A Multicenter, Randomized, Dose-Ranging, Double-Blind, Placebo-Controlled Study to Evaluate Safety and Efficacy of AbobotulinumtoxinA for the Treatment of Moderate to Severe Platysmal Bands

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CLINICAL STUDY PROTOCOL

PROTOCOL NUMBER: 43USD1804

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TITLE PAGE

A Multicenter, Randomized, Dose-Ranging, Double-Blind, Placebo-Controlled Study to Evaluate Safety and Efficacy of AbobotulinumtoxinA for the Treatment of Moderate to Severe Platysmal Bands

CTN: 43USD1804

[redacted]

SPONSOR:

Name: Q-Med AB, a Nestlé Skin Health affiliate
Address: [redacted]
Phone: [redacted]

CONTRACT RESEARCH ORGANIZATION (CRO):

Name: MedTrials, Inc
Address: [redacted]
Phone: [redacted]

SAFETY:
For safety questions, please contact the Sponsor Contact using the details provided in Section 11.9. Serious adverse events (SAEs) and pregnancy report forms should be submitted as described in Sections 7.2.5.2.3 and 7.2.5.2.4.

MEDICAL MONITOR:
For any medical questions related to the clinical study protocol, please contact the Medical Monitor using the details provided in Section 11.9.

This clinical study shall be performed in compliance with the clinical trial agreement (CTA), the clinical study protocol (CSP), ICH-Good Clinical Practice (GCP), and applicable regional and national regulations. The study shall be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki (https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/).

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SYNOPSIS	
Clinical Study Title: A Multicenter, Randomized, Dose-Ranging Double-Blind, Placebo-Controlled Study to Evaluate Safety and Efficacy of AbobotulinumtoxinA for the Treatment of Moderate to Severe Platysmal Bands	
Short Title: abobotulinumtoxinA for the treatment of moderate to severe platysmal bands	
Clinical Study Population:	Male and female subjects, 18 to 65 years of age with moderate to severe platysmal bands
Clinical Study Design:	This is a phase 2, multicenter, randomized, dose-ranging, double-blind, placebo-controlled study in the US to assess the efficacy, safety, and duration of response of abobotulinumtoxinA for the treatment of moderate to severe platysmal bands. [redacted]
[redacted]	[redacted]
Number of Clinical Study Centers (Planned):	Up to 8 centers
Region(s) / Country(ies) Involved (Planned):	US
Clinical Study Duration:	The planned duration of recruitment for each treatment group (from FSFV to LSFV) is approximately 4 months. [redacted]
Duration of Subject Participation:	[redacted]

SYNOPSIS	
Clinical Study Title: A Multicenter, Randomized, Dose-Ranging Double-Blind, Placebo-Controlled Study to Evaluate Safety and Efficacy of AbobotulinumtoxinA for the Treatment of Moderate to Severe Platysmal Bands	
Key Inclusion Criteria:	1. Male or female, 18 to 65 years of age. [redacted] 3. Moderate to severe platysmal bands [redacted] 5. Females of non-childbearing potential (i.e., post-menopausal [absence of menstrual bleeding for 1 year prior to screening, without any other medical reason], or has undergone hysterectomy or bilateral oophorectomy). or Females of childbearing potential with a negative urine pregnancy test at screening and baseline, and agrees to use a highly effective and approved contraceptive method for the duration of the study. [redacted] 6. Time and ability to complete the study and comply with instructions. 7. Understands the study requirements and signed the informed consent form (ICF).
Key Exclusion Criteria:	1. Botulinum toxin treatment of any serotype below the lower orbital rim, in the neck or chest [redacted] 2. Anticipated need for treatment with botulinum toxin of any serotype for any reason during the study (other than the investigational product). 3. Known hypersensitivity to any component of the study product, or allergy to cow's milk protein* (according to the package insert/information). [redacted]

SYNOPSIS

Clinical Study Title: A Multicenter, Randomized, Dose-Ranging Double-Blind, Placebo-Controlled Study to Evaluate Safety and Efficacy of AbobotulinumtoxinA for the Treatment of Moderate to Severe Platysmal Bands

fat to the lower face (i.e., below the subnasale), neck or chest within 24 months [redacted]

23. Treatment with any investigational drug or device within 30 days prior to study treatment. [redacted]

SYNOPSIS

Clinical Study Title: A Multicenter, Randomized, Dose-Ranging Double-Blind, Placebo-Controlled Study to Evaluate Safety and Efficacy of AbobotulinumtoxinA for the Treatment of Moderate to Severe Platysmal Bands

Investigational Product:	AbobotulinumtoxinA [redacted]
Strength/Concentration:	[redacted]
Reconstitution volume:	[redacted]
Dosage (total daily dose):	abobotulinumtoxinA [redacted] abobotulinumtoxinA [redacted] abobotulinumtoxinA [redacted]
Route:	[redacted]
Dose regimen:	[redacted]
Location of treated area:	Platysmal bands
Placebo Product:	Placebo [redacted]
Strength/Concentration:	[redacted]
Reconstitution volume:	[redacted]
Dosage (total daily dose):	[redacted]
Route:	[redacted]
Dose regimen:	[redacted]
Location of treated area:	Platysmal bands
Efficacy Assessment:	[redacted]

SYNOPSIS	
Clinical Study Title: A Multicenter, Randomized, Dose-Ranging Double-Blind, Placebo-Controlled Study to Evaluate Safety and Efficacy of AbobotulinumtoxinA for the Treatment of Moderate to Severe Platysmal Bands	
[redacted]	[redacted]
Study Objective:	The objective of this study is to evaluate the safety and efficacy of a single dose of [redacted] abobotulinumtoxinA, respectively, compared to placebo in the treatment of moderate to severe platysmal bands.
Primary Efficacy Objective and Endpoint:	The primary objective is to evaluate the efficacy of a single dose of [redacted] abobotulinumtoxinA, respectively, compared to placebo in the treatment of moderate to severe platysmal bands. For the primary endpoint, [redacted] will be evaluated using the ILA [redacted] Photographic Scale at maximum contraction at Month 1. [redacted]
Secondary Efficacy Objectives and Endpoints:	[redacted]

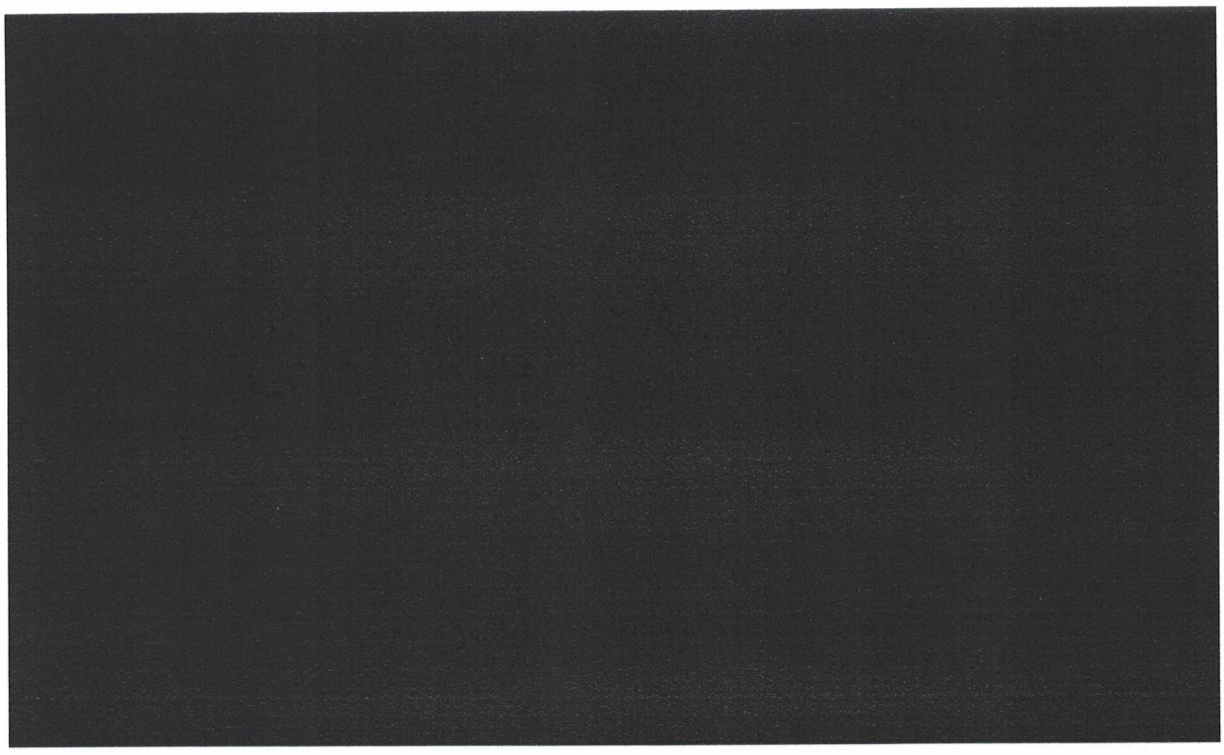
SYNOPSIS	
Clinical Study Title: A Multicenter, Randomized, Dose-Ranging Double-Blind, Placebo-Controlled Study to Evaluate Safety and Efficacy of AbobotulinumtoxinA for the Treatment of Moderate to Severe Platysmal Bands	
[redacted]	[redacted]
Exploratory Efficacy Objectives and Endpoints:	[redacted]
Safety Assessment:	• DSMC review of Month 1 safety data [redacted] • TEAEs • Focused physical examination findings • Vital signs • Jawline and oral commissures safety assessment at rest [redacted]

SYNOPSIS	
Clinical Study Title: A Multicenter, Randomized, Dose-Ranging Double-Blind, Placebo-Controlled Study to Evaluate Safety and Efficacy of AbobotulinumtoxinA for the Treatment of Moderate to Severe Platysmal Bands	
Safety Objectives and Endpoints:	To evaluate the safety of a single dose of [redacted] abobotulinumtoxinA and placebo in the treatment of platysmal bands. Endpoints: • Incidence and severity of treatment emergent adverse events (TEAEs) • Unexpected serious adverse reactions • Incidence of subjects assessed as "worse" at post-treatment visits [redacted] evaluation of the jawline and oral commissures at rest (Investigator assessment)
Other Assessments:	[redacted] • Pregnancy test
Blinding:	This is a double-blind study, therefore the Investigator, sub-Investigator, study center staff, and the subject will not know the subject's study product assignment (i.e., abobotulinumtoxinA or placebo). [redacted]
Principal Statistical Method:	The primary objective will be evaluated using the ILA [redacted] Photographic Scale at maximum contraction at Month 1. [redacted]

SYNOPSIS	
Clinical Study Title: A Multicenter, Randomized, Dose-Ranging Double-Blind, Placebo-Controlled Study to Evaluate Safety and Efficacy of AbobotulinumtoxinA for the Treatment of Moderate to Severe Platysmal Bands	
Sample Size:	The study is planned to enroll approximately 240 subjects, [redacted]
Interim Analysis (IA):	Not applicable. An interim analysis is not planned for this study.

CLINICAL STUDY SCHEMATIC AND FLOW CHART

[redacted]



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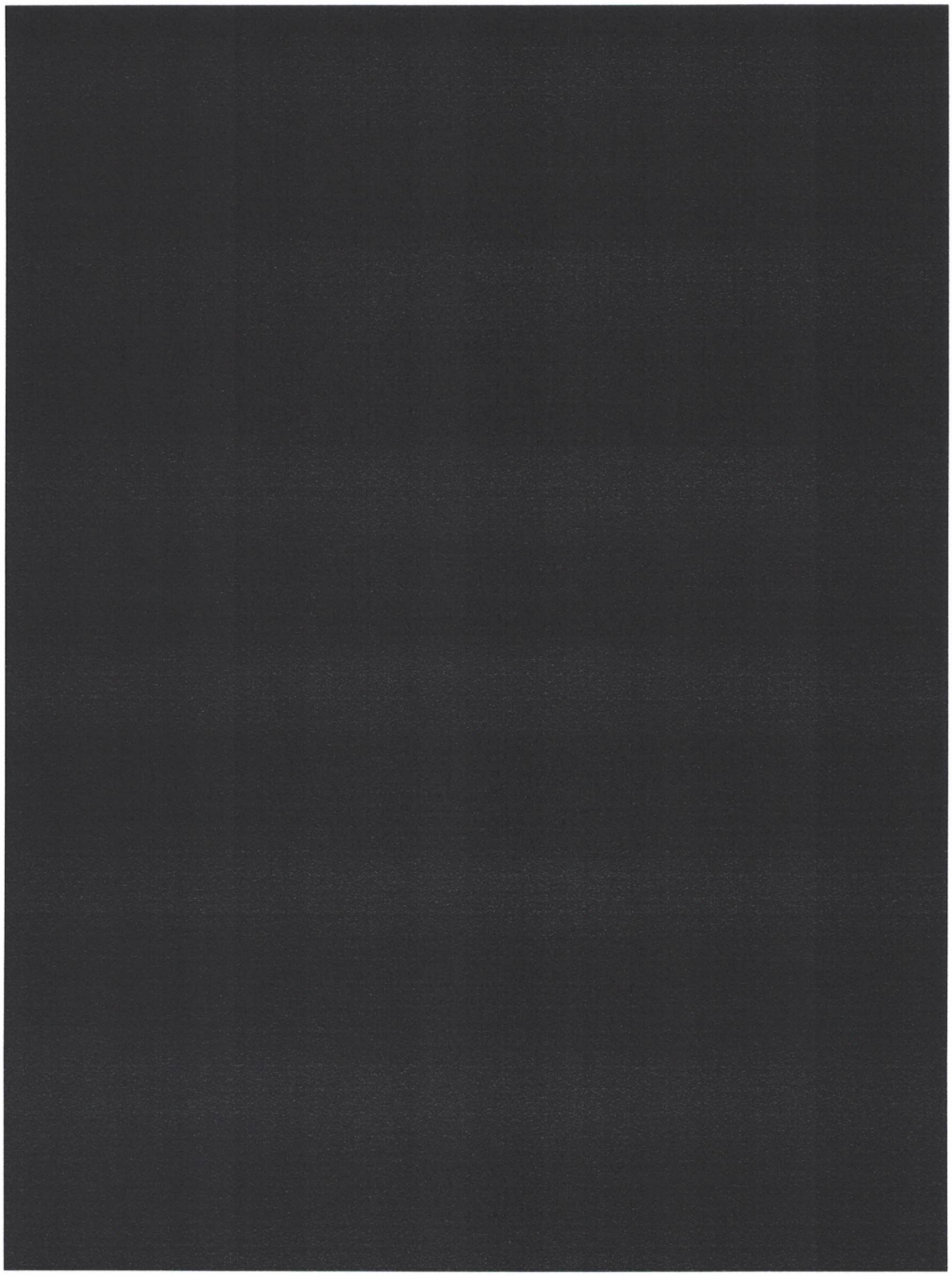

SCHEDULE OF ASSESSMENTS

[redacted]

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
AbobotulinumtoxinA	Commercially available Dysport®
AE	Adverse event
BOCF	Baseline observation carried forward
BoNT	Botulinum Toxin
BoNT-A	Botulinum Toxin Type A
CRF/ eCRF	Case Report Forms/electronic Case Report Forms
CRO	Contract Research Organization
CM	Concomitant Medication
CSP	Clinical Study Protocol
CTA	Clinical Trial Agreement
DMP	Data Management Plan
DSMC	Data and Safety Monitoring Committee
EDC	Electronic Data Capture
ET	Early Termination
EU	European Union
[redacted]	[redacted]
FDA	Food and Drug Administration
FPE	Focused Physical Exam
FSFV	First Subject First Visit (date of first subject included i.e., informed consent signature)
[redacted]	[redacted]
GCP	Good Clinical Practice
GL	Glabellar Lines
HA	Hyaluronic Acid
HIPPA	Health Insurance Portability and Access Act of 1996
HSA	Human serum albumin
IA	Interim analysis
IB	Investigators Brochure
ICF	Informed consent form
ICH	International Council for Harmonization
IEC	Independent Ethics Committee
ILA	Investigator live assessment
IND	Investigational New Drug
IRB	Institutional Review Board
ITT	Intent To Treat
LOCF	Last Observation Carried Forward
LSFV	Last Subject First Visit (date of last subject included i.e., informed consent signature)
LSLV	Last Subject Last Visit (date of last subject's last study visit)
MAH	Marketing Authorization Holder
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple Imputation

mL	Milliliter
N	Number of Observations
NaCl	Sodium chloride
OB	Observed Cases
PB	Platysmal bands
PI	Principal Investigator
PLLA	Poly-L-Lactic acid
PRP	Platelet rich plasma
PMMA	Polymethyl methacrylate acid
PP	Per Protocol
PTs	Preferred Terms
PQC	Product Quality Complaint
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SIN	Subject Identification Number
SOC	System organ class
SSA	Subject self-assessment
SUSARs	Suspected Unexpected Serious Adverse Reactions
TEAE	Treatment emergent adverse event
U	Unit
Mg	Microgram
UPT	Urine Pregnancy Test
US	United States
WHO	World Health Organization

1 BACKGROUND AND RATIONALE

1.1 Medical Background and Short Rationale for the Clinical Study

Botulinum toxin (BoNT) is a potent neurotoxic protein produced by the Gram-positive anaerobic bacterium, Clostridium botulinum. The molecule is produced naturally by these bacteria together with a series of accessory proteins, forming what is termed the "toxin complex". The neurotoxin is the cause of the severe and potentially fatal disease of botulism. In addition, the protein is used in very small quantities as a treatment modality for aesthetic and medical indications often characterized by increased muscle activity. [redacted]

In the early 1990s, patients treated with BoNT-A for blepharospasm were observed to lose their frown lines, and since publishing these observations, the use of BoNT-A in the aesthetic setting has accelerated. Injectable BoNT-A products have been investigated for multiple aesthetic indications in attempts to reverse the appearance of aging, in the facial and neck regions. [redacted] The platysma is a flat, thin muscle located between the superficial and deep cervical fascia. Platysmal bands are thickened vertical pleats extending from the submandibular area to the parasternal region. [redacted]

[redacted]

AbobotulinumtoxinA [redacted] received approval in 2009 for the temporary improvement of moderate to severe glabellar lines.[9] The off-label use of AbobotulinumtoxinA in the management of platysmal bands have been described in published literature using [redacted] divided injection points along platysmal bands [redacted]

[redacted]

The rational for the current study is to evaluate efficacy and safety of [redacted] abobotulinumtoxinA compared to placebo for the treatment of moderate to severe platysmal bands. The aim is to fulfil an unmet need for an approved BoNT-A product in the management of moderate to severe platysmal bands using doses of abobotulinumtoxinA that have shown to be safe and effective in the aesthetic setting from published literature. [redacted]

1.2 Drug Profile

AbobotuliniutoxinA contains a neurotoxin complex that is produced by fermentation of Clostridium botulinum bacteria toxin type A, Hall strain. This haemagglutinin complex is composed of a number of proteins naturally produced along with the toxin which is believed to stabilize it without apparent therapeutic effect in its own right. [redacted]

1.4 Risk/Benefit Assessment

[redacted]

[redacted]

2 CLINICAL STUDY OBJECTIVES, ENDPOINTS, AND CLINICAL HYPOTHESIS

2.1 Clinical Study Objectives

The objective of this study is to evaluate the safety and efficacy of a single dose [redacted] of abobotulinumtoxinA, respectively, compared to placebo in the treatment of moderate to severe platysmal bands.

2.1.1 Primary Efficacy Objectives and Endpoints

The primary objective is to evaluate the efficacy of a single dose [redacted] of abobotulinumtoxinA, respectively, compared to placebo in the treatment of moderate to severe platysmal bands.

For the primary endpoint, the responder rate will be evaluated using the Investigator Live Assessment (ILA) [redacted] Photographic Scale at maximum contraction at Month 1. [redacted]

[redacted]

[redacted]

2.1.4 Safety Objectives and Endpoints

The safety objective is to evaluate the safety of a single dose of [redacted] abobotulinumtoxinA and placebo in the treatment of platysmal bands.

Safety Endpoints include:

- Incidence and severity of TEAEs
- Unexpected serious adverse reactions
- Incidence of subjects assessed as "worse" at post-treatment visits [redacted] for the evaluation of the jawline and oral commissures at rest (Investigator assessment).

2.2 Clinical Hypothesis

The clinical hypothesis of the study is that [redacted] abobotulinumtoxinA is more effective than placebo in the treatment of moderate to severe platysmal bands, and has an acceptable safety profile.

3 OVERALL CLINICAL STUDY DESCRIPTION

This is a phase 2, multicenter, randomized, dose-ranging, double-blind, placebo-controlled study to evaluate safety and efficacy of abobotulinumtoxinA for the treatment of moderate to severe platysmal bands. Approximately 240 subjects, 18-65 years of age will be enrolled in up to 8 centers in the US.

[redacted]

[redacted]

4 CLINICAL STUDY DURATION AND TERMINATION

[redacted]

The planned clinical study duration (from FSFV to LSLV) is approximately 21.5 months. The date of end of the clinical study is defined as the date of the last subject visit.

[redacted]

5 SELECTION AND DISPOSITION OF CLINICAL STUDY POPULATION

5.1 Number of Subjects

Approximately 240 subjects will be enrolled. There will be 3 treatment groups and each treatment group will enroll 80 subjects (60 subjects will be treated with abobotulinumtoxinA, and 20 subjects will be treated with placebo).

5.2 Clinical Study Population Characteristics

In order to be eligible for the clinical study, subjects must fulfill all of the following criteria. These criteria are applicable at both screening and baseline unless otherwise specified.

5.2.1 Inclusion Criteria

1. Male or female, 18 to 65 years of age.

[redacted]

3. Moderate to severe platysmal bands [redacted]

5. Female of non-childbearing potential (i.e., post-menopausal [absence of menstrual bleeding for 1 year prior to screening, without any other medical reason], or has undergone hysterectomy or bilateral oophorectomy).

   or

   Female of childbearing potential with a negative urine pregnancy test at screening and baseline, and agrees to use a highly effective and approved contraceptive method for the duration of the study. [redacted]

[redacted]

6. Time and ability to complete the study and comply with instructions.
7. Understands the study requirements and signed the informed consent form (ICF).

5.2.2 Exclusion Criteria

1. Botulinum toxin treatment of any serotype below the lower orbital rim, in the neck, or in the chest [redacted]
2. Anticipated need for treatment with botulinum toxin of any serotype for any reason during the study (other than the investigational product).
3. Known hypersensitivity to any component of the study product, or allergy to cow's milk protein* (according to the package insert/information).

[redacted]

[redacted]

23. Treatment with any investigational drug or device within 30 days prior to study treatment.

[redacted]

[redacted]

5.3 Medical History

Relevant history of surgical events and medical conditions shall be documented in the electronic case report form (eCRF) using medical terminology.

5.4 Previous and Concomitant Therapies

5.4.1 Definition

Previous therapies are defined as therapies that have been stopped within the 4 weeks preceding the screening visit or within timeframes specified in the inclusion/exclusion criteria.

Concomitant therapies are defined as follows:

- any existing therapies ongoing at the time of the screening visit,
- any changes to existing therapies (such as changes in dose or formulation) during the course of the clinical study, or
- any new therapies received by the subject since the screening visit.

[redacted]

[redacted]

5.5 Procedures/Reasons for Subject Discontinuation

An Investigator may decide to discontinue a subject from the clinical study for safety reasons.

Although the importance of completing the entire clinical study should be explained to the subject by the clinical study personnel, any subject is free to discontinue participation in this clinical study at any time and for whatever reason, specified or unspecified, and without any prejudice. No constraints are to be imposed on the subject, and when appropriate, a subject may be treated with other conventional therapy when clinically indicated.

[redacted]

All discontinuations and the reason for discontinuation are to be documented by the Investigator on the exit form. For discontinuation due to an AE, the AE form is to be completed. The Investigator should also ensure that the subject receives suitable therapy for the AE.

[redacted]

Pregnancies occurring during the screening period are considered screen failures; they should be recorded as such in the eCRF and no pregnancy form is to be completed. In case of a pregnancy occurring after the baseline visit, follow the procedures described in Section 7.2.5.2.4. The subject may remain in the study, but no invasive procedure should be conducted (e.g. no sample taken for lab test).

The Sponsor may also decide to prematurely terminate or suspend a subject's participation in the clinical study.

6 CLINICAL SUPPLIES

Details of the drug composition and excipients are provided in the current Dysport Aesthetic Indications Investigator's Brochure.[13]

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6.1.3 Study Products(s) Description

Table 3 Description and Usage of the Study Products(s)

	Investigational product	Investigational product	Investigational product	Placebo product
Treatment Group	Group 1	Group 2	Group 3	All Groups
Trade Name	Dysport	Dysport	Dysport	N/A
Name of Drug Substance	abobotulinumtoxinA	abobotulinumtoxinA	abobotulinumtoxinA	N/A
Internal Code	N/A	N/A	N/A	Placebo
Pharmaceutical Form	[redacted]	[redacted]	[redacted]	[redacted]
Strength	[redacted]	[redacted]	[redacted]	[redacted]
Packaging	[redacted]	[redacted]	[redacted]	[redacted]
Storage conditions	[redacted]	[redacted]	[redacted]	[redacted]
Reconstitution volume	[redacted]	[redacted]	[redacted]	[redacted]
Dosage	[redacted]	[redacted]	[redacted]	[redacted]
Route	[redacted]	[redacted]	[redacted]	[redacted]
Dose regimen	[redacted]	[redacted]	[redacted]	[redacted]
Location of treated area	Platysmal bands	Platysmal bands	Platysmal bands	Platysmal bands

6.1.4 Subject Identification Number (SIN)

Each study participant who has signed the ICF will be entered into the eCRF system and a subject number will be assigned via the eCRF system. [redacted]

A log/listing should be maintained by each site for all subjects who have signed the ICF. There should be sufficient information to link the eCRF to a study subject's source documents and medical records.

6.1.5 Method of Treatment Assignment

Before starting the study, a randomization list stratified by study center will be generated. When the Investigator has confirmed subject eligibility, the subject will be assigned a study treatment within the Electronic Data Capture (EDC) system.

6.1.6 Kit Number/Randomization Number

A kit number/randomization number, a unique number on the label of the study products, will be assigned to each eligible subject[redacted]

[redacted]

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[redacted]

6.2 Study Products(s) Packaging and Labeling

The labels will be printed in English. The text of the label will detail the information requested by Good Manufacturing Practice and local regulations, and at a minimum include the protocol number, kit number, storage conditions, and an investigational test article disclaimer ("Caution: New Drug - Limited by Federal (or United States) law to investigational use.")

6.3 Supplies Management

6.3.1 Accountability

Upon receipt of the study products(s), the Investigator or designee will maintain accurate records of the study products(s) delivery to the clinical study center, the inventory at the clinical study center, the use by each subject, the reconciliation of all study products(s) received from the Sponsor's designee, and the return to the Sponsor's designee for disposal of unused study products(s).

All study products(s) sent to the Investigator/Institution will be accounted for and no unauthorized use is permitted.

6.3.2 Storage of Study Products(s)

Study products(s) must be stored in a safe and secure area with restricted access, under the storage conditions specified by the Sponsor (see Table 3).

6.3.3 Dispensing and Return

All study product(s) must be inventoried and a record of the dispensing for each subject must be appropriately documented. Any dispensing errors must be reported to the Sponsor/CRO and properly documented.

In the event of early termination/suspension of the clinical study, a rapid recall of study products(s) will be initiated.

6.3.4 Treatment Compliance Management and Record

The treatment is an injection administered by the Investigator. It will be recorded in the eCRF that the injection has been administered. No other measurements of treatment compliance will be made.

6.3.5 Dose Modification

Dose modifications are not permitted.

[redacted]

6.4 Blinding

This is a double-blind, placebo-controlled study in which neither the Investigator, sub-Investigator, study staff, nor the subject will know the subject's study product assignment. Preparation and administration of the study products, abobotulinumtoxinA or placebo, will be completed in exactly the same way.

[redacted]

6.4.1 Verification of Blinding

The Sponsor's staff or designees will assess and verify maintenance of the study blind during the study through routine monitoring visits.

6.4.2 Unblinding During the Clinical Study

Emergency un-blinding during the clinical study may be required for therapeutic or for regulatory reasons (for expedited safety reporting).

A blind-break system will be available for Investigators. In such an emergency, the Investigator will only break the blind for the subject involved.

The Investigator must notify the Sponsor immediately in the event of such an emergency (see contact details in Section 11.9. If possible, the Investigator should notify the Sponsor before breaking the blind in order to discuss this decision with the Sponsor. The Investigator is required to document each case of emergency unblinding, and inform the Sponsor immediately.

7 CLINICAL STUDY ASSESSMENT

7.1 Efficacy Assessments

7.1.1 Investigator Live Assessment using the [redacted] Photographic Scale of Platysmal Band Severity (ILA)

[redacted]

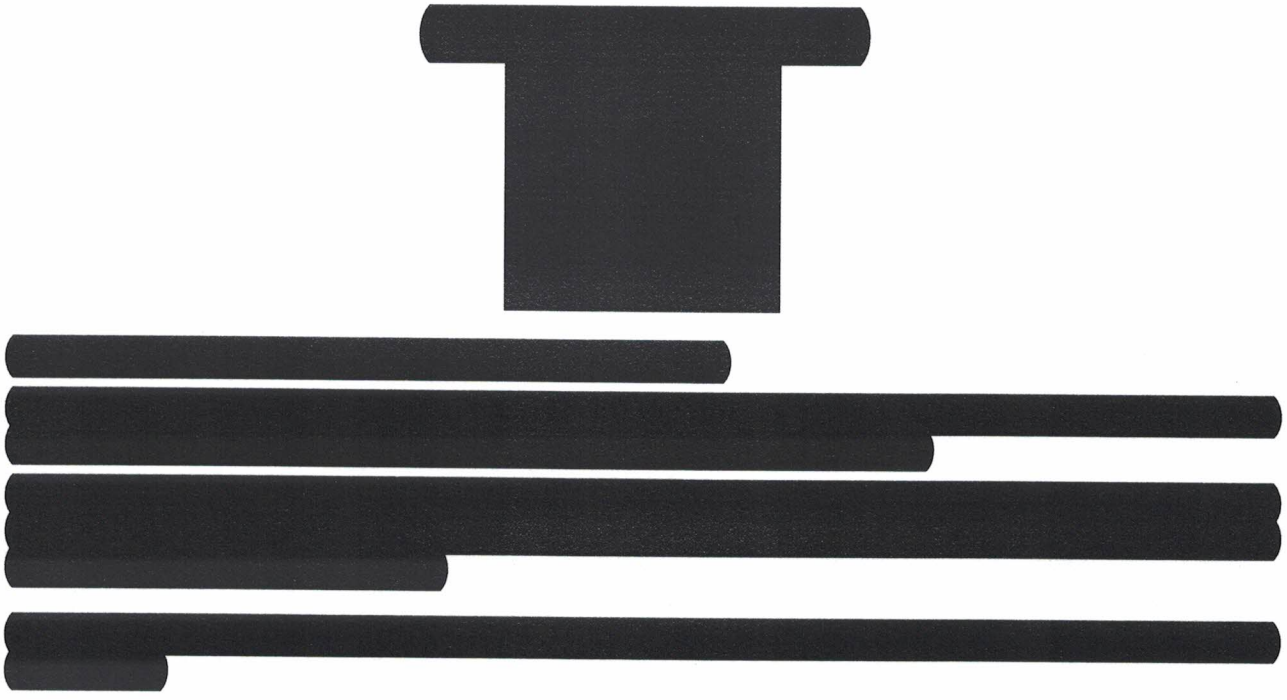
[redacted]

[redacted]

[redacted]

[redacted]

[redacted]



[redacted]

7.2 Safety Assessments

A safety assessment will be conducted for all subjects at the screening visit (from the informed consent signature) and at subsequent visits as outlined in the Schedule of Assessments (Table 2). Safety parameters include an evaluation of safety data by the DSMC, TEAEs, focused physical examination findings, vital signs, jawline and oral commissure safety assessment, and further targeted evaluation of remote spread of toxin effects and events suggestive of hypersensitivity like reactions will be included and reviewed throughout the course of the study.

7.2.1 Data and Safety Monitoring Committee (DSMC)

The un-blinded independent DSMC will be appointed by the Sponsor to include a minimum of three physicians with pertinent botulinum toxin expertise and a biostatistician.

The committee will review safety data after subjects [redacted] complete the Month 1 follow-up visit.

[redacted]

[redacted]

Evaluation of safety data for each dose group will include the following stopping criteria:

[redacted]

The study will discontinue enrollment if evaluation of the Month 1 safety data by the DSMC meets either of the stopping criteria, as outlined above. Further, the DSMC will review the list of AEs, including confirmed AEs of local or remote spread of toxin, to determine if there are safety findings that may result in discontinuation of study enrollment. [redacted]

7.2.2 Focused Physical Examination

At all visits the Investigator or designee will perform a physical examination of the subject that includes the face, head, and neck (Appendix 5).

[redacted]

The Investigator may choose to investigate any other sign that he/she observes during the physical examination and should assess all abnormal findings for clinical significance.

At the screening and baseline visits, record clinically significant and non-clinically significant findings as medical history. Clinically significant abnormal findings at these visits are exclusionary, and the subject should not be enrolled in the study. For any clinically significant changes from the baseline visit, an AE is to be recorded.

7.2.3 Vital Signs

Vital signs will be evaluated at the baseline visit (pre and post-treatment), and at each study visit thereafter [redacted]

Vital signs will include blood pressure, heart rate, and respiratory rate. The subject should be in a seated position and resting for at least 10 minutes prior to taking vital sign measurements.

All pre-treatment abnormal values identified as clinically significant by the Investigator, will be recorded in the medical history.

For any clinically significant changes from pre-treatment values, an AE is to be recorded.

7.2.4 Jawline and Oral Commissure Safety Assessment

[redacted]

7.2.5 Adverse Events

[redacted]

Adverse Events are to be monitored throughout the course of the clinical trial from the time the informed consent form has been signed to the end of the subject's participation. The Sponsor should be informed if the Investigator becomes aware of any unusual safety information or any safety

information that appears to be drug related involving a subject who has participated in a clinical study, even after a subject has completed the clinical study. All AEs are to be reported on the AE form of the eCRF with complete information as required.

If AEs occur, the main concern shall be the safety of the subjects. At the time of the ICF signature, each subject must be provided with the name and phone number of clinical trial center personnel for reporting AEs and medical emergencies.

[redacted]

7.2.5.1 Definitions

7.2.5.1.1 Adverse Events (AE)

According to ICH E2A, an AE is any untoward medical occurrence in a patient or a clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

Thus any new sign, symptom or disease, or any clinically significant worsening of an existing sign, symptom or disease (including new episodes of a chronic disease [e.g., hay fever, allergy]) compared to the condition at the first visit, should be considered as an AE. Lack of efficacy is not considered as an AE.

Notes:

- There should be an attempt to report a diagnosis rather than the signs, symptoms or abnormal laboratory values associated with the report of an AE. However, a diagnosis should be reported only if, in the investigator's judgment, it is relatively certain. Otherwise, symptoms, signs, or laboratory values should be used to describe the AE.
- Pregnancy is not to be considered as an AE; however, is a special situation that must be monitored as described in Section 7.2.5.2.4.
- [redacted]

7.2.5.1.2 Treatment Emergent Adverse Event (TEAE)

A TEAE is an event that emerges during treatment, having been absent pre-treatment, or worsens relative to the pretreatment state.

Investigators are responsible for monitoring, recording, and reporting all AEs that occur during the study as described. TEAEs will be delineated from AEs following database lock.

7.2.5.1.3 Serious Adverse Events (SAE)

A SAE is any untoward medical occurrence that at any dose:

- Results in death,
- Is life-threatening,
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the safety of the subject, and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasia, or convulsions that do not result in hospitalization.

Note: The term "life-threatening" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

Inpatient hospitalization is considered to have occurred if the subject has had to stay for a night at the hospital. The criterion for prolongation of hospitalization is also defined as an extra night at the hospital. Hospitalization may not constitute sufficient grounds to be considered as an SAE if it is solely for the purpose of a diagnostic test(s) (even if related to an AE), elective hospitalization for an intervention that was already planned before subject enrolment in the clinical study, admission to a day-care facility, social admission (e.g., if the subject has no place to sleep), or administrative admission (e.g., for a yearly examination).

7.2.5.1.4 Unexpected Adverse Drug Reaction

An unexpected adverse drug reaction is defined as an adverse reaction, the nature or severity of which is not consistent with the applicable study product information (e.g., Investigator's Brochure for an unapproved investigational product or the medicinal package insert/summary of product characteristics for an approved investigational product).

7.2.5.1.5 Adverse Event Reporting Period

The clinical study period during which AEs must be reported is the period from when the subject signed the ICF to the end of the subject's participation.

The Sponsor should be informed if the Investigator becomes aware of any unusual safety information or any safety information that appears to be drug-related involving a subject who has participated in a clinical study, even after a subject has completed the clinical study.

7.2.5.1.6 Severity

Severity is a clinical determination of the intensity of an AE and not the severity of a disease.

The Investigator is to classify the intensity of AEs using the following definitions as a guideline. For this classification, the Investigator will take into account the possible range of the intensity of the event and report the grade of intensity which is the most appropriate according to his/her medical judgment.

Mild	Awareness of signs or symptom, but easily tolerated.
Moderate	Discomfort, enough to cause interference with usual activity.
Severe	Incapacitating with inability to work or perform usual activity.

7.2.5.1.7 Relationship to the Study Product and/or Clinical Study Procedure

The Investigator is to determine whether there is a reasonable causal relationship between the occurrence of the AE and exposure to the study product and/or clinical study procedure.

Medical judgment should be used to determine the relationship, considering all relevant factors including the pattern of reaction, temporal relationships, relevant medical history, and confounding factors such as co-medication or concurrent diseases.

The expression "reasonable causal relationship" is meant to convey in general that there are facts or arguments to suggest a causal relationship (ICH E2A, Section IIIA 1).

The relationship assessment for an AE is to be completed using the following definitions as a guideline:

Reasonable Possibility:

According to the reporting Investigator, there is a reasonable possibility (i.e., suggestive evidence or arguments) that there is a causal relationship irrespective of the dose administered between:

- The study product (active or placebo) and the AE.
- The clinical study protocol procedure (e.g., bruising or marks from blood draws, injection related trauma, etc.) and the AE.

A two-point scale (Yes or No response) shall be used for the causality assessment. The Investigator shall be asked to indicate a response to each of the following questions in the eCRF:

- "Do you consider that there is a reasonable possibility that the event may have been caused by the study product?", and
- "Do you consider that there is a reasonable possibility that the event may have been caused by the study product injection procedure?"

If any of these questions is answered Yes, the AE is considered related.

No Reasonable Possibility:

No suggestive evidence or arguments can be identified regarding a causal relationship between the study product or the clinical study protocol procedure and the AE.

7.2.5.2 Reporting Procedures

7.2.5.2.1 Procedure for Reporting Adverse Events

The collection of AEs is from the time that a subject signs the ICF to their final visit.

At each post-enrollment visit, the Investigator (or sub-Investigator) will question the subject about AEs using an open non-persuasive question to elicit reporting of AEs, for example "Have you noticed any change in your health since the last visit?" Directed questioning and examination will then be performed as appropriate.

Any AE occurring during the AE reporting period, whether it is related to the study product or not, will be recorded immediately in the source document, and described on the AE form of the eCRF along with the date of onset, severity, relationship to the study product, action taken and outcome, without omitting any requested and known information. Additional information may be requested under certain circumstances.

Adverse Events (AEs) assessed as related to the treatment or study procedure will be monitored until they have resolved or reached a stable condition. Other AEs will be monitored until the last visit if they have not resolved or reached a stable condition.

The Investigator will obtain and maintain in the subject's files all pertinent medical records, information and medical judgment from colleagues who assisted in the treatment and follow-up of the subject. If necessary, the Investigator will contact the subject's personal physician or hospital staff to obtain further details.

For SAEs (see Section 7.2.5.2.3) and pregnancies (see Section 7.2.5.2.4), the Sponsor is to be informed immediately. The event must be reported by e-mail to the Safety email within 24 hours of receipt of the information (contact details in Section 7.2.5.2.3).

7.2.5.2.2 Procedure for Reporting an Adverse Event that may indicate remote spread of toxin effect or a hypersensitivity reaction

Adverse events that may indicate remote spread of toxin or hypersensitivity reactions (Appendix 6) should be reported to the Safety email [redacted] within 24 hours of awareness using the AE Clarification Form.

In case of difficulty to obtain all the required information within 24 hours, an initial report can be submitted with follow up information provided within 24 hours of awareness of the new information.

The following information should be provided on the AE Clarification Form:

- Subject identification (subject number and initials)
- Event description including observed symptoms
- Medical history related to event
- Event onset date and time
- Depth of injections
- Interventions implemented to treat event
- Event outcome (with resolution date and time if applicable)
- Relatedness to study product or procedure
- Seriousness of event
- Study treatment information (number of injections, date of injections, name of product injected, volume injected, etc.)

If the Investigator assesses the AE as serious, an SAE report should be submitted as specified in section 7.2.5.2.3.

Upon receipt of the AE Clarification Form, the Medical Monitor and Sponsor will review the information, assess the event, and report to the IRB and RA as applicable.

7.2.5.2.3 Procedure for Reporting a Serious Adverse Event

For a SAE occurring during the period of the clinical study, regardless of whether it is related to the treatment or not, and of whether it is expected or not, the Investigator must do the following:

1. Take prompt and appropriate medical action, if necessary. The safety of the subject is the first priority.

2. Ensure that the event is classified as an SAE (Section 7.2.5.1.3).

3. Complete the AE form provided in the eCRF as fully as possible.

   Print and complete the SAE form. E-mail the completed form, accompanied by any other relevant information or anonymized medical records (e.g., laboratory test results) within 24 hours of receipt of the information to Safety email listed below. The demographics, medical history, drugs/therapies form, medical and surgical procedures form, and AE pages of the eCRF must be completed and available for review in the EDC system at the time of the report.

4. Immediately send the completed SAE report form to the Safety e-mail:

   [redacted]

5. Monitor and record the progress of the event until it resolves or reaches a clinically stable outcome, with or without sequelae. For all additional follow-up evaluations, send by e-mail all additional follow-up information on the SAE to the Safety email within 24 hours of receipt of the updated information. SAEs will be monitored until the Investigator and Sponsor agree that the event is satisfactorily resolved.

6. Obtain and maintain all pertinent medical records and information in the subject's study file.

7. Inform the Sponsor of the final outcome of the event. Send a revised or updated SAE form and AE form, if appropriate to the Safety email.

8. Prompt notification of SAEs by the Investigator to the Sponsor is essential so that legal obligations and ethical responsibilities towards the safety of subjects are met. The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. The Sponsor will comply with country specific regulatory requirements relating to safety reporting to regulatory authorities, Institutional Review Boards (IRBs), and Investigators. Investigator safety reports are prepared for Suspected Unexpected Serious Adverse Reactions (SUSARs) according to local regulatory requirements and the Sponsor policy and are forwarded to Investigators as necessary. An Investigator who receives an Investigator safety report describing a SAE(s) or other specific safety information (e.g., summary or listing of SAEs) from the Sponsor will file it with the Investigator's Brochure (IB) and will notify the IRB, if appropriate according to local requirements.

9. Comply with the applicable regulatory requirement(s) related to the reporting of SAEs to the IRB.

7.2.5.2.4 Procedure for Reporting Pregnancies

Any pregnancy occurring during the clinical study, where the fetus could have been exposed to the study product, must be monitored until its outcome in order to ensure the complete collection of safety data.

Pregnancies occurring during the screening period are considered as screening failures; they are recorded as such in the eCRF and no pregnancy form is to be completed.

If a subject becomes pregnant after the screening period, the Investigator is to do the following:

1. The subject does not need to be withdrawn from the clinical study, i.e. she may continue to attend the planned study visits, but no invasive procedure should be conducted.

2. Complete the Pregnancy Report – Part A as fully as possible. Send the form within 24 hours of receipt of the information to the Safety email listed above (and in Section 11.9).

3. Monitor and record the progress of the pregnancy until its outcome.

4. Inform the Sponsor of the final outcome of the pregnancy by completing the Pregnancy Report – Part B. Follow-up information should be sent to the Safety email within 24 hours of receipt of the information. If the subject can no longer be reached (lost to follow-up), documentation

of the non-response/contact with two phone calls and a letter (certified with return receipt) is required.

5. If the pregnancy leads to an abortion (voluntary abortion, spontaneous abortion or therapeutic abortion), *in utero* death or congenital anomaly, follow the procedure for declaration of an SAE (see Section 7.2.5.2.3).

7.3 Other Assessments

[redacted]

7.3.2 Pregnancy Test

For all women of childbearing potential, a urine pregnancy test will be performed [redacted] A negative pregnancy test is required for study inclusion. The result will be documented.

7.4 Appropriateness of Measurements

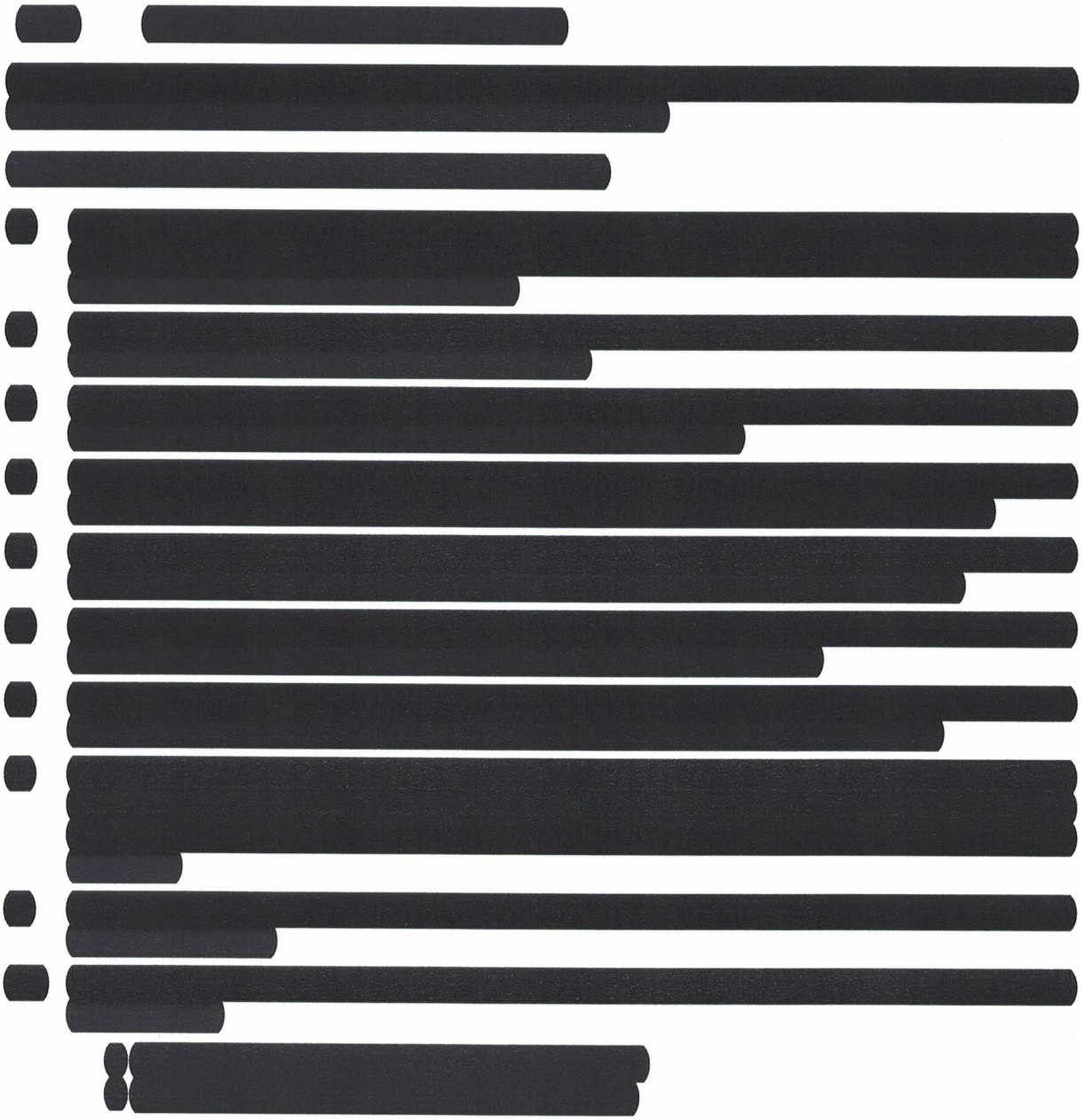
The efficacy and safety measurements used in this study are considered standard measurements, and are generally recognized as reliable, accurate, and relevant. [redacted]

8 CLINICAL STUDY VISITS DESCRIPTIONS AND PROCEDURES

8.1 Description of Clinical Study Visits

Please refer to the Schedule of Assessments table in the Synopsis (Table 2).

A written, signed ICF (inclusive of HIPAA and photo consent) must be obtained prior to performing any clinical study-related evaluations and/or procedures. The subject must be provided with a fully completed, dated, and signed copy.



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9 STATISTICAL METHODS PLANNED

[redacted]

9.1.2.3 Safety Population

The safety population includes all subjects who were administered the study product [redacted]

9.1.2.4 Imputation of Missing Data

The Observed Cases (OC) will be used for all secondary efficacy analyses, safety analyses as well as the exploratory analyses. The primary ITT analysis will be performed using the baseline observation carried forward (BOCF) method for missing values. A sensitivity analysis of the primary endpoint will be performed using multiple imputation (MI) [redacted]

9.1.3 Data Presentation and Graphics

[redacted]

Subject disposition, completion and discontinuation by study visit, protocol deviations, demographics and baseline characteristics, medical history, medical and surgical procedures, prior and concomitant medications, will be summarized by treatment group.

All efficacy variables will be summarized by treatment at each visit. [redacted]

9.1.3.1 Safety Analysis

AEs will be summarized descriptively by treatment group, SOC and PT using number and percentage of subjects with at least one event and number of events. The results will be further broken down by other factors such as severity, causality, seriousness, and whether the event led to discontinuation, and action taken for the event. Duration and time to onset of related AEs will also be presented by treatment group, SOC and PT.

The numbers and percentages of subjects with abnormalities in physical examination will also be summarized, as well as vital signs and safety assessment of jawline and oral commissures. The results of the urine pregnancy tests will be listed.

All AEs will be monitored by the Sponsor to determine if they meet the criteria of remote spread of effect of the toxin or hypersensitivity. A list of preferred terms for these types of events will be provided in the SAP, and will be further analyzed to determine if there is a plausible possibility that they represent distant spread of toxin or hypersensitivity. In order to perform the analysis, variables including alternative etiology (medical history, concomitant medication, or diagnosis which could account for the symptoms), location of Dysport administration, and temporal relationship to Dysport administration will be considered by the Sponsor.

9.1.4 Withdrawals and Deviations

All withdrawn subjects will be listed individually, including at least subject number, date and reason for withdrawal, and last visit performed.

[redacted]

9.2 Sample Size Determination

[redacted]

[redacted]

9.2.3 Sample Size Calculation

[redacted]

Thus, a sample size of 60 in each group is planned to be sufficient to explore the safety and responder rates.

9.2.4 Interim Analysis

Not applicable. An interim analysis is not planned for this study.

10 TRAINING / MONITORING / DATA MANAGEMENT / QUALITY ASSURANCE

10.1 Personnel Training

Investigators and other responsible persons should be documented together with their study responsibilities on a log maintained by the Investigator or designee. Study staff shall provide a curriculum vitae or equivalent, as appropriate.

It is the responsibility of the PI to ensure that all personnel involved in the study are fully informed of all relevant aspects of the study, including detailed knowledge of and documented training in all procedures to be followed.

10.2 Clinical Monitoring

The conduct of the clinical study will be closely monitored by representatives of the Sponsor to verify adherence to the clinical study protocol, ICH-GCP guidelines, and applicable SOPs.

The Investigator will allow the CRO/Sponsor's representatives, to have direct access to all clinical study records, CRFs, corresponding subject medical records, study product(s) dispensing records, and any other documents considered source documentation. Additionally, the CRO/Sponsor representative is to have access to the study product storage area and clinical study facilities.

The Investigator also agrees to assist the representative if required.

10.3 Data Management

Data management based on GCP refers to the activities defined to achieve safe routines to enter clinical data information into a database, efficiently and avoiding errors. The data management routine includes procedures for database set-up and management, data entry and verification, data validation, and documentation of the performed activities including information of discrepancies in the process. The data management process will be described in detail in the data management plan (DMP).

The database, the data entry screens and program will be designed in accordance with the CSP and CRF template. Data validation will be performed by computerized logical checks and manual review. Drugs and events will be coded in accordance with World Health Organization (WHO) Drug and medical dictionary for regulatory activities (MedDRA) dictionaries as specified in the DMP. Safety data (SAE and if applicable AE of special interest) in the clinical database will be reconciled against the data in the safety database.

When all efforts have been made to ensure that the data recorded in the eCRFs and entered in the database is as correct and complete as possible, the clinical database will be locked. Study data will be transferred to SAS datasets, which thereafter will be write-protected. Statistical analyses will be generated in SAS using data from the locked datasets.

10.4 Quality Assurance/Audit/Inspection

The clinical study is conducted under the sponsorship of the Sponsor in compliance with the applicable international and local regulatory requirements as well as applicable ICH guidelines and in accordance with the SOPs for clinical study conduct and monitoring from the Sponsor and/or the Contract Research Organization (CRO).

Audits of clinical study centers may be conducted by the Sponsor/CRO representatives, and inspection may be performed by Regulatory Authority inspectorates or IRBs/IECs before, during, or after the clinical study.

The Investigator will allow and assist the CRO/Sponsor's representatives, IRBs/IECs and any regulatory agency to have direct access to all requested clinical study-related records.

For the audits performed by, or on behalf of, the Sponsor auditors, audit certificate(s) will be provided by Quality Assurance.

[redacted]

[redacted]

11 ETHICS AND GENERAL CLINICAL STUDY CONDUCT CONSIDERATIONS

11.1 Independent Ethics Committee (IEC) or Institutional Review Board (IRB)

This clinical study protocol and all applicable amendments will be reviewed and approved by the appropriate IECs/IRBs.

11.2 Ethical Conduct of the Clinical Study

This clinical study will be conducted in accordance with the protocol, the HELSINKI declaration (1964) and subsequent amendments, and the ICH GCP, and in compliance with applicable regulatory requirements.

11.3 Subject Information and Consent

All subjects who participate in this clinical study are required to be fully informed about the clinical study in accordance with GCPs guidelines, federal regulations, HIPAA, and guidelines and in accordance with local requirements.

The ICF (inclusive of HIPPA and photo consent), approved by an IRB/IEC, will be fully explained to the subject. The subject must agree to photo consent in order to participate in the clinical study.

Prior to enrollment into the clinical study, the subject and the PI or designee must sign and date the consent form(s). The Investigator is responsible for maintaining each subject's consent form(s) in the Investigator's site file and providing each subject with a copy of the signed and dated consent form(s).

11.4 Protection of Personal Data

The completion of the study involves the gathering and processing of Personal Data as specified in the Regulation (EU) 2016/679 on the protection of individuals with regard to the processing of personal data and on the free movement of such data. For the purposes of the study, Sponsor will be considered the Data Controller, and Principal Investigator and Institution will both be considered Data Processors.

All processing of Personal Data must be carried out in accordance with national legislation concerning the protection of Personal Data. The Institution and Principal Investigator are responsible for complying with all requirements pursuant to national legislation in the country in which the Institution and Principal Investigator are located.

The Principal Investigator understands that clinical studies conducted under an IND are exempt from the study subject identifier confidentiality provisions of the Health Insurance Portability and Access Act of 1996 (HIPAA), as provided at CFR § 512(b)(iii), and the study subject should be made aware of this exception in the informed consent. The Sponsor shall, to the extent feasible, protect study subject identifier information.

The Institution and Principal Investigator are jointly responsible for obtaining the appropriate informed consent of each subject for the processing of Personal Data required in order to complete the study. Such consent shall include the consent to the transfer of Personal Data to government authorities located in countries outside the US.

The Institution and Principal Investigator are jointly responsible for providing sufficient information to all subjects to enable them to give their informed consent not only to the participation in the study, but also to the processing of Personal Data. Such information includes information regarding the purposes of the processing, the length of time during which Personal Data will be stored, the right of access to stored Personal Data and the right to correction or purging of incorrect or obsolete Personal Data. A subject may also withdraw his or her consent at any time during or after the study. A subject who withdraws his or her consent to the processing of Personal Data must be considered to have withdrawn from the study but the data collected until the consent was withdrawn may be used in the statistical analyses or to comply with legal or administrative requirements.

All collection, processing and analyses of protected health information, personal data or similar will be conducted in compliance with applicable local, national and international rules, regulations and guidelines.

11.5 Contractual Requirements

A contractual agreement will be signed between the CRO/Sponsor and each Investigator/Institution. This document will contain supplementary information, including financial terms, confidentiality, the clinical study schedule, third party responsibility, and publication rights.

11.6 Data Collection and Archiving

11.6.1 Data Collection

The Investigator must maintain all required records for all subjects. Data for this clinical study will be recorded in the subject's source documents and in the eCRFs provided by the Sponsor. All data should be recorded in the eCRFs completely and promptly.

11.6.2 Source Documentation

The Investigator must keep accurate separate records (other than the eCRFs) of all subject visits, being sure to include all pertinent clinical study-related information. A statement should be made indicating that the subjects have been included in this clinical study and have provided signed written Informed Consent. All AEs must be thoroughly documented.

Results of any diagnostic tests conducted during the clinical study should also be included in the source documentation.

11.6.3 Archives

All pertinent data, samples, photographs, correspondence, and reports, the original or amended clinical study protocol, and all other material relating to the clinical study will be maintained securely in Sponsor/CRO/Investigator/Institution archives for the legally required duration for archiving.

The Investigator/Institution should maintain the essential clinical study documents as specified in Section 8 of ICH-GCP, and according to the applicable regulatory requirements.

The Investigator/Institution should take measures to prevent accidental or premature destruction of these documents.

If the Principal Investigator retires, relocates, or withdraws from the responsibility of keeping the clinical study records for any other reasons, custody must be transferred to a person who will accept the responsibility. The Sponsor/CRO must be notified in writing of the name and address of the new custodian.

11.7 Insurance

A certificate attesting Third Party coverage of CRO/Sponsor will be provided upon request.

[redacted]

[a] Defining the role of authors and contributors, compiled by the International Committee of Medical Journal Editors (ICMJE) (http://www.icmje.org).

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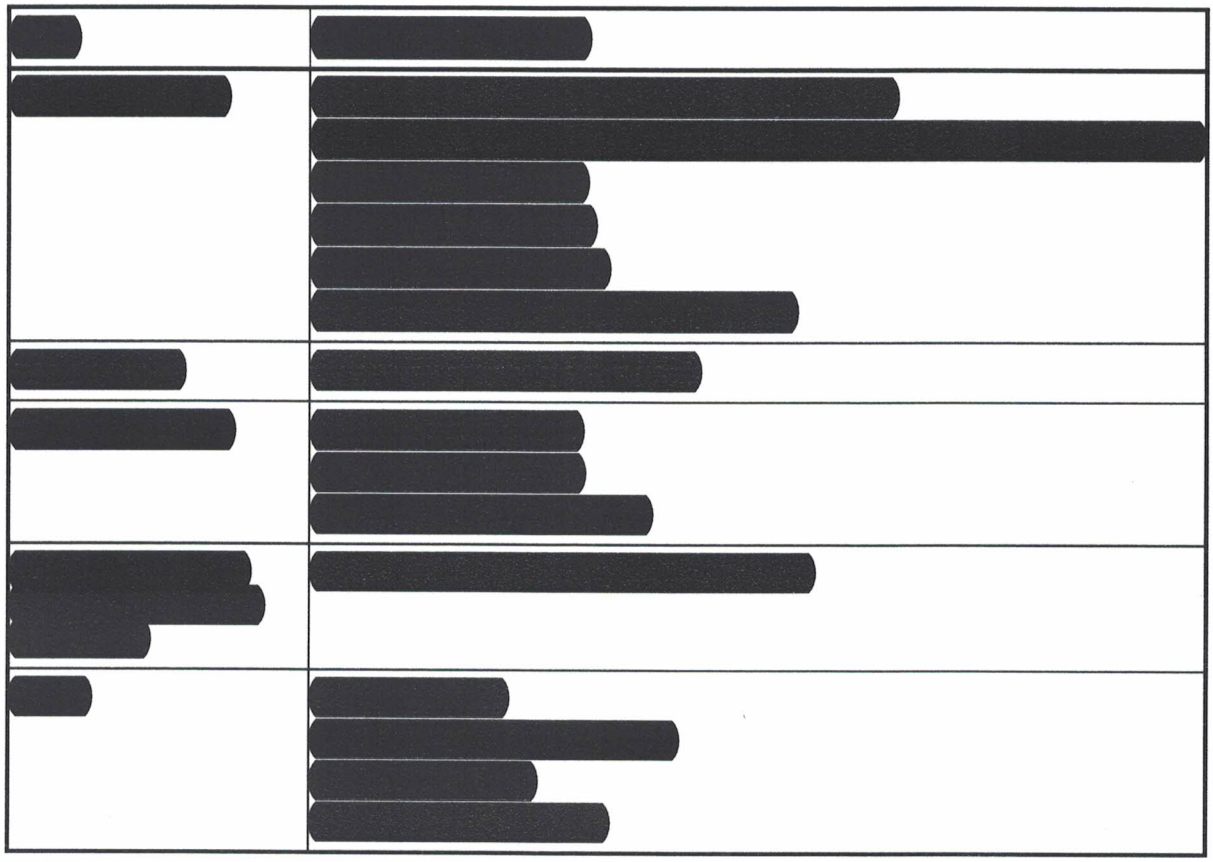

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13 Appendices

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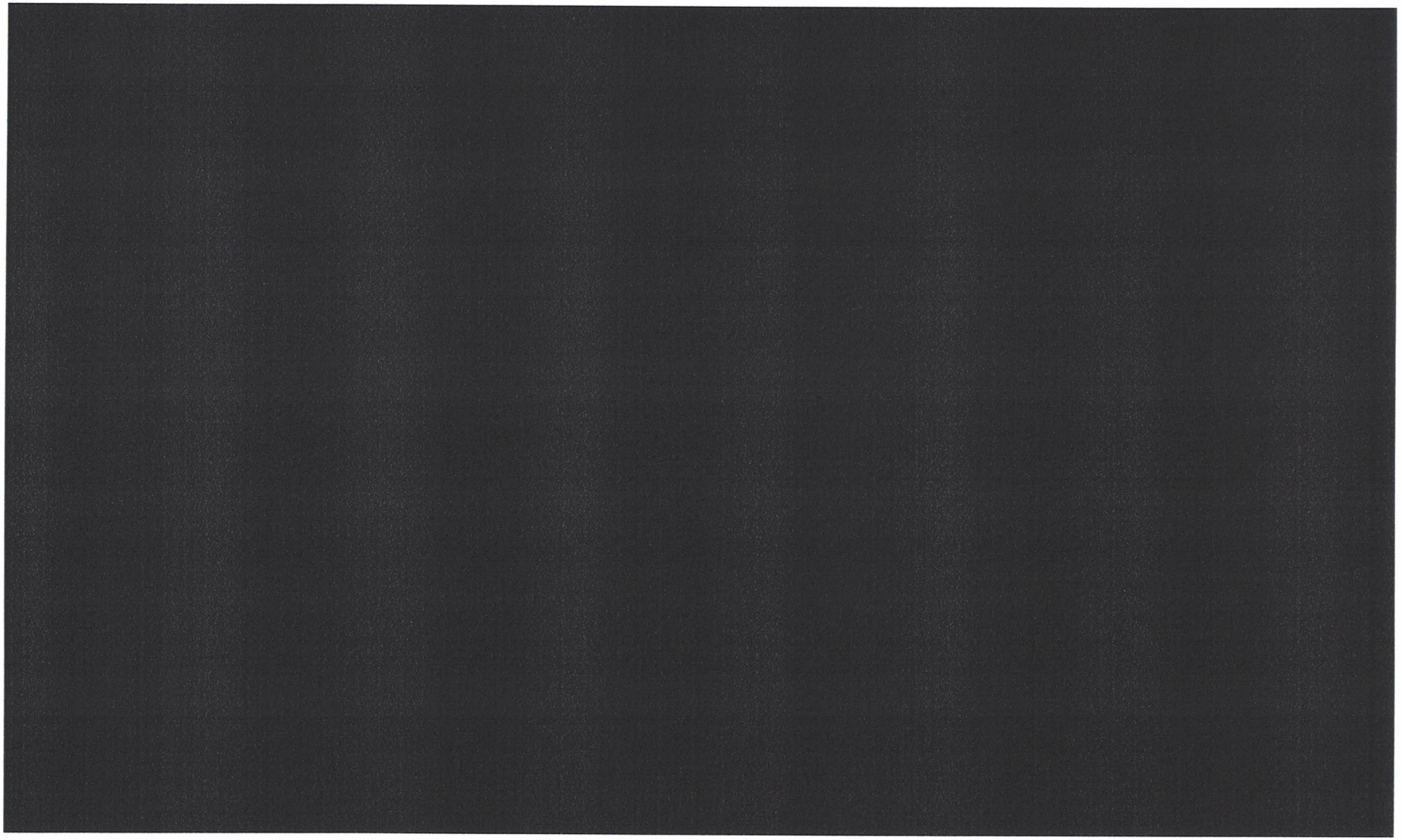

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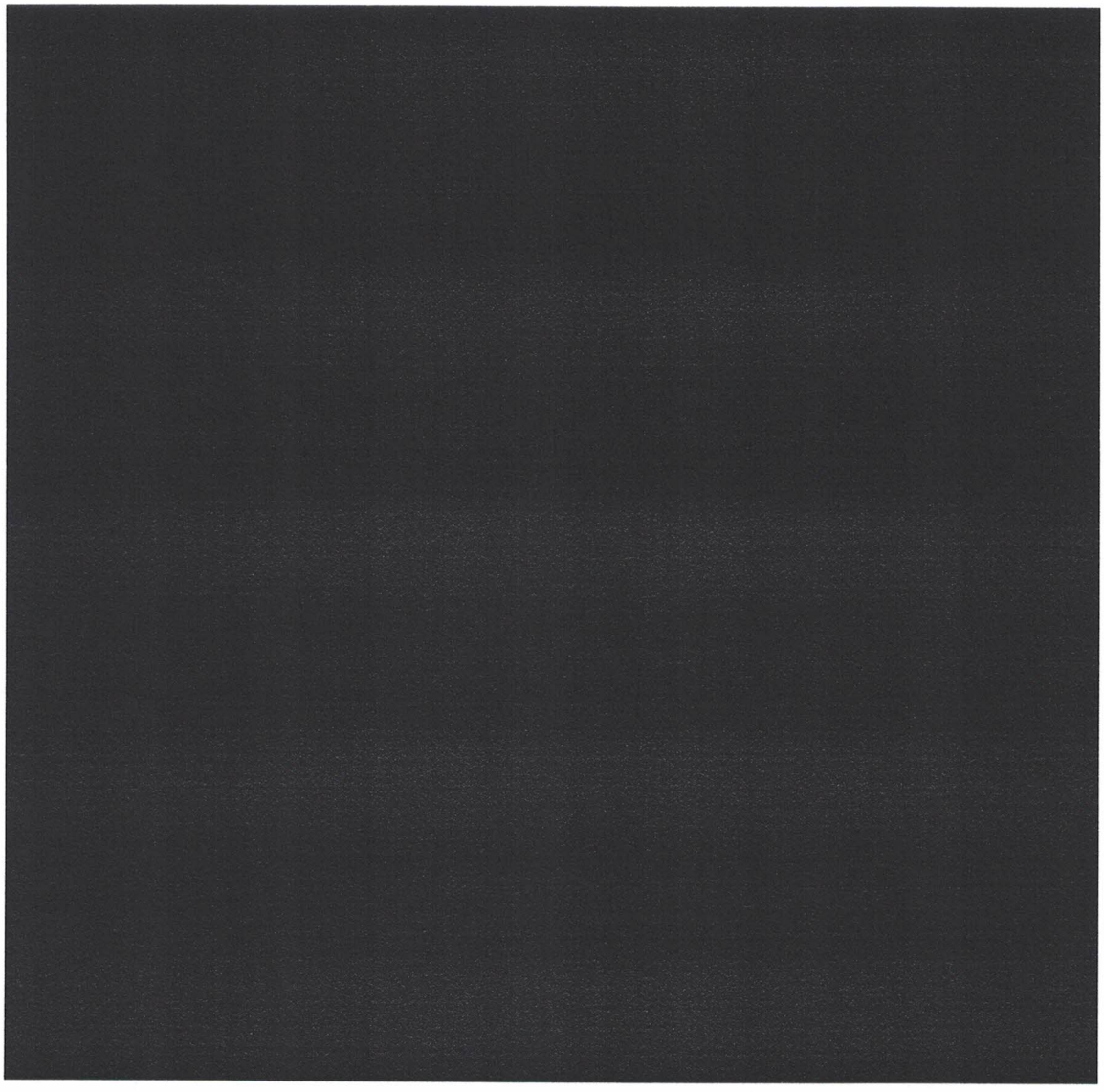

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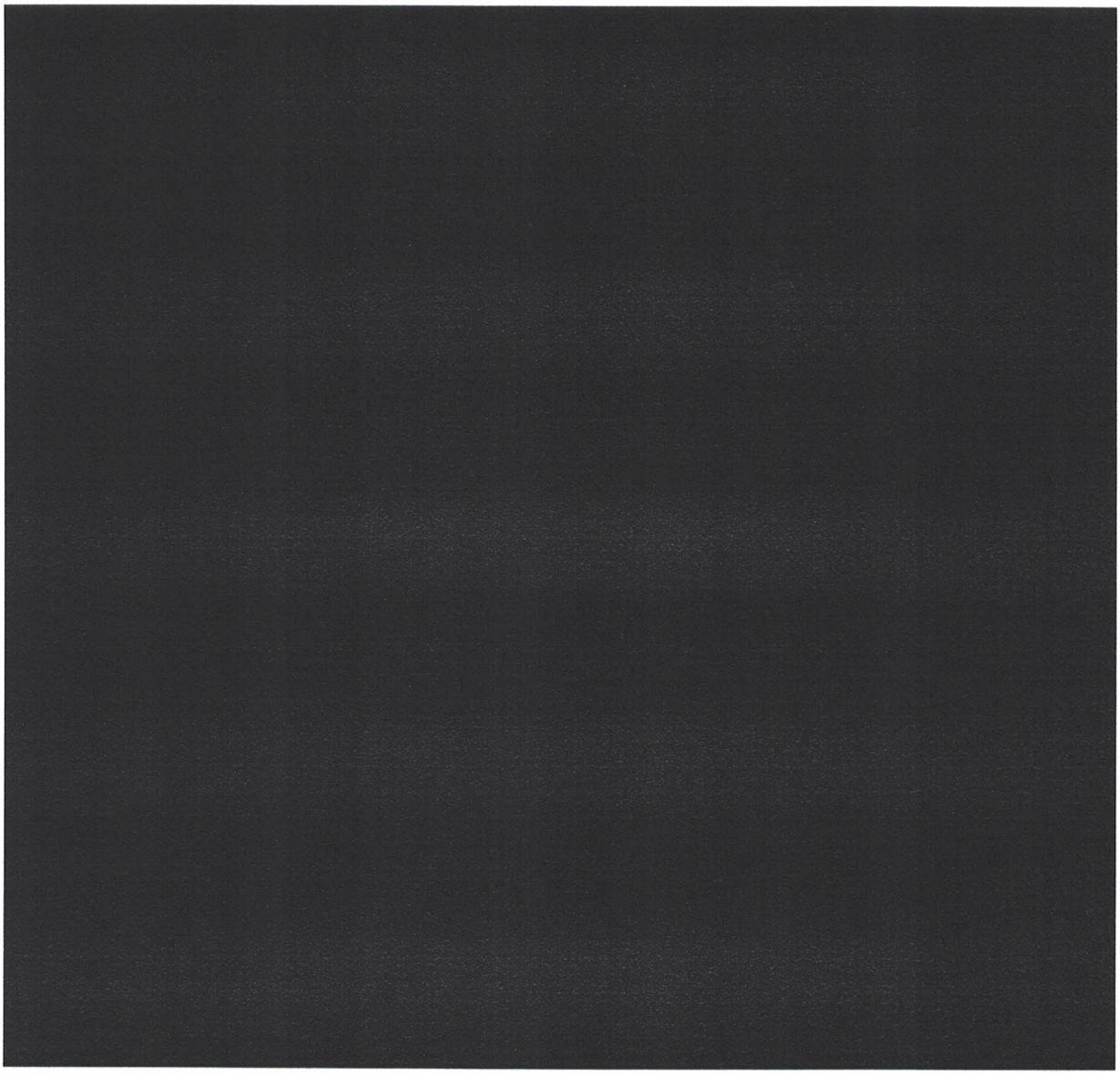

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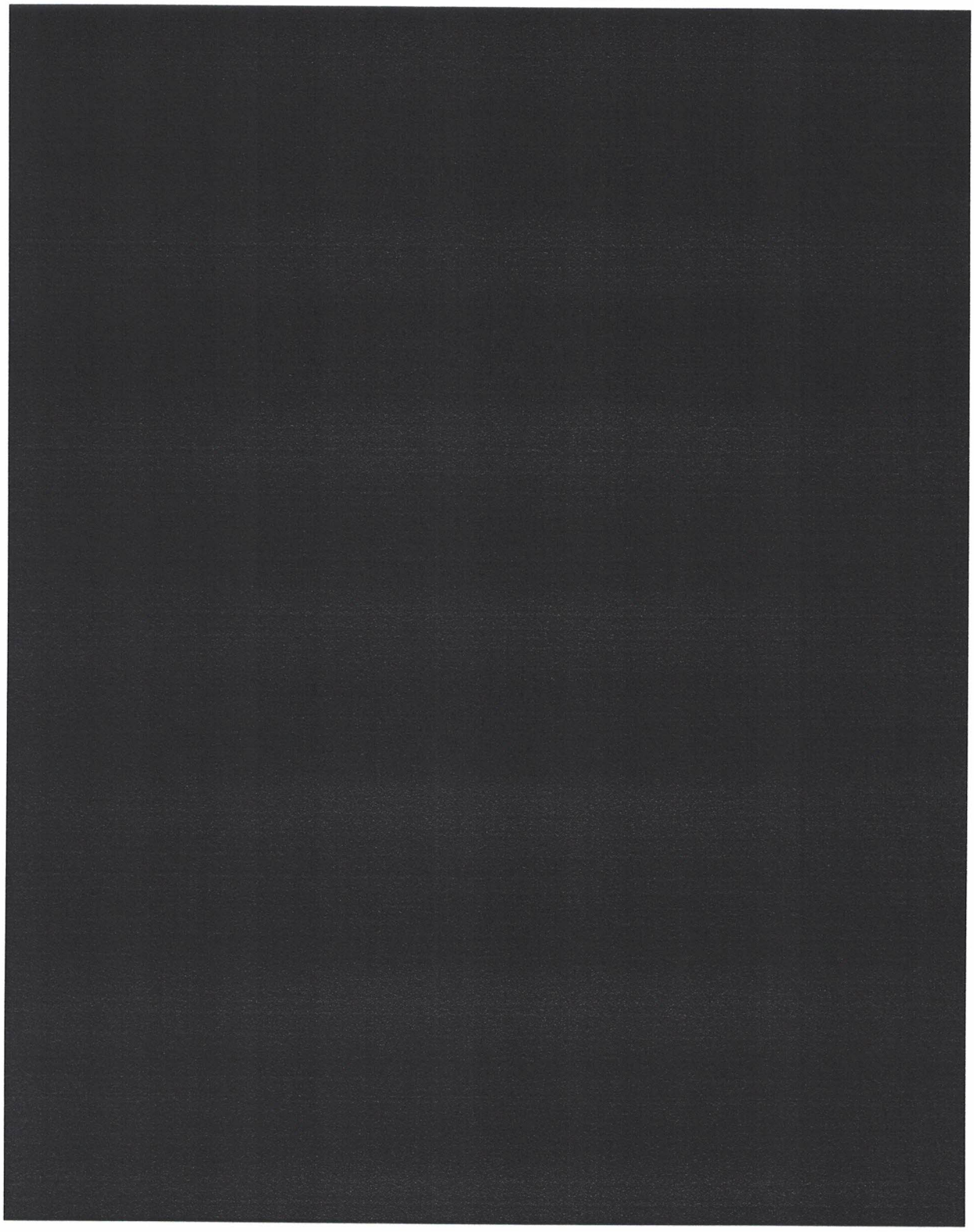

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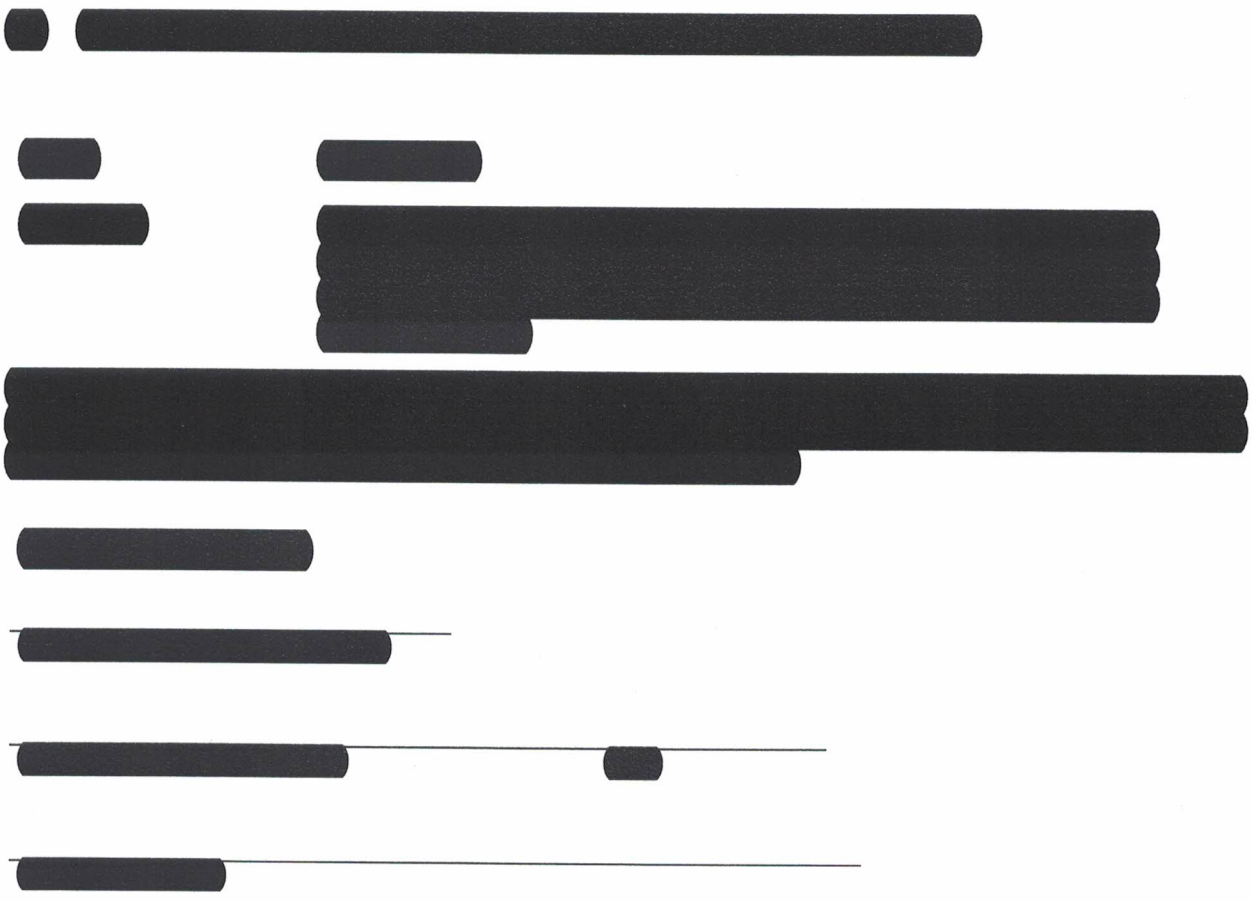

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