A Proof of Concept, Phase IIa, Open Label Study to Evaluate the Safety and Efficacy of Afamelanotide in Patients with Variegate Porphyria (VP)-related skin disease.

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[*Short Title: Phase IIa VP Study*]

Protocol No: CUV040

[redacted]**14 December 2022**

SPONSOR
CLINUVEL (UK) LTD
Wesley House, Bull Hill
Leatherhead, KT22 7AH
United Kingdom

This study will be conducted in compliance with Good Clinical Practices (GCP) and ICH guidelines, and all patient study documents will be archived by CLINUVEL (UK) LTD.

SIGNATURES OF AGREEMENT FOR PROTOCOL AND AMENDMENTS

Protocol Title: A Proof of Concept, Phase IIa, Open Label Study to Evaluate the Safety and Efficacy of Afamelanotide in Patients with Variegate Porphyria (VP)-related skin disease [CUV040]

[redacted] **14 December 2022**

I have read this protocol and agree to conduct the study as outlined herein, complying with the obligations and requirements of clinical investigators and ICH Guidelines.

Principal Investigator:

[redacted]

Signature: [redacted] Date: [redacted]

Study Director, Sponsor:

[redacted]

Signature: [redacted] Date: [redacted]

PROTOCOL SYNOPSIS

Name of company: CLINUVEL (UK) LTD	**Name of finished product:** SCENESSE®	**Name of active ingredient:** Afamelanotide

Title of study: A Proof of Concept, Phase IIa, Open Label Study to Evaluate the Safety and Efficacy of Afamelanotide in Patients with Variegate Porphyria (VP)-related skin disease

Study number: CUV040	**Phase of development:** IIa

Study period: 8 months including the screening and follow-up period.

Objectives:

Primary objective

- Evaluate the impact of afamelanotide on the severity of skin disease in patients with VP.

Secondary objectives

- Evaluate the safety and tolerability of afamelanotide in patients with VP.
- Evaluate the impact of afamelanotide on the quality of life of patients with VP.

Methodology:

This is an 8-month open label study in adult patients with confirmed VP-related skin disease. To determine eligibility for entry [redacted] Eligible patients will be enrolled [redacted]

Clinical evaluations will be performed by the same Investigator over the course of the study during the Screening period (Day -28 and Day 0) and on Days 28, 56, 84, 112, 140, 168 and 196 or Premature Termination (if applicable).

The evaluations will include assessments of disease severity using an 11-point Likert-type Visual Analogue Scale (VAS), a 5-point Investigator's Global Assessment (IGA) scale and a clinical global impression of change (CGIC) as well as a count of skin lesions [redacted]

A mapping of the skin lesions will be performed at the same time using digital photography.

The patient will also assess disease severity during the Screening period (Day -28 and Day 0) and on Days 28, 56, 84, 112, 140, 168 and 196 or Premature Termination (if applicable) through a VAS and a patient global impression of change (PGIC). Quality of life will be evaluated at the same time [redacted] Outdoors light exposure and trauma will be recorded daily by the patient [redacted].

Safety assessments (including laboratory evaluations, review of adverse events) will be carried out at each study visit and in between, if required for safety-related reasons, at the Investigator's discretion.

[redacted]

[redacted]

No. of participants planned: 6

Treatment:

Afamelanotide [redacted]

Diagnosis and main criteria for entry:

To be eligible to enter the study, patients must meet the following ***inclusion criteria***:

- Male or female patients with a biochemically and/or molecular-genetically confirmed diagnosis of VP.
- Patients with VP-related skin symptoms. [redacted]
- Aged 18-70 years.
- Providing written Informed Consent prior to the performance of any study-specific procedure.
- Willing and able to comply with the conditions specified in the protocol and study procedures, in the opinion of the Investigator.

To be eligible to enter the study, patients must not meet any of the following ***exclusion criteria***:

- [redacted]
- Had two or more acute attacks of hepatic porphyria, as defined by the occurrence or acute porphyric symptoms [redacted] lasting more than two days, within 12 months prior to the Screening period.
- [redacted]
- [redacted]
- Presence of severe hepatic disease [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

Test product:
Afamelanotide [redacted]

Dose:
[redacted]

Mode of administration:
Subcutaneous injection

Reference therapy:
Not applicable

Criteria for evaluation:
Efficacy Endpoints:
Efficacy of the treatment will be assessed by:

- Clinical Global Impression of Change (CGIC)
- IGA of disease severity using an 11-point VAS (**VAS IGA**);
- Static IGA of disease severity on a 5-point scale (**5-point IGA**);
- Patient's Global Assessment of disease severity evaluating skin fragility using a **VAS**;
- Patient Global Impression of Change (PGIC)
- Number of new skin lesions (blisters/wounds) [redacted] as counted by the Investigator and mapped by standardised digital photography;
- Quality of Life, [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
- Patient records [redacted] of outdoors light exposure and trauma.

Safety and Tolerability Endpoints:
Safety and tolerability will be assessed by measuring treatment-emergent adverse events (TEAEs) (coded as MedDRA Preferred Terms).

Statistical Methods:

Efficacy analysis:
Primary efficacy endpoint:

- The change in severity [redacted] as measured by the CGIC.

The null hypothesis is formulated as:
H_0: there is no change in CGIC score at one or more timepoints after treatment.

Secondary efficacy endpoints:

- The change in severity [redacted] as measured by:
  - 5-point IGA;
  - 11-point VAS IGA;
  - The Patient's Global Assessment of disease severity using a VAS;
  - The Patient Global Impression of Change using PGIC.

- The change in the number of new skin lesions [redacted] as counted by the Investigator.
- The change in Quality of Life [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
- Change in outdoors light exposure over time [redacted] Trauma events will be tabulated.

[redacted]

[redacted]

All the applied instruments will be analysed using appropriate methods to evaluate their suitability to assess changes in skin disease severity, [redacted] The patient-related outcome (PRO) instruments will be assessed based on the judgement of the patients on their suitability to document their skin disease.

Safety Analyses:
The number of participants with TEAEs will be summarised by MedDRA preferred term and body system. TEAEs will be further summarised by intensity, seriousness, outcome and relationship to study drug. Participants who prematurely terminate treatment due to adverse events related to study medication will be summarised.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ADR	Adverse drug reaction
AE	Adverse event
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
β-HCG	Beta Human Chorionic Gonadotropin
CGIC	Clinical Global Impression of Change
[redacted]	[redacted]
CRF	Case report form
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
GCP	Good Clinical Practice
GGT	Gamma Glutamyl Transferase
[redacted]	[redacted]
HREC	Human Research Ethics Committee
ICH	International Council for Harmonization
IGA	Investigator global assessment
[redacted]	[redacted]
ITT	Intention-to-treat
kg	Kilogram
LPI	Last patient in
[redacted]	[redacted]
LPLV	Last patient last visit
[redacted]	[redacted]
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
mL	Milliliter
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
PGIC	Patient Global Impression of Change
PPIX	Protoporphyrin IX
[redacted]	[redacted]
[redacted]	[redacted]
PRO	Patient reported outcome
QoL	Quality of life
[redacted]	[redacted]
[redacted]	[redacted]
SADR	Serious adverse drug reaction
SAE	Serious adverse event

SOM	Study Operating Manual
[redacted]	[redacted]
SUSAR	Suspected unexpected serious adverse reaction
TEAEs	Treatment-emergent adverse events
UK	United Kingdom
[redacted]	[redacted]
[redacted]	[redacted]
VP	Variegate porphyria
[redacted]	[redacted]
WMA	World Medical Association
[redacted]	[redacted]

1.0 ETHICS

1.1 Human Research Ethics Committee (HREC)

An appropriate HREC will approve the protocol and the Participant Information and Informed Consent Form before the study is initiated at each study centre. Documentation of this approval will be provided to the Sponsor and/or the Sponsor's designee. The Investigator(s) will have the following responsibilities:

[redacted]

1.2 Ethical Conduct of the Study

This study will be conducted in accordance with the Declaration of Helsinki (see Appendix 1), its revisions and International Council for Harmonization (ICH) guidelines for Good Clinical Practice (GCP) governing the conduct of studies, and all applicable local regulations. [redacted]

1.3 Participant Information and Informed Consent

The treating physician will make the initial contact with the patient. Prior to any study specific screening procedures, the Investigator will explain to each participant the nature of the study, its purpose, procedures to be performed, the necessity for withdrawal of prohibited medication, expected duration, and the benefits and risks of study participation. After this explanation and before any study specific screening procedures are performed, the subject must voluntarily sign an informed consent

statement in the presence of a witness, if applicable. The inclusion and exclusion criteria will be reviewed at Days -28 and 0 prior to study medication administration.

1.4 Protocol Amendments

Changes in any portion of this protocol will be documented in the form of a protocol amendment and signed by the appropriate CLINUVEL (UK) LTD personnel and the Investigator(s).

Depending on the requirements of the study centre's HREC and relevant Competent Authority (where applicable), protocol amendments will either need to be submitted for approval or advised by notification. Where formal approval is required, the revision will not be implemented until approval has been obtained.

1.5 Confidentiality

All information provided to the Investigator by the Sponsor, including clinical observations at the investigative centre, are held strictly confidential and confined to the clinical personnel involved in conducting the study, under the supervision of the Investigator.

2.0 STUDY PERSONNEL AND STUDY ADMINISTRATION

[redacted]

3.0 INTRODUCTION AND STUDY RATIONALE

Variegate porphyria (VP) is a rare autosomal dominant inherited disorder characterised by the deficiency of the mitochondrial enzyme protoporphyrinogen oxidase (PPOX), the penultimate enzyme in the haem biosynthesis pathway. VP presents with phototoxicity, leading to chronic blistering and fragility of sun/light-exposed areas of the skin, acute attacks of neurovisceral symptoms, or both cutaneous and acute symptoms[1,2]. Manifestations of VP appear typically in adulthood, and rarely before puberty[1]. Although the acute neurovisceral attacks can respond to treatment used for other acute porphyrias, at present there is no effective intervention for the chronic skin symptoms[1,2]. SCENESSE® (afamelanotide 16mg) was granted marketing authorisation in the European Union in December 2014 and in Australia in October 2020 for the prevention of phototoxicity in adult patients with erythropoietic protoporphyria (EPP) and in the United States in October 2019 to *increase pain free light exposure in adult patients with a history of phototoxic reactions from EPP*, another cutaneous porphyria. In VP and EPP patients present with phototoxicity due to accumulation of protoporphyrin. [redacted]

The reported prevalence of VP varies from 0.3 to 2 cases per 100,000 inhabitants but has been reported as more common in the Caucasian South African population (up to 1 in 300 people) due to a founder effect. In Europe, the prevalence varies from 0.32 to 1 cases per 100,000 inhabitants[3, 4].
The occurrence of skin disease in VP patients varies; studies from Finland, France, the UK and Switzerland reported that symptomatic patients had either cutaneous symptoms only, acute attacks only or both acute attacks and cutaneous symptoms[5,6,7].

Phototoxicity in VP leads to chronic fragility and blistering, [redacted] The lesions result from sun/light exposure that activates porphyrins and makes the skin fragile as well as prone to blister formation and damage to the superficial layers from minor mechanical trauma (e.g. slight knock on the back of the hand). The subepidermal vesicles, bullae, and erosions crust over and heal slowly [redacted] When blisters rupture they may become infected and result in pigmented or, more rarely, depigmented scars. [redacted] Pain occurs from the superficial wounds and secondary infections[8]. Some patients develop

progressive pseudosclerodermatous changes in the hands and fingers[8]. Other chronic skin findings include milia (more commonly seen in porphyria cutanea tarda; PCT), scarring, thickening, and areas of decreased and increased skin pigmentation. Facial hyperpigmentation and hypertrichosis may also occur[8,9].

With the exception of haem arginate for the treatment of acute attacks, there are no authorised medicinal products for VP, in particular for the prevention of phototoxicity and related skin-manifestations. Current advice for the skin complaints of VP patients includes protective clothing and avoidance of sunlight exposure. Analgesics and antibiotics may be used for treating painful and superimposed infections. Topical steroids have been found to have little or no benefit[1]. Advice regarding the avoidance of exacerbating factors such as some drugs, smoking and excessive alcohol consumption has been shown to be effective in reducing the number of acute neurovisceral attacks in VP, although the effect of such measures on phototoxicity and skin complaints has been limited[5].

VP and EPP share similar clinical features. In both forms, patients experience phototoxicity and suffer episodes most severely in spring and summer when the atmospheric intensity of light increases. Phototoxicity is due to overproduction and accumulation of protoporphyrin IX (PPIX). Light exposure of the skin will result in activation of protoporphyrin in plasma and in interstitial fluids. The activated porphyrins will induce activated oxygen and reactive oxygen species, which in turn induce

lipid- and DNA damage, damage to macromolecules, degranulation of mast cells, inflammatory reaction and endothelial damage. VP and EPP share very similar histopathological changes, with abnormal superficial dermal vessels which are often tube-like with thickened walls containing periodic acid Schiff (PAS)-positive material. In both forms of porphyria, the histological changes are to be found in light and sun-exposed areas[23,24,25].

Afamelanotide is a potent analogue of α-MSH which stimulates the production of eumelanin in the skin (epidermis) without the specific cell damage that usually occurs when melanin production is stimulated by UV radiation[20,21]. Melanin, in the form of eumelanin, is a photoprotective agent. The mechanisms proposed for photoprotection include, but are not limited to, the absorption and scattering of UV light, free radical scavenging and quenching of UV light[16,17]. There is also increasing evidence that melanogenesis represents a major antioxidant defense mechanism in melanocytes, neutralising the deleterious effects of free radicals and active oxygen species[18]. Eumelanin acts as a neutral density filter and, unlike most sunscreens, reduces all wavelengths of light equally so that the photoprotection provided by epidermal melanin pigmentation is essentially independent of wavelength[19]. Moreover, alpha-MSH signalling induces antioxidative enzymes and improves DNA repair processes[22].

[redacted]

Afamelanotide 16mg has been shown to be effective in the prevention of phototoxicity in EPP and had obtained marketing authorisation in the European Union and to increase pain free light exposure in adult patients with a history of phototoxic reactions from EPP in the United States for this

indication in adult patients. The results of the clinical trials conducted by CLINUVEL, as well as of one long term observational study and the ongoing post-authorisation pharmacovigilance activities, confirmed the positive safety profile of afamelanotide to date[26,27].

Due to the lack of an effective therapy as well as due to the rarity of the disease no instrument to assess VP-related skin manifestations and therapeutic effects of an intervention have been developed until now. Physician's global assessment tools and patient reported outcomes have been developed in collaboration with expert physicians for use and evaluation in this study[29].

The primary endpoint chosen for this study uses the Clinical Global Impression of Change (CGIC) tool.

[redacted]

This study aims to extend knowledge of the photoprotective effects of afamelanotide in the cutaneous porphyria patients.

4.0 STUDY OBJECTIVES

4.1 Primary Objective

The primary objective of this study is to evaluate the impact of afamelanotide on the severity of the skin disease in patients with VP.

4.2 Secondary Objectives

The secondary objectives of this study are to:

- Evaluate the safety and tolerability of afamelanotide in patients with VP;
- Evaluate the impact of afamelanotide on the quality of life of patients with VP.

5.0 INVESTIGATIONAL PLAN

5.1 Overall Design and Plan of the Study

This is an open label, phase IIa pilot study to be conducted in 6 patients with VP skin disease during an 8-month period [redacted]

To determine eligibility for study inclusion, [redacted] Eligible patients will be enrolled and will receive [redacted]

Clinical evaluations will be performed by the same Investigator over the course of the study during the Screening period (Day -28 and Day 0) and on Days 28, 56, 84, 112, 140, 168 and 196 or Premature Termination (if applicable).

The evaluations will include assessments of disease severity using an 11-point Likert-type Visual Analogue Scale (VAS IGA), a 5-point Investigator's Global Assessment (IGA) scale and a clinical global impression of change (CGIC) as well as a count of skin lesions [redacted]

A mapping of the skin lesions will be performed at the same time using digital photography.
The patient will also assess disease severity during the Screening period (Day -28 and Day 0) and on Days 28, 56, 84, 112, 140, 168 and 196 or Premature Termination (if applicable) through a VAS and a patient global impression of change (PGIC). Quality of life will be evaluated at the same time [redacted] Outdoors light exposure and trauma will be recorded daily by the patient [redacted]

Safety assessments (including laboratory evaluations, review of AEs) will be carried out at each study visit and in between, if required for safety-related reasons, at the Investigator's discretion.

[redacted]

5.2 Selection of Study Population

The target population consists of male and female patients with VP who have chronic skin changes including blisters, wounds and infected wounds. [redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]

The following inclusion and exclusion criteria must be met by each patient before enrolment in the study.

5.2.1 Inclusion Criteria

The participants have to fulfil all of the following ***inclusion criteria*** for study participation:

- Male or female patients with a biochemically and/or molecular-genetically confirmed diagnosis of VP.
- Patients with VP-related skin symptoms. [redacted]
- Aged 18-70 years.
- Providing written Informed Consent prior to the performance of any study-specific procedure.
- Willing and able to comply with the conditions specified in the protocol and study procedures, in the opinion of the Investigator.

5.2.2 Exclusion Criteria

To be eligible to enter the study, patients must **not** meet any of the following ***exclusion criteria***:

- [redacted]
- Had two or more acute attacks of hepatic porphyria, as defined by the occurrence or acute porphyric symptoms [redacted] lasting more than two days, within 12 months prior to the Screening period.
- [redacted]
- [redacted]
- Presence of severe hepatic disease [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

5.2.3 Patient Recruitment Management

Patients known to the principal investigator to potentially fulfil inclusion criteria, will be contacted and asked for study participation. Please refer to the CUV040 Study Operating Manual (SOM) section 5 for a detailed description of the method for patient recruitment management.

5.2.4 Withdrawals and Replacement of Participants

Patient discontinuation occurs when a patient does not complete the study as required by the study protocol. Participants will be free to discontinue their participation in this trial at any time for any reason. In addition, participants may be withdrawn from the trial at the discretion of the Sponsor, the Investigator or medically qualified nominee. A patient may withdraw for any of, but not limited to, the following reasons:

- Informed consent withdrawn by the patient;
- AE requiring study discontinuation of patient;
- When the Investigator's or nominee's best professional judgment would indicate that it would be in the patient's best interest to be withdrawn;
- Violation of inclusion/exclusion requirements.

The reasons for withdrawal or discontinuation of a patient will be recorded in the patient's CRF as well as in the patient's medical notes. If an AE is the reason for discontinuation, the event must be followed up and documented as described in *5.5.3.2 Safety variables* of the protocol. If the patient discontinued for any reason after the enrolment into the study, during the treatment period, a study termination visit, as described in *5.5.1 Description of Study Days* of the protocol, should be performed at the time of study discontinuation, or as soon as possible after discontinuation. This visit will be documented in the patient's CRF as well as in the patient's medical notes.

Any patient(s) withdrawn from the trial prior to their completion, for any reason, will not be replaced. Data compiled to the point of discontinuation will be used for 'intent to treat' analysis. Participants deviating any of the inclusion and exclusion criteria will be described as protocol deviators. The way in which protocol deviators will be handled in the statistical analysis is described in the present protocol.

5.3 Study Medication

5.3.1 Description of Study Medication

[redacted] afamelanotide. [redacted]

5.3.2 Treatment Group

There is only one treatment group in this study. As such, all patients who satisfy the inclusion/exclusion criteria will be allocated a study subject number and receive afamelanotide. Study subject number allocation will be detailed in the CUV040 SOM.

5.3.3 Dosage and Administration of Study Medication

Afamelanotide [redacted] will be administered [redacted] on the designated study days. [redacted]

5.3.4 Packaging and Labeling of Study Medication

The implant will be packaged in amber glass vials. The label will include information in compliance with the local regulatory requirements for clinical trials / investigational medicinal products.

5.3.5 Storage and Accountability

Study medication will be maintained in a safe and secure (locked, restricted access) location and kept at 2-8°C. The expiry or retest date for each afamelanotide implant will be printed on the label. The Investigator will agree not to supply study drug to any persons other than those enrolled in the study. Current and accurate drug receipts, inventory, accountability and dispensing records will be kept for all study drug in the Pharmacy/Investigator Site File(s), and upon study completion, a final inventory and reconciliation of all study drug will be compiled. [redacted]

5.3.6 Compliance

Data related to the administration of the study drug will be recorded on the CRF.

5.4 Prior and Concomitant Therapy

5.4.1 Prior Therapy

All subjects will be instructed to report to the Investigator any kind of treatments, prescribed medicines, over-the-counter medications, dietary supplements or nutraceuticals that are being used. Use of any other prior and concomitant therapy which may interfere with the objective of the study, [redacted]

5.4.2 Concomitant Therapy

The Investigator must be informed as soon as possible about any medication taken from the time of screening until the end of the study and these will be fully documented in the CRF. In the event that a subject has taken a medication which has not been pre-approved, the Investigator will make a decision to continue or discontinue the subject, based whether the medication may interfere with the objectives of the study. These include medications which cause photosensitivity or skin pigmentation.

During the study, contraceptive therapy must not be changed.

5.5 Study Procedures

This will be an outpatient study (see flowchart in Appendix 3). [redacted]

5.5.1 Description of Study Days

5.5.1.1 Screening Period

Screening [redacted]

The Screening Visit and related procedures will only occur after the informed consent process is performed and a signed and dated informed consent form has been obtained from the patient. The Investigator will assess eligibility for the study after the following procedures are performed:

- [redacted]

[redacted]

Visit 2 [redacted]

[redacted] After patient's eligibility has been confirmed by the Investigator, the following procedures will be performed:

[redacted]

[redacted]

[redacted]

[redacted]

5.5.2 Study Procedures Flowchart

Please refer to Appendix 3 for the full study flowchart.

5.5.3 Methods of Assessment

5.5.3.1 Efficacy variables

The efficacy endpoints will be as follows:

Primary Efficacy Endpoint

- The change in severity [redacted] as measured by the CGIC.

Secondary Efficacy Endpoints

- The change in severity [redacted] as measured by:
  - The 5-point IGA
  - 11-point VAS IGA scale;
  - The Patient Global Impression of Change using PGIC
  - The Patient's Global Assessment using a VAS.
- The change in the number of new skin lesions [redacted] as counted by the Investigator.
- The change in Quality of Life [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
- Change in outdoors light exposure over time [redacted] Trauma events will be tabulated.

All the applied instruments will be analysed using appropriate methods to evaluate their suitability to assess changes in skin disease severity, [redacted] The PRO instruments will be assessed based on the judgement of the patients on their suitability to document their skin disease. [redacted]

5.5.3.1.1 Clinical Global Impression of Change (CGIC)

A CGIC scale will be used to assess disease severity changes at Days 28, 56, 84, 112, 140, 168 and 196, or Premature Termination Visit, if applicable. [redacted]

5.5.3.1.2 VAS IGA

An 11-point Likert-type Visual Analogue Scale (VAS IGA) scale will be used to assess disease severity at Days -28, 0, 28, 56, 84, 112, 140, 168 and 196, or Premature Termination Visit, if applicable. [redacted]

5.5.3.1.3 5-point IGA

A 5-point Investigator's Global Assessment (IGA) scale will be used to assess disease severity at Days -28, 0, 28, 56, 84, 112, 140, 168 and 196, or Premature Termination Visit, if applicable. [redacted]

5.5.3.1.4 Patient Global Impression of Change (PGIC)

A PGIC scale will be used to assess disease severity changes at Days 28, 56, 84, 112, 140, 168 and 196, or Premature Termination Visit, if applicable. [redacted]

5.5.3.1.5 Patient's Global Assessment using a VAS

A Patient's Global Assessment scale of disease severity evaluating skin fragility using a VAS will be used at Days -28, 0, 28, 56, 84, 112, 140, 168 and 196, or Premature Termination Visit, if applicable. [redacted]

5.5.3.1.6 Skin Mapping Photography

A mapping of the skin will be performed at Days -28, 0, 28, 56, 84, 112, 140, 168 and 196, or Premature Termination Visit, [redacted]

[redacted]

5.5.3.1.7 Skin Lesions Count

The number of skin lesions [redacted] will be assessed at Days -28, 0, 28, 56, 84 112, 140, 168 and 196, or Premature Termination Visit, if applicable. [redacted]

5.5.3.1.8 Quality of Life

The patient's Quality of Life, [redacted] will be assessed at Days -28, 0, 28, 56, 84, 112, 140, 168 and 196, or Premature Termination Visit, if applicable. [redacted]

[redacted]

5.5.3.2 Safety variables

The number of participants with TEAEs will be summarised by MedDRA preferred term and body system. TEAEs will be further summarised by intensity, seriousness, outcome and relationship to study drug. Participants who prematurely terminate treatment due to AEs related to study medication will be summarised.

5.5.3.2.1 Clinical Laboratory Evaluations

[redacted]

The Investigator will sign and date all laboratory reports and review all laboratory test results. The Investigator will evaluate the clinical significance of all values outside the reference range and will document within the laboratory report as well as in the patient's CRF. If a laboratory value is outside the reference range and felt to represent a clinically significant change from the baseline value, this will be reported as an AE in the patient's medical notes and on the AE CRF page. Clinically significant is defined as a change in the patient's clinical status that is regarded as important, whether or not it is due to the Investigational Medicinal Product. An assessment of this AE will be made by the Investigator, in particular regarding the relationship and seriousness of the event to the study drug.

5.5.3.2.2 Physical Examination

A general physical examination will be performed

5.5.3.2.3 Weight and Height

Weight in kilograms (kg) will be recorded [redacted]

5.5.3.2.4 Vital Signs Measurements

Vital signs (blood pressure, temperature and pulse rate) will be recorded [redacted]

5.5.3.2.5 Dermatology Examination and Full Body Photography

Examination of the skin and oral mucosa and full body photography will be performed [redacted]

5.5.3.2.6 Adverse Events

An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE may be a symptom, sign, or abnormal finding or test result. Whenever possible, the Investigator will group together into a single term, signs and symptoms that constitute a single diagnosis. For example, cough, rhinitis and sneezing might be grouped together as “upper respiratory tract infection”.

The Investigator will monitor each patient closely for the development of AEs, and any adverse event spontaneously reported by or elicited from the patient itself or observed by the Investigators (physician or study staff) will be recorded in the patient’s medical notes and on the appropriate AE page of the CRF, when applicable. [redacted]

[redacted] It is the responsibility of any member of the study site staff to immediately report any suspected AE to the Investigator.

The Investigator will assess the AE(s) in the patient's medical notes and provide the date and time of onset, severity, seriousness, action taken, outcome, date of resolution (or comment that the event is still continuing) and relationship to study medication.

An Adverse Drug Reaction is a noxious and unintended response to a medicinal product related to any dose.

All AEs will be followed up. AEs will be graded for severity as defined below:

- **Mild** - The AE is transient and easily tolerated by the patient. Specific action is optional.
- **Moderate** - The AE causes the patient discomfort and interrupts the patient's usual activities.
- **Severe** - The AE causes considerable interference, preventing the patient's usual activities.

Outcome of the event must be described as one of the following:

- Recovered without sequelae;
- Recovered with sequelae;
- Recovering;
- Not recovered;
- Death.

The Investigator will be asked to document his/her opinion of the relationship of the event to the study drug as follows:

- **Related** - There are facts or arguments to suggest a causal relationship, i.e. there is a reasonable possibility of a causal relationship between the drug and the AE(s).
- **Not Related** - There is not a reasonable possibility that the AE(s) is/are related to the drug – alternative aetiology, diagnosis, or explanations for the AE(s) exist, or the time from suspect drug intake make a relationship improbable.

- **Not Assessable** - Report suggesting an adverse reaction BUT cannot be judged because information is insufficient or contradictory OR cannot be supplemented or verified. Non-assessable cases by the site will be assessed by CLINUVEL and reported if deemed related to study drug.

Serious Adverse Events

A Serious Adverse Event (SAE) is any adverse event occurring at any dose that results in any of the following outcomes:

- Death (due to any cause);
- Is life-threatening;
- Requires inpatient hospitalisation or a prolongation of an existing hospitalisation;
- Results in a persistent or significant disability/incapacity;
- Is a congenital anomaly/birth defect;
- Important medical events that may not be immediately life threatening, result in death or require hospitalisation but may be considered a serious adverse event when, based upon appropriate medical judgment, they may jeopardise the patient or may require medical or surgical intervention to prevent one of the outcomes listed in the definition above.

Reporting: Any SAE, including death due to any cause, which occurs during this study, has to be reported to CLINUVEL **within 24 hours** of the Investigator or their delegate becoming aware of the event, even if only limited information regarding the event is available.

In the event that the investigator becomes aware of an SAE which is thought to be related to the IMP, even months or years after the end of the clinical trial, it should be reported to the sponsor.

A SAE report form will be completed and sent to CLINUVEL Safety Team at [redacted] or fax to the number provided in the CUV040 SOM within 24 hours of the event occurring or within 24 hours of becoming aware of the event. In addition to completing the SAE report form (one form completed for each case), additional supporting information should be provided as appropriate, such as photocopies of pertinent test results and medical notes, trial records, consultant report(s), hospital discharge summary and autopsy report (if relevant and as soon as available to the Investigator). All SAEs will be recorded in the patient's medical notes and on the AE page of the CRF.

The Investigator will determine whether the seriousness of the event warrants removal of any patient from the study. The Investigator will institute appropriate diagnostic and therapeutic measures and keep the patient under observation for as long as is medically indicated.

Certain AEs and/or SAEs, including suspected unexpected serious adverse reactions (SUSARs), may warrant expediting to IECs, according to the regulatory requirements for the individual countries or sites involved, either by the Investigator or the Sponsor. The modalities for reporting and filing relevant documentation will be detailed in the CUV040 SOM.

[redacted]

- [redacted]
- [redacted]

Pregnancy and/or Breastfeeding

The following situations must be reported to CLINUVEL **within 24 hours** of the Investigator or their delegate becoming aware of the event, even if only limited information regarding the event is available.

- Pregnancy occurring in a female patient, when the start of the pregnancy is less than three months after the last afamelanotide implant was administered;
- Pregnancy occurring in the female partner of a male patient treated, when the start of the pregnancy is less than three months after the last afamelanotide implant was administered to the male patient;
- Female patient breastfeeding when the start of breastfeeding is less than three months after the last afamelanotide implant was administered;
- Birth of a child from a female patient, when the start of the pregnancy was less than three months after the last afamelanotide implant was administered;
- Birth of a child from the female partner of a male patient, when the start of the pregnancy is less than three months after the last afamelanotide implant was administered to the male patient.

[redacted] Report Form and/or a Pregnancy Outcome/Breastfeeding Report form will be completed and sent to CLINUVEL Safety Team at [redacted] or fax to the number provided in the CUV040 SOM within 24 hours of becoming aware of the event. All pregnancies will be followed from the date of pregnancy detection until pregnancy outcome and/or lactation and breastfeeding (when applicable).

Female patients who become pregnant, give birth or begin breastfeeding during the treatment period will be withdrawn from treatment and complete the Premature Termination and Follow-Up Visits.

For male patients of female partners who become pregnant, the responsible Investigator will determine whether the event warrants removal of any patient from the study.

Documentation and submission:

The sponsor ensures to keep detailed records of all AEs which are reported to him by the investigators. Submission of SUSARs to the ethics committee (EC) and regulatory authorities will follow pertinent national legislation.

These events are in particular:

- single cases of expected SADRs with an unexpected outcome,
- an increased incidence of expected SADRs considered clinically significant,
- SUSARs occurring after a concerned person has completed the trial,
- events related to the conduct of the trial or the development of the investigational medicinal product possibly affecting the safety of the concerned persons.

All additional measures deemed necessary through new findings and taken by the Sponsor or the investigator to protect the safety of the persons concerned and their triggering circumstances will be reported as soon as possible to the concerned regulatory authorities and the ECs, if applicable.

Periodic safety reporting to regulatory authorities and the IECs will follow pertinent national legislation.

Follow Up:

All SAEs judged to be related to the investigational medicinal product must be followed by the investigator until their conclusion or until the investigator determines that the patient's condition is stable. All other ADRs must be followed by the investigator until the conditions mentioned above are met or until Day 196±5 or 28±5 Days after End of Treatment Visit, whichever comes first, and until all ADR-related queries for the subject have been resolved. The investigator will take all appropriate and necessary therapeutic measures required for resolution of the ADRs, if applicable. All efforts to collect follow-up information must be documented in the source data.

[redacted]

5.6.2 Database Management and Quality Control

The study will be monitored by the Clinical Monitor, and/or representatives of CLINUVEL, or its delegated representative, as frequently as is necessary to determine that data recording and protocol adherence are satisfactory. [redacted]

The detailed procedures for data entry, data coding, cleaning and electronic data transfer will be provided in a Data Management Plan.

5.7 Statistical Methods and Determination of Sample Size

5.7.1 Statistical and Analytical Plans

A formal statistical analysis plan will be prepared prior to completion of the study and before data analysis is undertaken.

5.7.2 Efficacy Assessment

5.7.2.1 Specification of Efficacy Endpoints

Efficacy of the treatment will be assessed by:

- CGIC
- IGA of disease severity using an 11-point VAS (**VAS IGA**);
- Static IGA of disease severity on a 5-point scale (**5-point IGA**);
- Patient's Global Assessment of disease severity evaluating skin fragility using a VAS;
- PGIC
- Number of new skin lesions [redacted] as counted by the Investigator [redacted]
- Quality of Life, [redacted]
  - [redacted]
  - [redacted]

- [redacted]
- Patient records [redacted] of outdoors light exposure and trauma.

All the applied instruments will be analysed using appropriate methods to evaluate their suitability to assess changes in skin disease severity, [redacted] The PRO instruments will be assessed based on the judgement of the patients on their suitability to document their skin disease. The methodology for analysis of the applied instruments, as well as for assessment of the PRO instruments, will be described in a separate document.

5.7.3 Safety Assessment

5.7.3.1 Specification of Safety Endpoint

The safety endpoint will be the incidence of TEAEs occurring during the study period, including clinically significant changes in laboratory parameters, which will be listed by intensity, seriousness, outcome, and relationship to study drug.

5.7.4 Sample Size

[redacted] A total of six (6) patients are planned to be enrolled in this study, [redacted] The data collected from these six patients will inform whether further trials will be needed.

5.7.5 Analysis Plan

5.7.5.1 Safety Population

The safety population will include all subjects who participate in the study and receive at least one study treatment. Participants screened but not enrolled will be shown in separate listings.

5.7.5.2 Intention To Treat (ITT) Population

The ITT population will include all treated participants, who provide at least one post dose efficacy assessment. This will be the main population for all efficacy analyses.

5.7.5.3 Handling of Missing and Incomplete Data

[redacted]

5.7.5.4 Per Protocol Analysis (PPA) Population

[redacted]

5.7.5.5 Demographic and Initial Characteristics

Demographic and baseline characteristics will be summarised using descriptive statistics.

5.7.5.6 Efficacy

Primary and secondary efficacy endpoints are described under section 5.5.3.1 Efficacy variables of the Study Protocol.

[redacted]

[redacted]

Since this study is in a rare disease, the clinical relevance of changes in the study endpoints has not yet been established, and so a minimal clinically importance change is not defined *apriori*.
Further details will be included in the statistical analysis plan.

5.7.5.7 Safety

Descriptive methods will be used to summarise the safety data. These will be based upon the safety population.

5.7.5.8 Adverse Events

All AEs, including non-TEAEs, will be listed. A TEAE is defined as:

- An event that was not present prior to or on the day of the first study medication administration but was present after study medication was administered.
- An event that was present prior to first administration of study medication and continued to occur after the administration of the first dose at an increased level of severity.
- An event that was present prior to administration of study medication and was documented as completely resolved and re-emerged after the administration of the first dose.

The MedDRA dictionary (Version 23.0) will be used to map verbatim AE terms to preferred terms and body systems. The number of participants with TEAEs will be summarised by preferred term and body system. TEAEs will be further summarised by intensity, seriousness and relationship to study medication. The number of participants who terminate treatment early due to AEs related to study medication will be tabulated. Summaries of the incidence of toxicities will be prepared, as appropriate.

SAEs and SUSARs will be listed individually. Any SAE that occurs after the first dose of the study medication, will be documented in the study report.

5.7.5.9 Clinical Laboratory Data

[redacted]

5.7.5.10 Other Clinical Data Analyses

[redacted]

[redacted]

5.7.5.11 Interim Evaluation

[redacted]

5.8 Early Termination of the Study

The study may be terminated early if the Sponsor, Investigator or Clinical Monitor discovers conditions arising during the course of the study which indicate that the clinical investigation should be halted. The study may then be terminated after appropriate consultation and discussion.

Conditions that may warrant study termination include, but are not limited to, the discovery of a significant, unexpected, and unacceptable risk to the participants, failure of the Investigator to enrol participants at an acceptable rate, insufficient adherence to the protocol requirements, completion of study objectives or at the discretion of the Sponsor.

6.0 STUDY REPORT, PUBLICATION POLICY & ARCHIVING OF STUDY DOCUMENTATION

Investigators are required to maintain all study documentation, including copies of CRFs, Informed Consents, and adequate records for the receipt and disposition of study medications, for a period of 25 years following study close-out.

The Investigator will ensure to make all study data accessible to the Clinical Monitor, Sponsor, or other authorised representatives of the Sponsor and Regulatory Agencies during the conduct of the study as well as during the archiving period. A file for each patient will be maintained that includes the signed Informed Consent form and copies of all source documentation related to that patient. The Investigator will ensure the availability of the source documents from which the information on the CRF is derived.

All information provided to the Investigator dealing with this study drug or the methodologies used in the protocol, as well as information obtained during the course of the study will be regarded as strictly confidential and proprietary to the Sponsor ("Proprietary Information"). The Investigator agrees not to disclose any information supplied by the Sponsor in any way without written permission as outlined in the Confidentiality section of this protocol. For the purposes of this section, "Investigator" includes, but is not limited to, the Principal Investigator and/or his/her agents, designees, sub-investigators, or other individuals involved in the running, administration, or collection/handling of participants/data for this study.

[redacted]

- Projected starting date (first-patient-in [FPI])* March 2023
- Projected number of patients 6
- Projected completion of patient accrual (last-patient-in [LPI])* June 2023

Patient study end date (last-patient-last-visit [LPLV])* March 2024

* These are approximate timeframes which are dependent of regulatory and ethics approvals.

[redacted]

[redacted]

[redacted]

9.0 APPENDICES

APPENDIX 1: WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI

Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53th WMA General Assembly, Washington 2002 (Note of Clarification on paragraph 29 added)
55th WMA General Assembly, Tokyo 2004 (Note of Clarification on Paragraph 30 added)
59th WMA General Assembly, Seoul, October 2008
64th WMA General Assembly, Fortaleza, Brazil, October 2013

Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words, “The health of my patient will be my first consideration,” and the International Code of Medical Ethics declares that, “A physician shall act in the patient’s best interest when providing medical care.”

4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician’s knowledge and conscience are dedicated to the fulfilment of this duty.

5. Medical progress is based on research that ultimately must include studies involving human subjects.

6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.

10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

11. Medical research should be conducted in a manner that minimises possible harm to the environment.

12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.

14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Risks, Burdens and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens.

Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee.

After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

Informed Consent

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

All medical research subjects should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject's dissent should be respected.

30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.

31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.

32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention

and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Research Registration and Publication and Dissemination of Results

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make

publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Interventions in Clinical Practice

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.

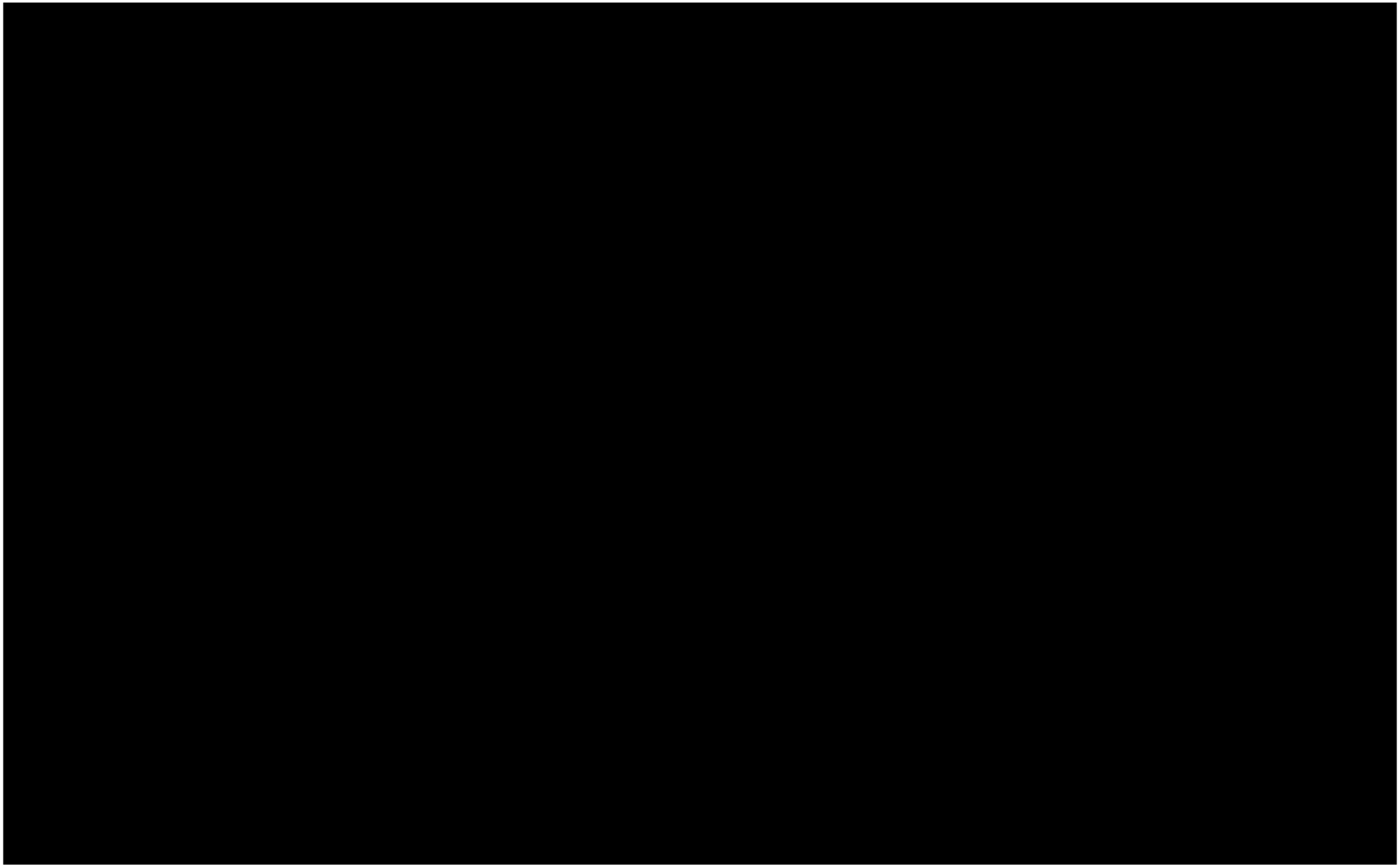
APPENDIX 2: ELEMENTS OF INFORMED CONSENT DOCUMENTATION

In seeking informed consent, the following information shall be provided to each patient:

1. A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the patient's participation, a description of the procedures to be followed, and identification of any procedures which are experimental;
2. A description of any reasonably foreseeable risks or discomforts to the patient;
3. A description of any benefits to the patient or to others which may reasonably be expected from the research;
4. Disclosures of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the patient;
5. A statement describing the extent, if any, to which confidentiality of records identifying the patient will be maintained; and,
6. An explanation of whom to contact for answers to pertinent questions about the research and participants' rights. It is the Sponsor's policy to reimburse an institution or Investigator for expenditures for the medical treatment of normal and patient volunteers who are injured as a direct result of their participation in the Sponsor's protocol as long as the Investigator has complied with the provisions of the protocol. Therefore, the consent form should reflect this in its explanation of the institution's policy. Further details on whom the volunteer should contact in case of injury should also be included.
7. An explanation of whom to contact for answers to pertinent questions about the research and research patient's rights and whom to contact in the event of a research-related injury to the patient.
8. A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the patient is otherwise entitled, and that the patient may discontinue participation at any time without penalty or the loss of benefits to which the patient is otherwise entitled.

When appropriate, one or more of the following elements of information shall also be provided to each patient (required under ICH):

1. A statement that the particular treatment or procedure may involve risks to the patient (or to the embryo or foetus, if the patient is or may become pregnant) which are currently unforeseeable;
2. Anticipated circumstances under which the patient's participation may be terminated by the Investigator without regard to the patient's consent;
3. Any additional costs to the patient that may result from participation in the research;
4. The consequences of a patient's decision to withdraw from the research and the procedures for the orderly termination of participation by the patient;
5. A statement that significant new findings that develop during the course of the research which may relate to the patient's willingness to continue participation will be provided to the patient; and,
6. The approximate number of participants involved in the study.



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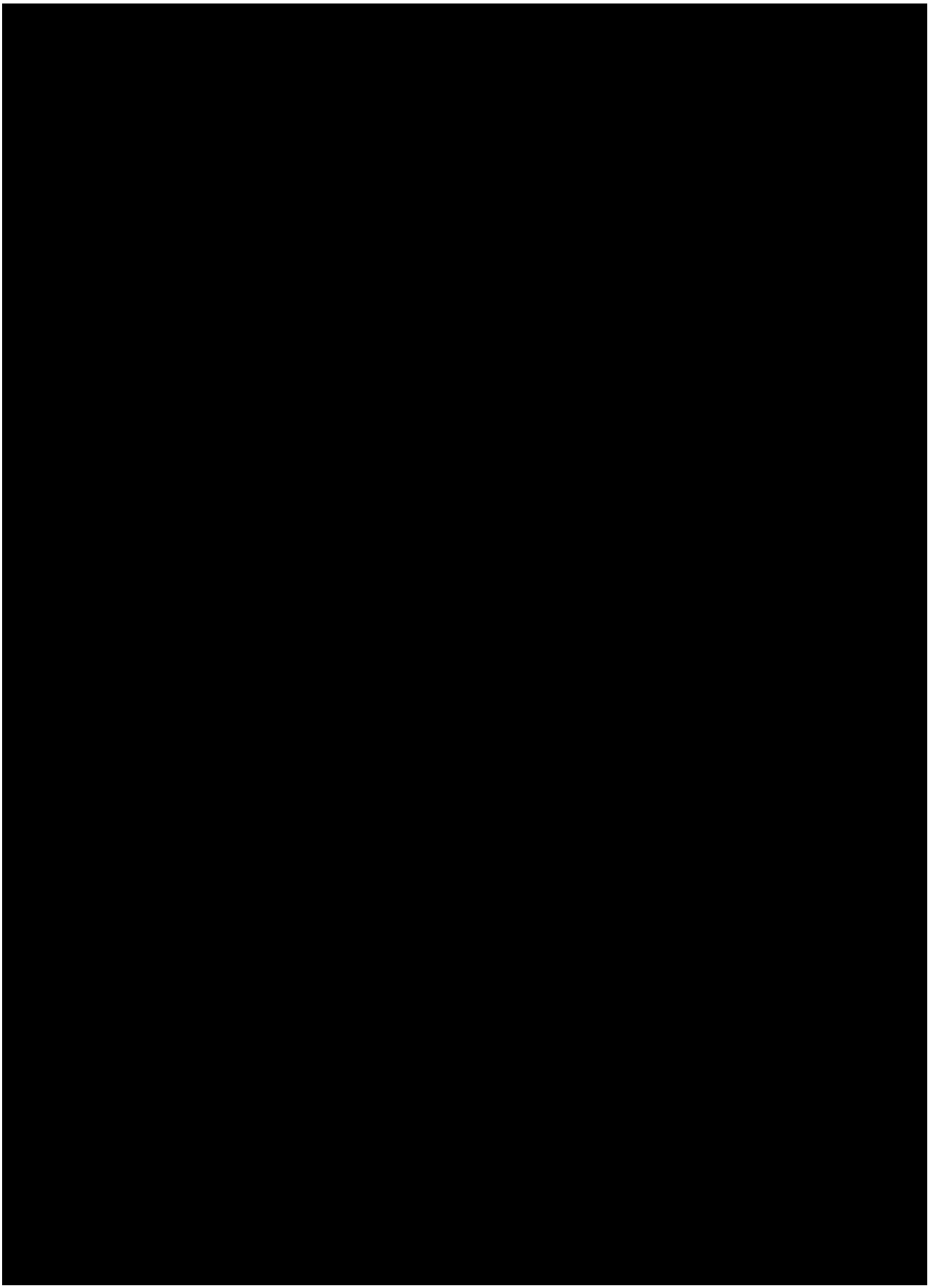

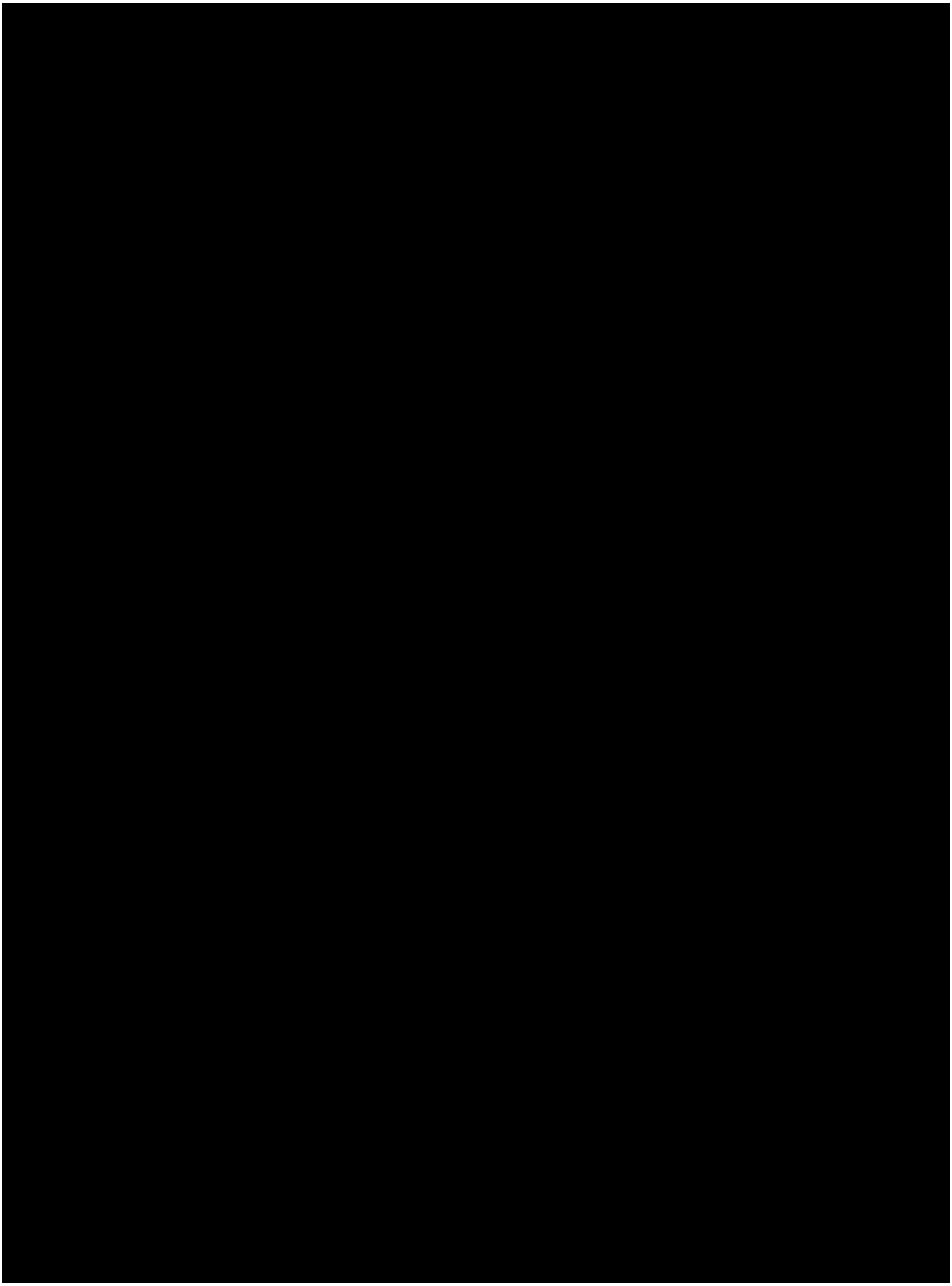

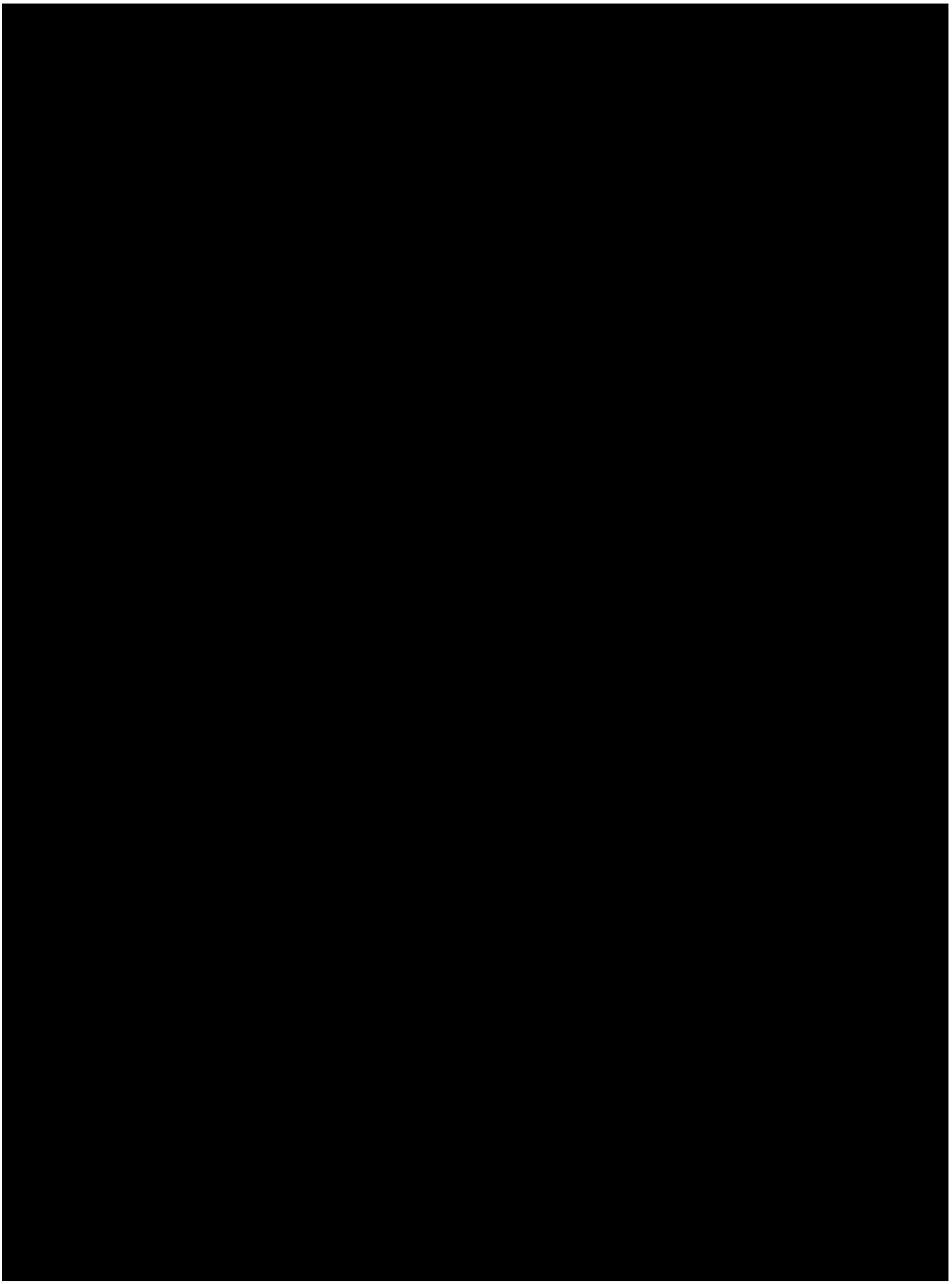

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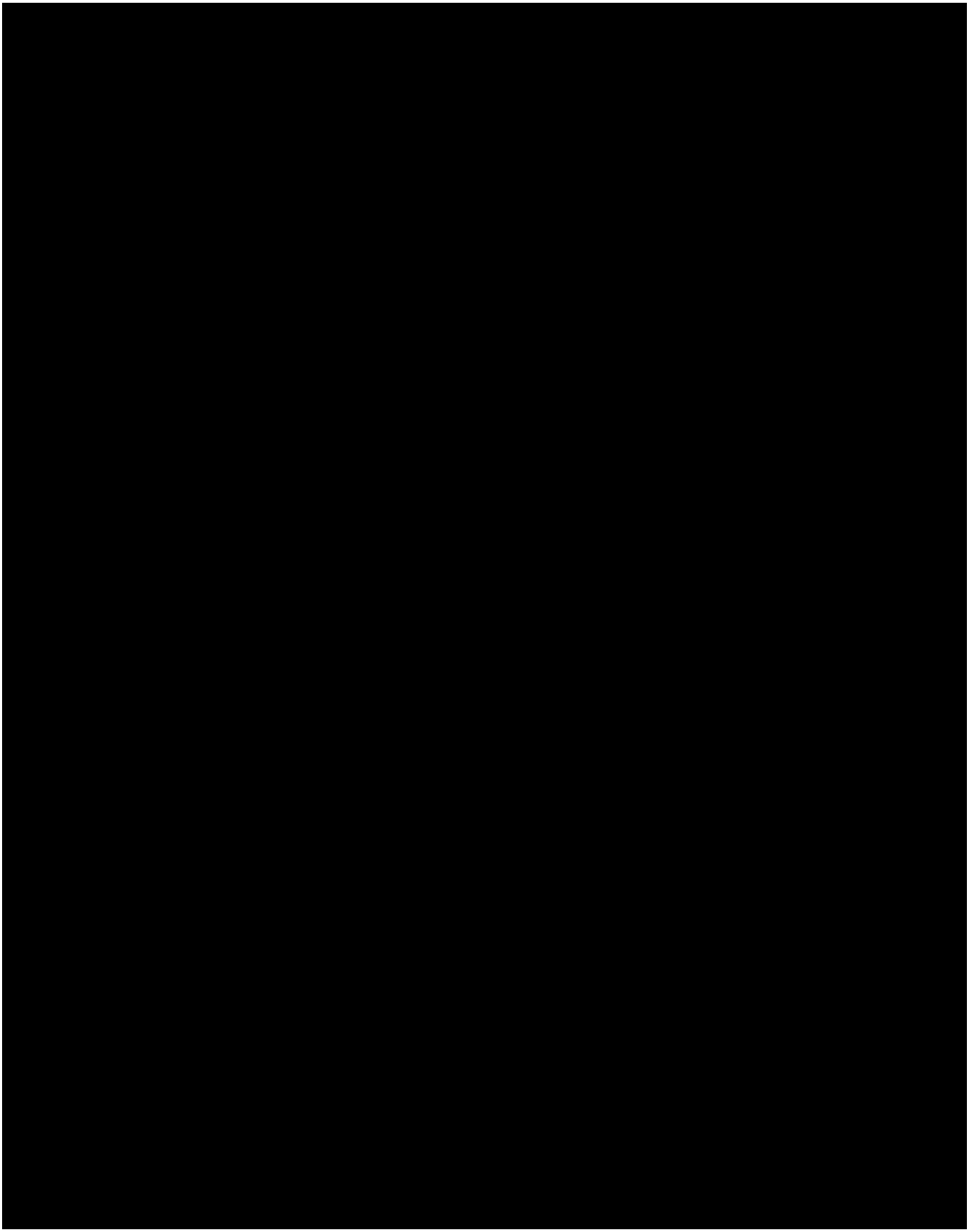

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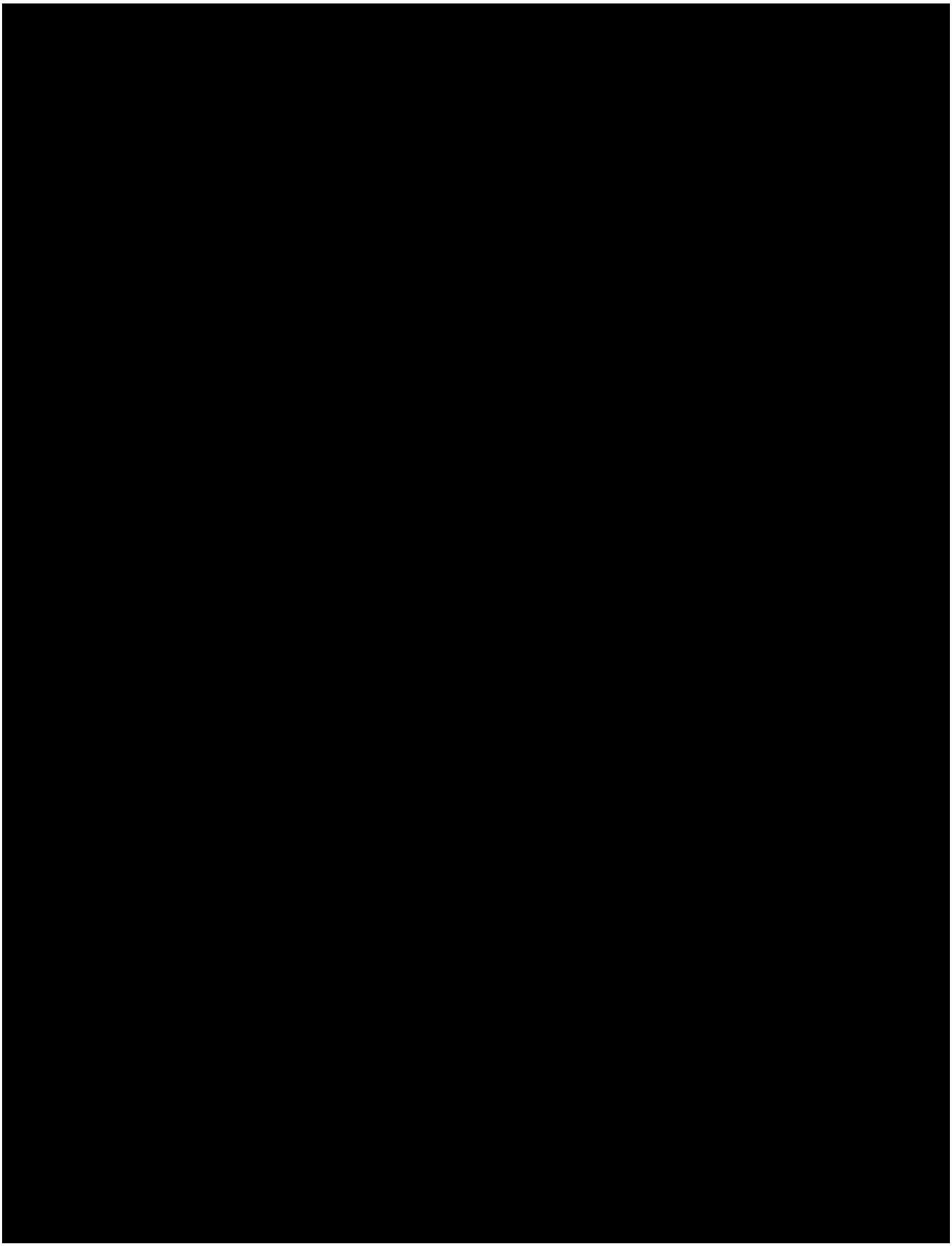

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