be described in more details in specific guidelines which will be provided to each involved persons (investigators, Investigational team, Hospitals etc…) and to Institutions if necessary (IEC, CA etc...). This could be done by submitting a notification (in case of emergency) and/or a substantial modification.

17 PUBLICATION POLICY

By signing the CIP, the investigator agrees that the results of the clinical investigation may be used for the purposes of national and international registration, publication, and information for medical and pharmaceutical professionals. If necessary, the CAs will be notified of the investigator's name, address, qualifications, and extent of involvement.

The data resulting from this clinical investigation will be the proprietary information of Sponsor. An investigator shall not publish any data (poster, abstract, paper, *etc.*) without having consulted with Laboratoires THÉA in advance.

At the end of the clinical investigation, Laboratoires THÉA will prepare a Clinical Investigation Report.

For any manuscript for publication prepared by Laboratoires THÉA, Laboratoires THÉA reserves the right to select the investigators who will be the authors to review the manuscript. Laboratoires THÉA will allow the selected investigators sufficient time for full review of the manuscript before publication.

18 BIBLIOGRAPHY

Aragona, Pasquale; Simmons, Peter A.; Wang, Hongpeng; Wang, Tao (2019) Physicochemical Properties of Hyaluronic Acid-Based Lubricant Eye Drops. In : Translational vision science & technology, vol. 8, n° 6, p. 2. DOI: 10.1167/tvst.8.6.2.

Baudouin, Christophe; Aragona, Pasquale; Messmer, Elisabeth M.; Tomlinson, Alan; Calonge, Margarita; Boboridis, Kostas G. et al. (2013) Role of hyperosmolarity in the pathogenesis and management of dry eye disease: proceedings of the OCEAN group meeting. In : The ocular surface, vol. 11, n° 4, p. 246–258. DOI: 10.1016/j.jtos.2013.07.003.

Baudouin, Christophe; Figueiredo, Francisco C.; Messmer, Elisabeth M.; Ismail, Dahlia; Amrane, Mourad; Garrigue, Jean-Sébastien et al. (2017) A randomized study of the efficacy and safety of 0.1% cyclosporine A cationic emulsion in treatment of moderate to severe dry eye. In : European journal of ophthalmology, vol. 27, n° 5, p. 520–530. DOI: 10.5301/ejo.5000952.

Begley, Carolyn; Caffery, Barbara; Chalmers, Robin; Situ, Ping; Simpson, Trefford; Nelson, J. Daniel (2019) Review and analysis of grading scales for ocular surface staining. In : The ocular surface, vol. 17, n° 2, p. 208–220. DOI: 10.1016/j.jtos.2019.01.004.

Chiambaretta, Frédéric; Doan, Serge; Labetoulle, Marc; Rocher, Nicolas; Fekih, Lamia El; Messaoud, Riadh et al. (2017) A randomized, controlled study of the efficacy and safety of a new eyedrop formulation for moderate to severe dry eye syndrome. In : European journal of ophthalmology, vol. 27, n° 1, p. 1–9. DOI: 10.5301/ejo.5000836.

Craig, Jennifer P.; Nichols, Kelly K.; Akpek, Esen K.; Caffery, Barbara; Dua, Harminder S.; Joo, Choun-Ki et al. (2017) TFOS DEWS II Definition and Classification Report. In : The ocular surface, vol. 15, n° 3, p. 276–283. DOI: 10.1016/j.jtos.2017.05.008.

Fariselli, Chiara; Giannaccare, Giuseppe; Fresina, Michela; Versura, Piera (2018) Trehalose/hyaluronate eyedrop effects on ocular surface inflammatory markers and mucin expression in dry eye patients. In : Clinical ophthalmology (Auckland, N.Z.), vol. 12, p. 1293–1300. DOI: 10.2147/OPTH.S174290.

Holland, Edward J.; Darvish, Mahshad; Nichols, Kelly K.; Jones, Lyndon; Karpecki, Paul M. (2019) Efficacy of topical ophthalmic drugs in the treatment of dry eye disease: A systematic literature review. In : The ocular surface, vol. 17, n° 3, p. 412–423. DOI: 10.1016/j.jtos.2019.02.012.

Jones, Lyndon; Downie, Laura E.; Korb, Donald; Benitez-Del-Castillo, Jose M.; Dana, Reza; Deng, Sophie X. et al. (2017) TFOS DEWS II Management and Therapy Report. In : The ocular surface, vol. 15, n° 3, p. 575–628. DOI: 10.1016/j.jtos.2017.05.006.

Labetoulle, Marc; Schmickler, Stefanie; Galarreta, David; Böhringer, Daniel; Ogundele, Abayomi; Guillon, Michel; Baudouin, Christophe (2018) Efficacy and safety of dual-polymer hydroxypropyl guar- and hyaluronic acid-containing lubricant eyedrops for the management of dry-eye disease: a randomized double-masked clinical study. In : Clinical ophthalmology (Auckland, N.Z.), vol. 12, p. 2499–2508. DOI: 10.2147/OPTH.S177176.

Mateo Orobia, A. J.; Casas Pascual, P.; Perez Pascual, P.; Cristobal Bescos, J. A.; Perez Garcia, D.; Peiro Embid, C. et al. (2017) Effects of 3% trehalose as an adjuvant treatment after lasik. In : Clinical ophthalmology (Auckland, N.Z.), vol. 11, p. 347–353. DOI: 10.2147/opth.s125203.

Nasser, Linda; Rozycka, Malgorzata; Gomez Rendon, Gabriela; Navas, Alejandro (2018) Real-life results of switching from preserved to preservative-free artificial tears containing

hyaluronate in patients with dry eye disease. In : Clinical ophthalmology (Auckland, N.Z.), vol. 12, p. 1519–1525. DOI: 10.2147/OPTH.S160053.

Pinto-Bonilla, Juan Carlos; Del Olmo-Jimeno, Alberto; Llovet-Osuna, Fernando; Hernández-Galilea, Emiliano (2015) A randomized crossover study comparing trehalose/hyaluronate eyedrops and standard treatment: patient satisfaction in the treatment of dry eye syndrome. In : Therapeutics and clinical risk management, vol. 11, p. 595–603. DOI: 10.2147/TCRM.S77091.

Pucker, Andrew D.; Ng, Sueko M.; Nichols, Jason J. (2016) Over the counter (OTC) artificial tear drops for dry eye syndrome. In : The Cochrane database of systematic reviews, vol. 2, CD009729. DOI: 10.1002/14651858.CD009729.pub2.

Schmidl, Doreen; Schmetterer, Leopold; Witkowska, Katarzyna J.; Unterhuber, Angelika; dos Santos, Valentin Aranha; Kaya, Semira et al. (2015) Tear film thickness after treatment with artificial tears in patients with moderate dry eye disease. In : Cornea, vol. 34, n° 4, p. 421–426. DOI: 10.1097/ICO.0000000000000358.

Stapleton, Fiona; Alves, Monica; Bunya, Vatinee Y.; Jalbert, Isabelle; Lekhanont, Kaevalin; Malet, Florence et al. (2017) TFOS DEWS II Epidemiology Report. In : The ocular surface, vol. 15, n° 3, p. 334–365. DOI: 10.1016/j.jtos.2017.05.003.

Lam H, Bleiden L, de Paiva CS, Farley W, Stern ME, Pflugfelder SC. Tear cytokine profiles in dysfunctional tear syndrome. Am J Ophthalmol. 2009 Feb;147(2):198-205.

Novack et al., 2017; Wolffsohn et al., 2017; Begley et al., 2019; Nichols et al., 2021; Begley et al., 2022

Wolffsohn JS, Arita R, Chalmers R, Djalilian A, Dogru M, Dumbleton K, Gupta PK, Karpecki P, Lazreg S, Pult H, Sullivan BD, Tomlinson A, Tong L, Villani E, Yoon KC, Jones L, Craig JP. TFOS DEWS II Diagnostic Methodology report. Ocul Surf. 2017 Jul;15(3):539-574.

Nichols KK, Evans DG, Karpecki PM. A Comprehensive Review of the Clinical Trials Conducted for Dry Eye Disease and the Impact of the Vehicle Comparators in These Trials. Curr Eye Res. 2021 May;46(5):609-614.

Begley C, Caffery B, Chalmers R, Situ P, Simpson T, Nelson JD. Review and analysis of grading scales for ocular surface staining. Ocul Surf. 2019 Apr;17(2):208-220.

Begley CG, Caffery B, Nelson JD, Situ P. The effect of time on grading corneal fluorescein and conjunctival lissamine green staining. Ocul Surf. 2022 Jul;25:65-70.

Labetoulle M, Mortemousque B; CBL-101 Study Group. Performance and Safety of a Sodium Hyaluronate Tear Substitute with Polyethylene Glycol in Dry Eye Disease: A Multicenter, Investigator-Masked, Randomized, Noninferiority Trial. J Ocul Pharmacol Ther. 2022 Nov;38(9):607-616

Baudouin C, Cochener B, Pisella PJ, Girard B, Pouliquen P, Cooper H, Creuzot-Garcher C. Randomized, phase III study comparing osmoprotective carboxymethylcellulose with sodium hyaluronate in dry eye disease. Eur J Ophthalmol. 2012 Sep-Oct;22(5):751-61.

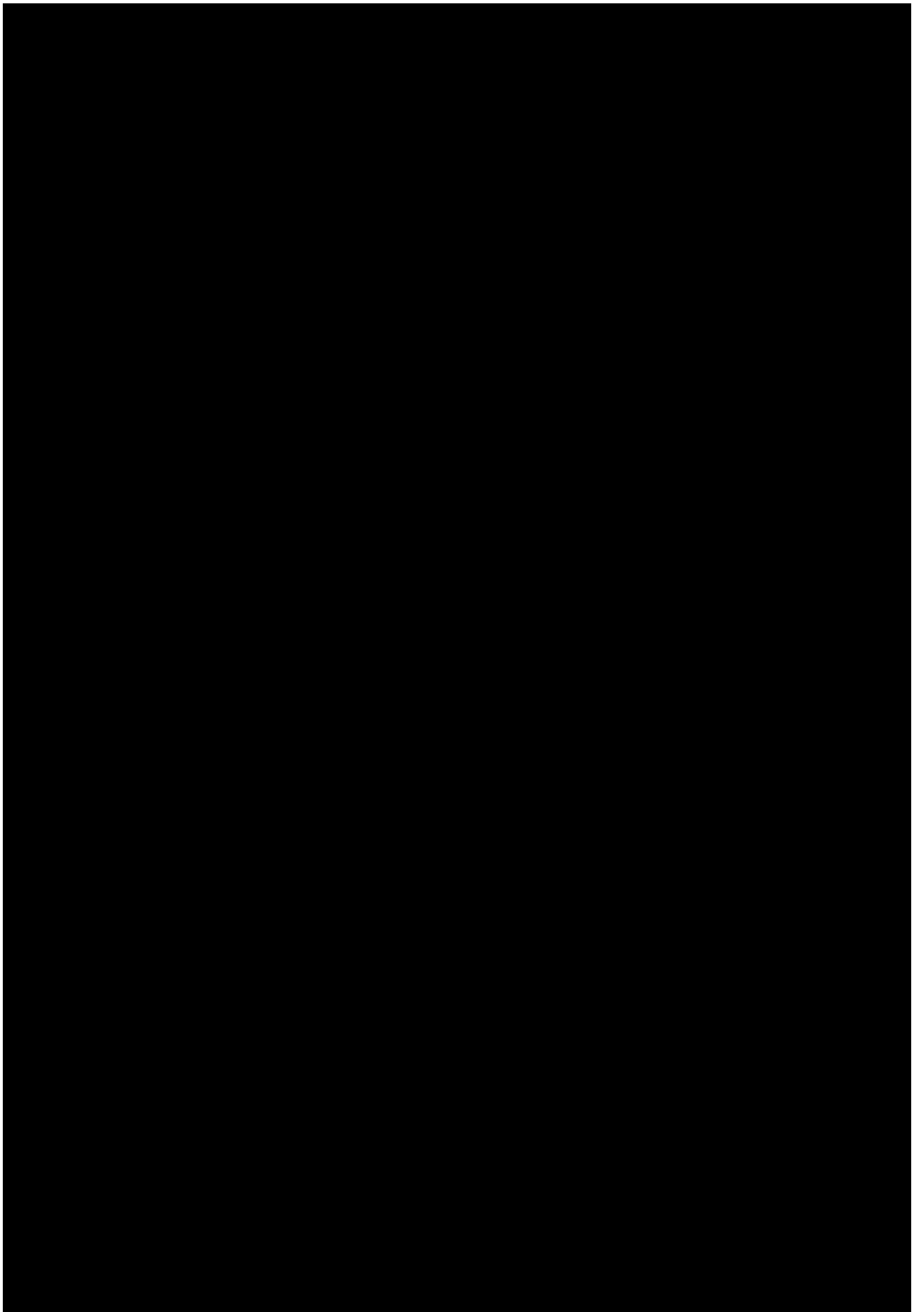
Schiffman RM, Christianson MD, Jacobsen G, Hirsch JD, Reis BL. Reliability and validity of the Ocular Surface Disease Index. Arch Ophthalmol. 2000 May;118(5):615-21. doi: 10.1001/archopht.118.5.615. PMID: 10815152.

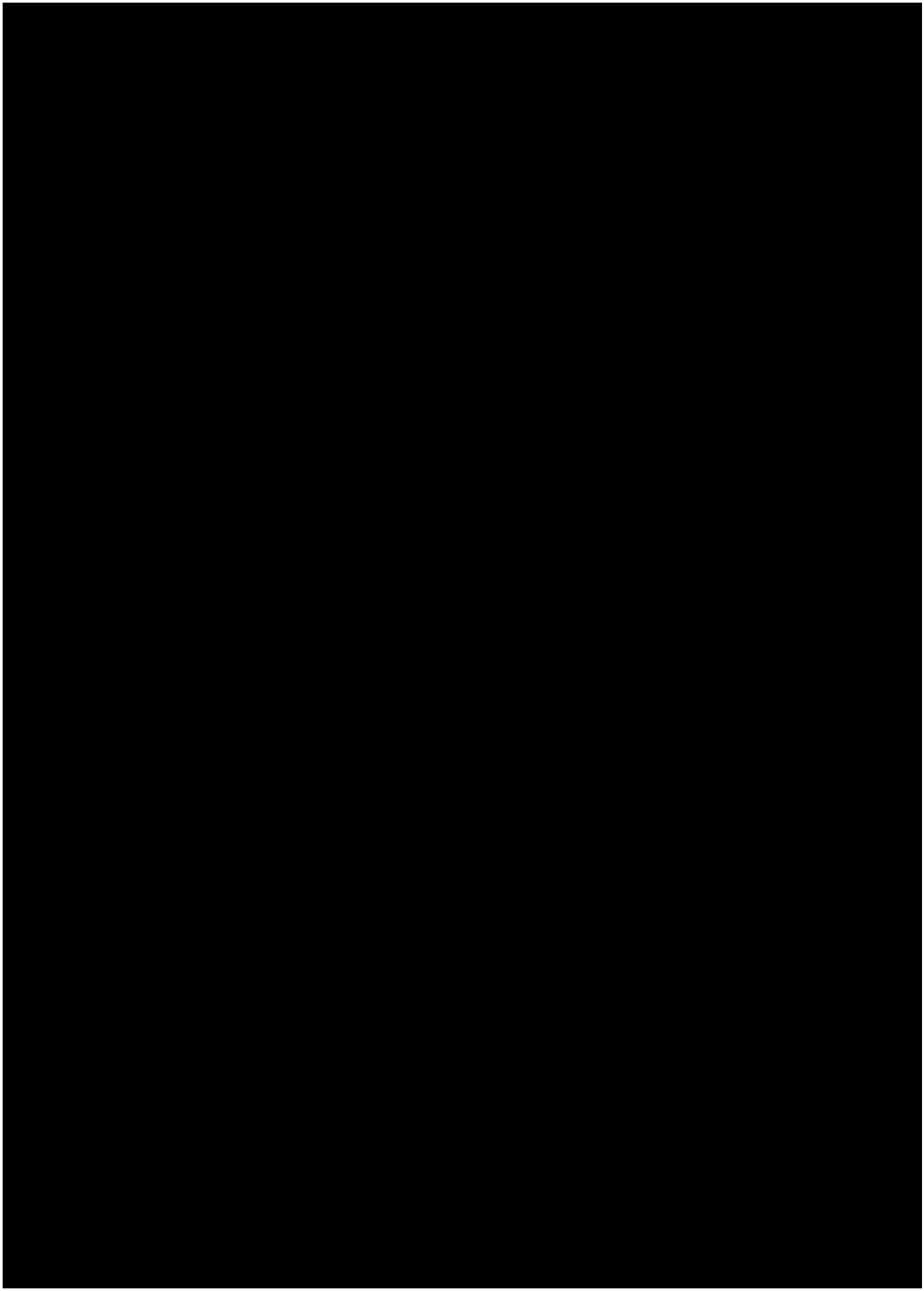
Kimberly L. Miller, PhD; John G. Walt, MBA; David R. Mink, MS; Sacha Satram-Hoang,PhD; Steven E. Wilson, MD; Henry D. Perry, MD; Penny A. Asbell, MD, MBA; Stephen C. Pflugfelder, MD. Minimal Clinically Important Difference for the Ocular Surface Disease Index. Arch Ophthalmol. 2010;128(1):94-101

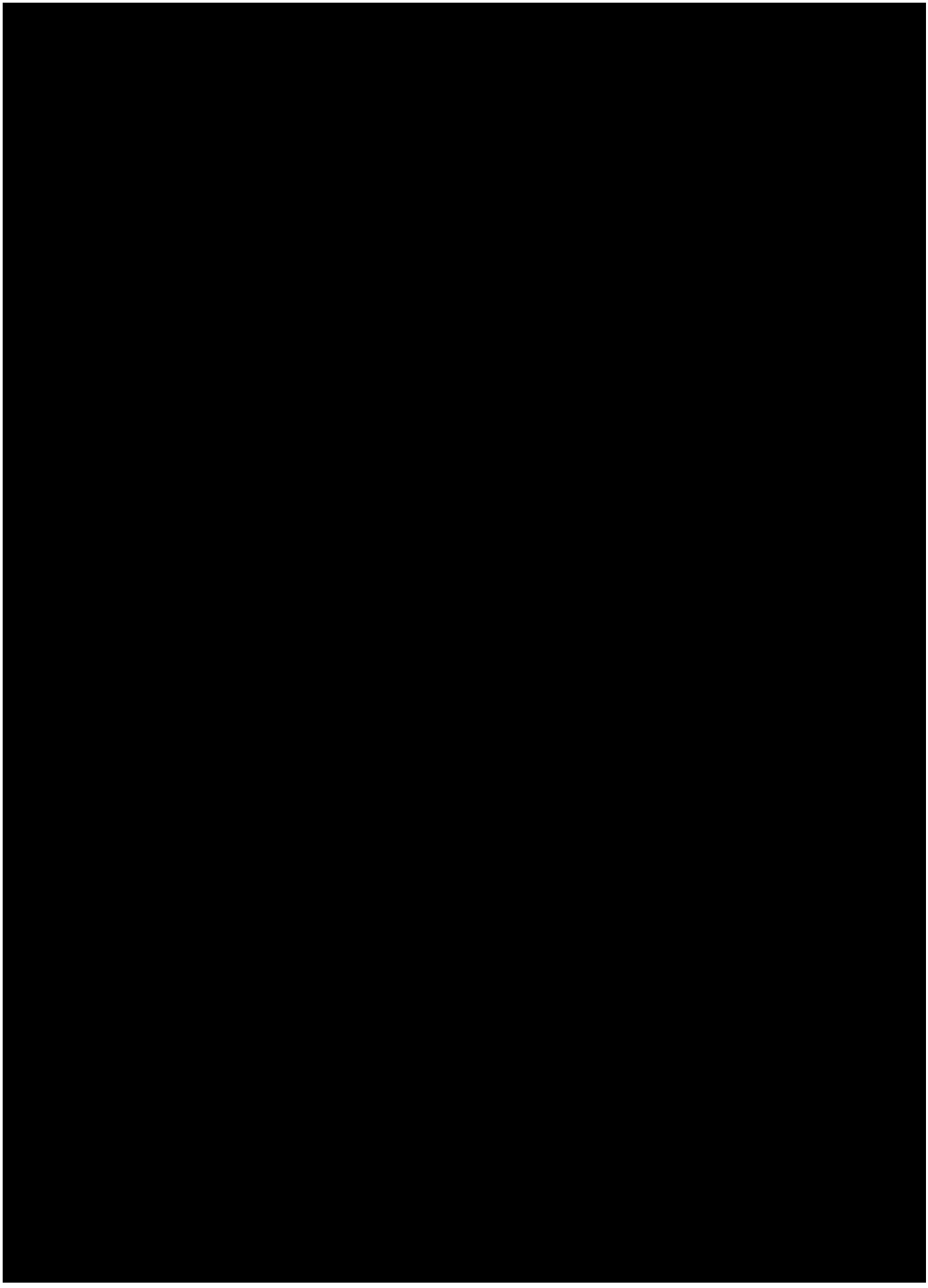
Thomas Kaercher, Elisabeth M Messmer, Thomas Berninger, Klaudia K Huber-van der Velden, Raphaela Geiger, Pauline Cipriano-Bonvin, Christina Jacobi. Topical Omega-3 Polyunsaturated Fatty Acids for the Treatment of Dry Eye – Results from a Pilot Randomized Controlled Masked-Observer Study. Clinical Ophthalmology 2022:16 4021–4031

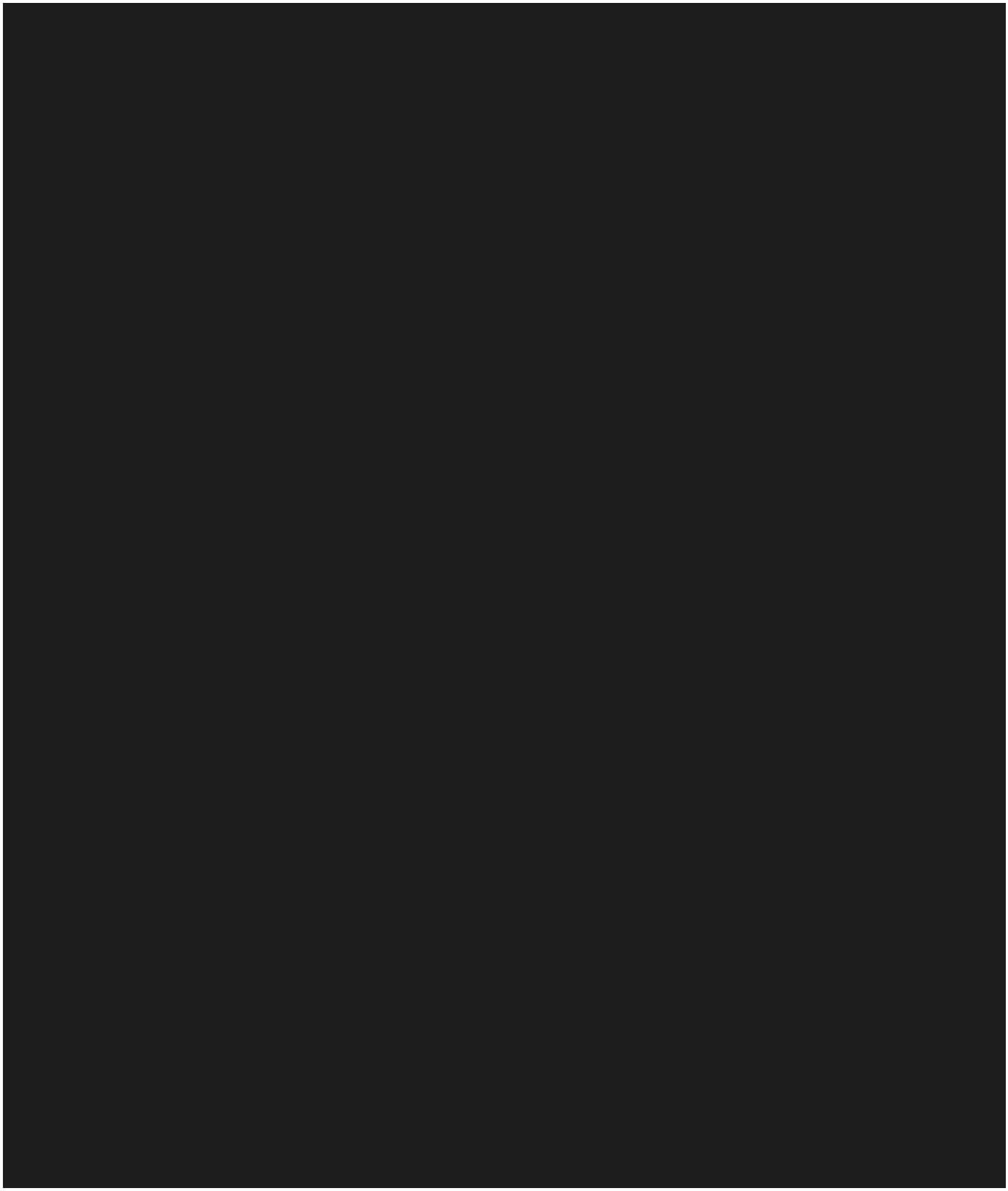
Duracinsky M, Gryparis A, Chassany O. Impact of Dry Eye on Daily Life and Patient Satisfaction Using Eye Drops. Psychometrics Properties of a New Scale. ISPOR Europe, Vienna, October 2022. Value in Health 2022 (Suppl.); 12: S415. DOI: 10.1016/j.jval.2022.09.2062.

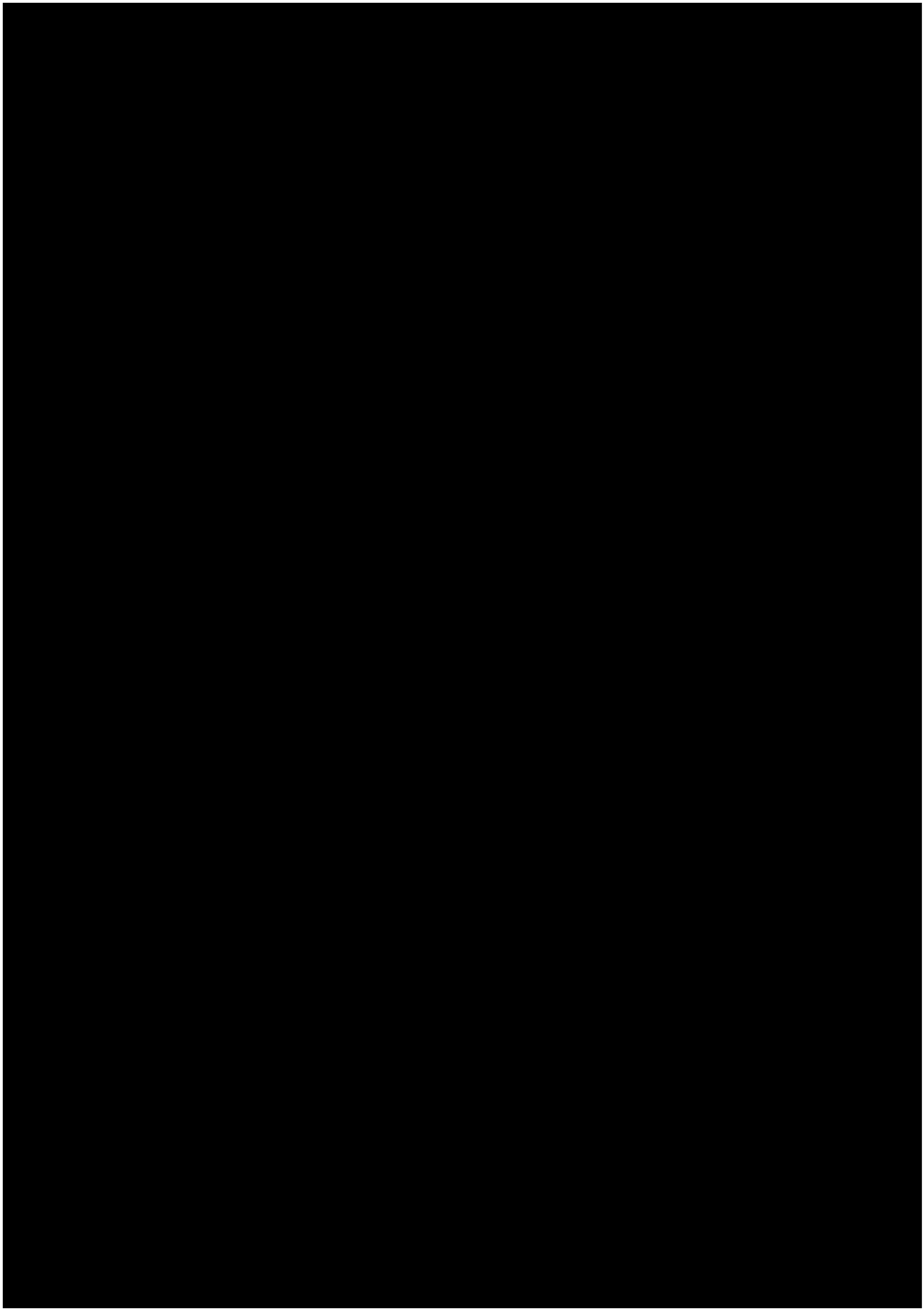
US Food and Drug Administration. (2009). Guidance for industry patient-reported outcome measures: Use in medical product development to support labeling claims. Food and Drug Administration. Retrieved August 2023, from https://www.fda.gov/media/77832/download

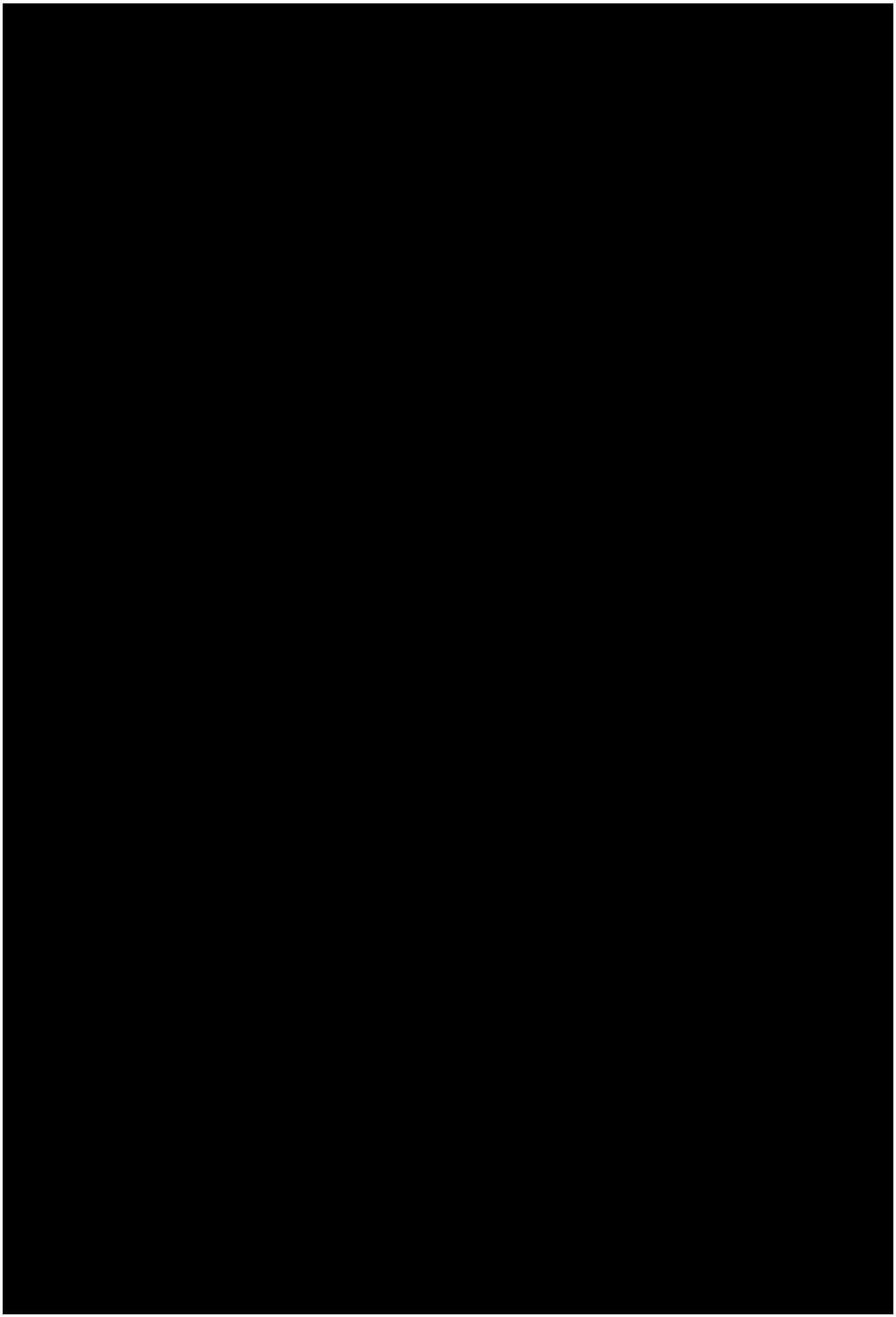




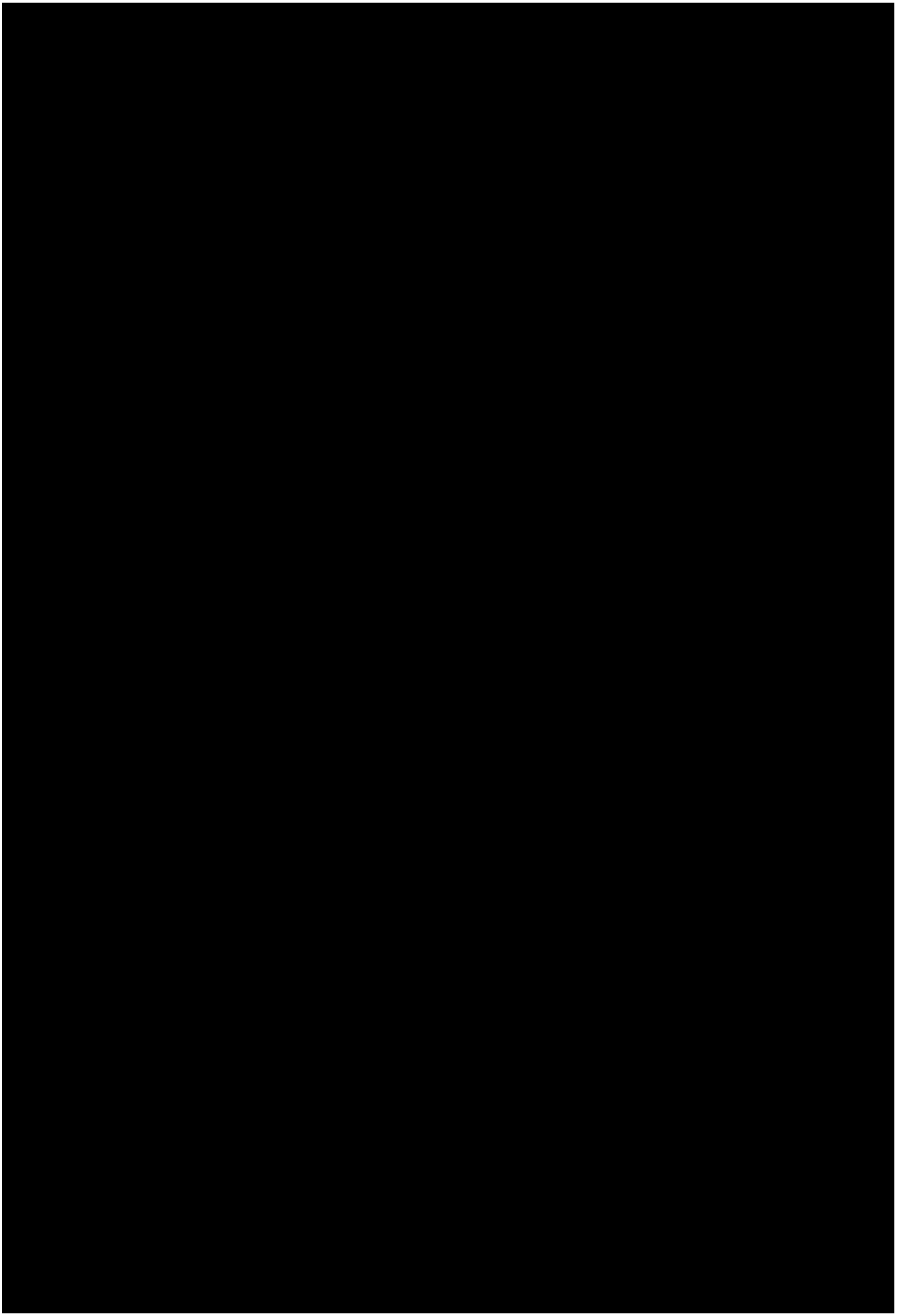


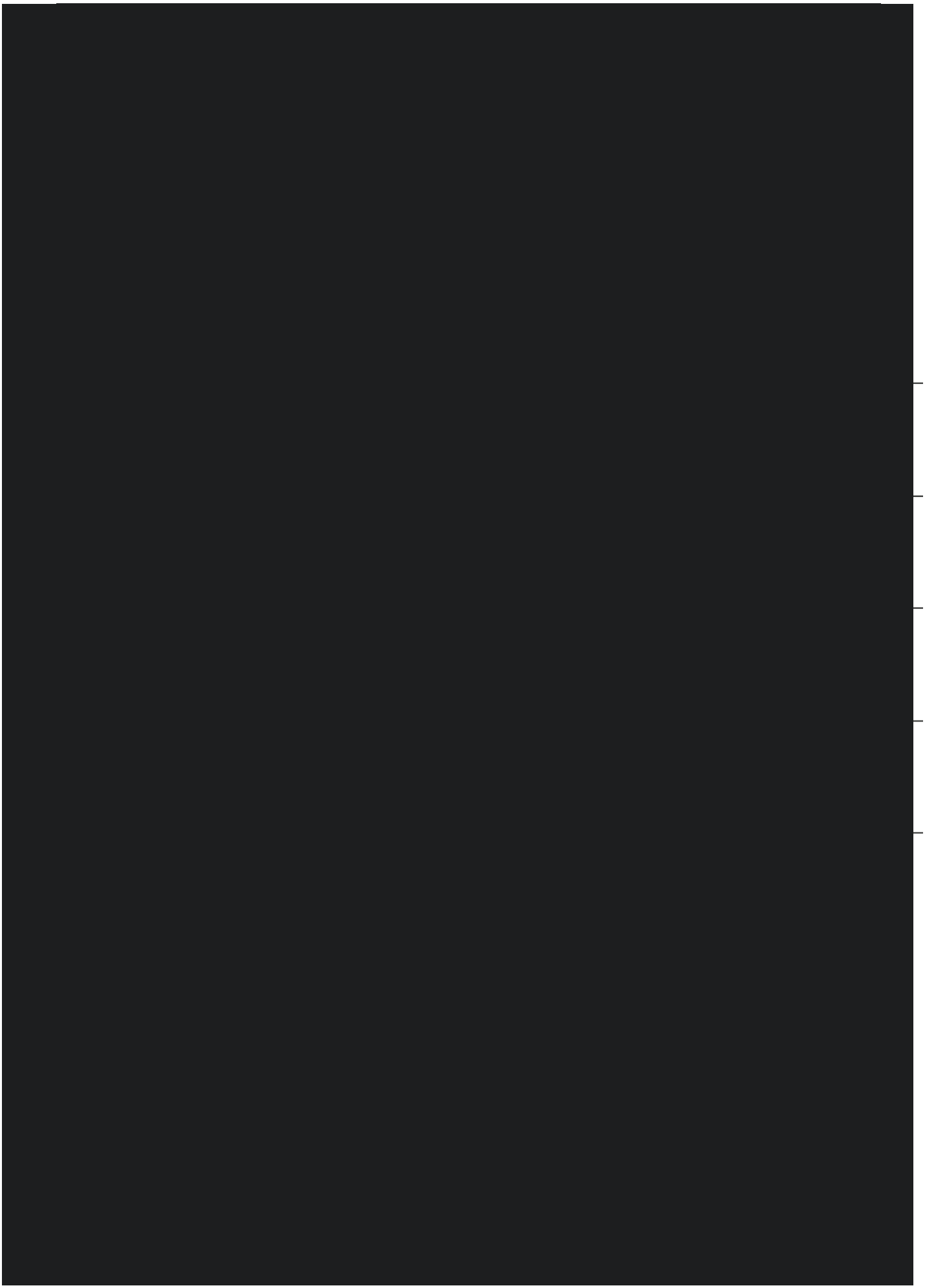


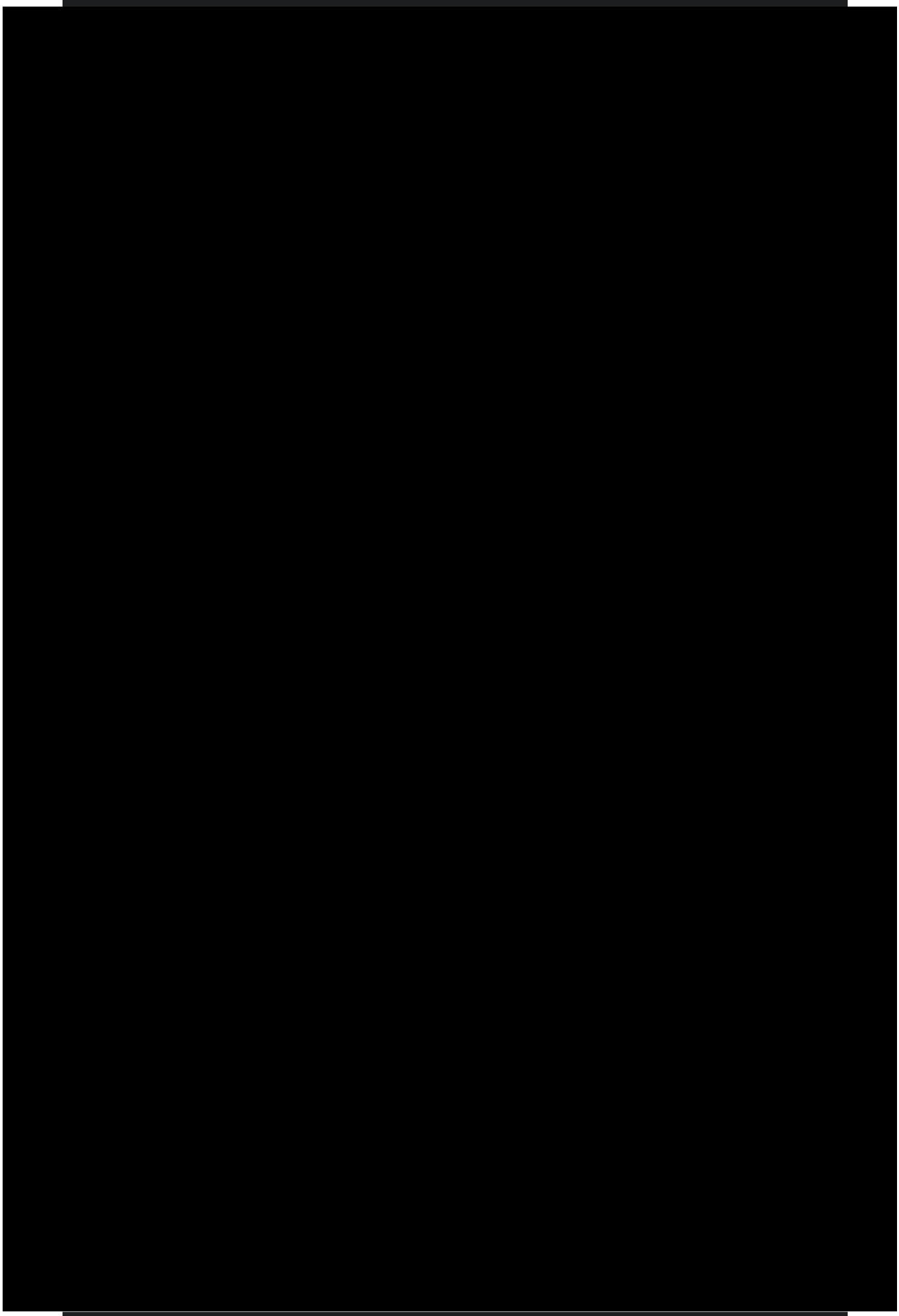


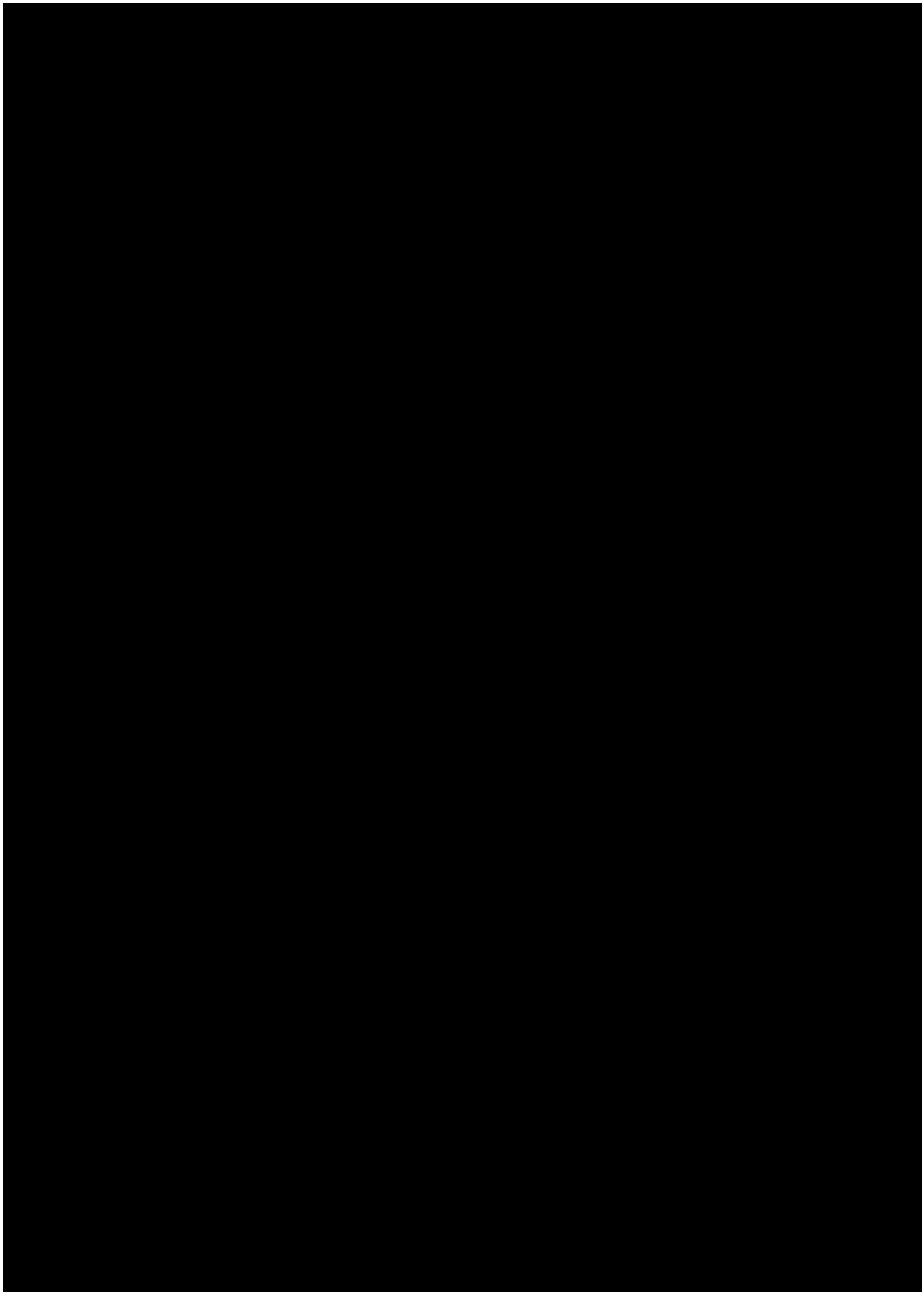


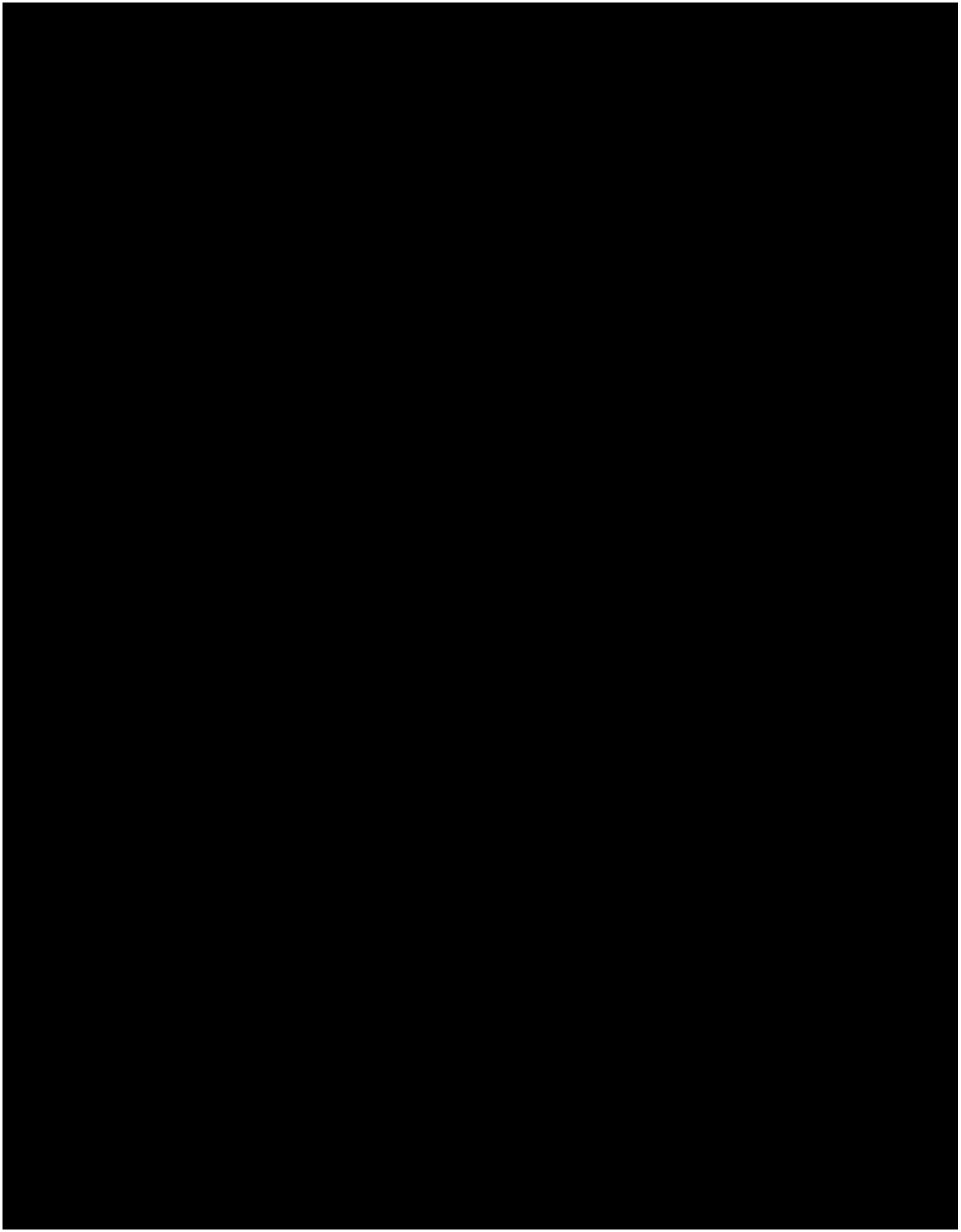
[redacted]











[redacted]