


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

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**CLINICAL STUDY PROTOCOL**  
**PROTOCOL NUMBER: 43USD1801**

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## TITLE PAGE

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

**CTN: 43USD1801**

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### SPONSOR:

Name: Q-Med AB, a Nestlé Skin Health affiliate

Address: [REDACTED]

Phone: [REDACTED]

### CONTRACT RESEARCH ORGANIZATION (CRO):

Name: MedTrials, Inc.

Address: [REDACTED]

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### SAFETY:

For safety questions, please contact the Sponsor Contact using the contact details provided in Section 11.9. Serious adverse events (SAEs) and pregnancy report forms should be submitted as described in Sections 7.2.6.2.2 and 7.2.6.2.3.

### MEDICAL MONITOR:

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

This clinical study shall be performed in compliance with the clinical trial agreement (CTA), the 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	
<b>Clinical Study Title:</b> A Multicenter, Randomized, Dose-Ranging, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of AbobotulinumtoxinA for the Treatment of Moderate to Severe Glabellar Lines	
<b>Short Title:</b> AbobotulinumtoxinA for the Treatment of Moderate to Severe Glabellar Lines	
<b>Clinical Study Population:</b>	Male and female subjects, 18 to 65 years of age with moderate to severe glabellar lines at maximum frown.
<b>Clinical Study Design:</b>	<p>This is a phase 2, multicenter, randomized, dose-ranging, double-blind, placebo-controlled, US study to assess the safety and efficacy of abobotulinumtoxinA for the treatment of moderate to severe glabellar lines.</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <ul style="list-style-type: none"> <li>[REDACTED]</li> <li>[REDACTED]</li> </ul> <p>[REDACTED]</p> <ul style="list-style-type: none"> <li>[REDACTED]</li> </ul> <p>[REDACTED]</p> <ul style="list-style-type: none"> <li>[REDACTED]</li> </ul> <p>[REDACTED]</p>
[REDACTED]	[REDACTED]
<b>Number of Clinical Study Centers (Planned):</b>	Up to 15 centers.
<b>Region(s) / Country(ies) Involved (Planned):</b>	US
<b>Clinical Study Duration:</b>	<p>The planned clinical study duration (from first subject first visit [FSFV] to last subject last visit [LSLV]) is approximately 21.5 months.</p> <p>[REDACTED]</p>
<b>Duration of Subject Participation:</b>	[REDACTED]

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SYNOPSIS	
<b>Clinical Study Title:</b> A Multicenter, Randomized, Dose-Ranging, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of AbobotulinumtoxinA for the Treatment of Moderate to Severe Glabellar Lines	
<b>Key Inclusion Criteria:</b>	<ol style="list-style-type: none"><li>1. Male or female, 18 to 65 years of age.</li><li>2. Moderate to severe glabellar lines [REDACTED] [REDACTED] [REDACTED] [REDACTED]</li><li>4. 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 enrollment in the study. [REDACTED] [REDACTED]<ul style="list-style-type: none"><li>• [REDACTED]</li><li>• [REDACTED]</li><li>• [REDACTED]</li><li>• [REDACTED]</li><li>• [REDACTED]</li><li>• [REDACTED]</li><li>• [REDACTED]</li><li>• [REDACTED]</li></ul></li><li>5. Time and ability to complete the study and comply with instructions.</li><li>6. Understands the study requirements and signed the informed consent form (ICF).</li></ol>
<b>Key Exclusion Criteria:</b>	<ol style="list-style-type: none"><li>1. Botulinum toxin treatment in the face [REDACTED]</li><li>2. Anticipated need for treatment with botulinum toxin of any serotype for any reason during the study (other than the investigational product).</li><li>3. Known allergy or sensitivity to any component of the study product, or allergy to cow's milk protein. [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED]</li></ol>

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SYNOPSIS	
<b>Clinical Study Title:</b> A Multicenter, Randomized, Dose-Ranging, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of AbobotulinumtoxinA for the Treatment of Moderate to Severe Glabellar Lines	
<b>Investigational Product:</b>	AbobotulinumtoxinA / Dysport
<b>Strength/Concentration:</b>	
<b>Reconstitution volume:</b>	
<b>Dosage (total daily dose):</b>	
<b>Route:</b>	
<b>Dose regimen:</b>	
<b>Location of treated area:</b>	Glabellar region
<b>Investigational Product:</b>	AbobotulinumtoxinA / Dysport
<b>Strength/Concentration:</b>	
<b>Reconstitution volume:</b>	
<b>Dosage (total daily dose):</b>	
<b>Route:</b>	
<b>Dose regimen:</b>	
<b>Location of treated area:</b>	Glabellar region
<b>Investigational Product:</b>	AbobotulinumtoxinA / Dysport
<b>Strength/Concentration:</b>	
<b>Reconstitution volume:</b>	
<b>Dosage (total daily dose):</b>	
<b>Route:</b>	
<b>Dose regimen:</b>	
<b>Location of treated area:</b>	Glabellar region
<b>Placebo Product:</b>	Placebo
<b>Strength/Concentration:</b>	
<b>Reconstitution volume:</b>	
<b>Dosage (total daily dose):</b>	
<b>Route:</b>	
<b>Dose regimen:</b>	
<b>Location of treated area:</b>	Glabellar region
<b>Efficacy Assessment:</b>	<ul style="list-style-type: none"> <li>Efficacy assessments include:</li> </ul>

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For the primary endpoint, [REDACTED] will be evaluated using the ILA [REDACTED] Photographic Scale and the SSA Static [REDACTED] Categorical Scale at maximum frown at Month 1. [REDACTED]

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SYNOPSIS	
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	<p>[REDACTED]</p> <p>• [REDACTED]</p> <p>• [REDACTED]</p> <p>• [REDACTED]</p> <p>[REDACTED]</p> <p>• [REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p>

SYNOPSIS	
<b>Clinical Study Title:</b> A Multicenter, Randomized, Dose-Ranging, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of AbobotulinumtoxinA for the Treatment of Moderate to Severe Glabellar Lines	
<b>Safety Assessment:</b>	<p>Safety assessment include:</p> <ul style="list-style-type: none"> <li>• DSMC review of Month 1 safety data</li> <li>• TEAEs</li> <li>• Laboratory safety tests (clinical chemistry and hematology)</li> <li>• Focused physical examination (PE)</li> <li>• Vital signs</li> <li>• Neutralizing antibodies test against abobotulinumtoxinA</li> </ul>
<b>Safety Objective and Endpoints:</b>	<p>The safety objective of the study is to evaluate a single dose of [REDACTED] abobotulinumtoxinA compared to placebo in the treatment of glabellar lines.</p> <p>Endpoints:</p> <ul style="list-style-type: none"> <li>• Incidence and severity of treatment emergent adverse events (TEAEs)</li> <li>• New and unexpected serious adverse reactions</li> <li>• Neutralizing antibody production</li> </ul>
<b>Other Assessments:</b>	<p>Other assessments include:</p> <ul style="list-style-type: none"> <li>• [REDACTED]</li> <li>• Pregnancy test</li> </ul>
<b>Blinding:</b>	<p>This is a double-blind study in which neither the Investigator, sub-Investigator, study center staff, nor the subject will know the subject's study product assignment (i.e., abobotulinumtoxinA or placebo).</p> <p>All treatments will be prepared by a staff member at each study center (other than the Investigator administering the study medication) who will not take part in the treatments or assessments in the study. [REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p>
<b>Principal Statistical Method:</b>	<p>The primary objective will be evaluated using the ILA [REDACTED] Photographic Scale and the SSA Static [REDACTED] Categorical Scale at maximum frown at Month 1.</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>Safety data will be analyzed descriptively using standard methods.</p>
<b>Sample Size:</b>	<p>The study is planned to enroll approximately 400 subjects [REDACTED]</p>

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Thus, a sample size of 80 in each group is planned to be sufficient to explore the safety and responder rates over time.

**Interim Analysis (IA):**

[REDACTED]				
[REDACTED]				
[REDACTED]				
[REDACTED]				
[REDACTED]				
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]				

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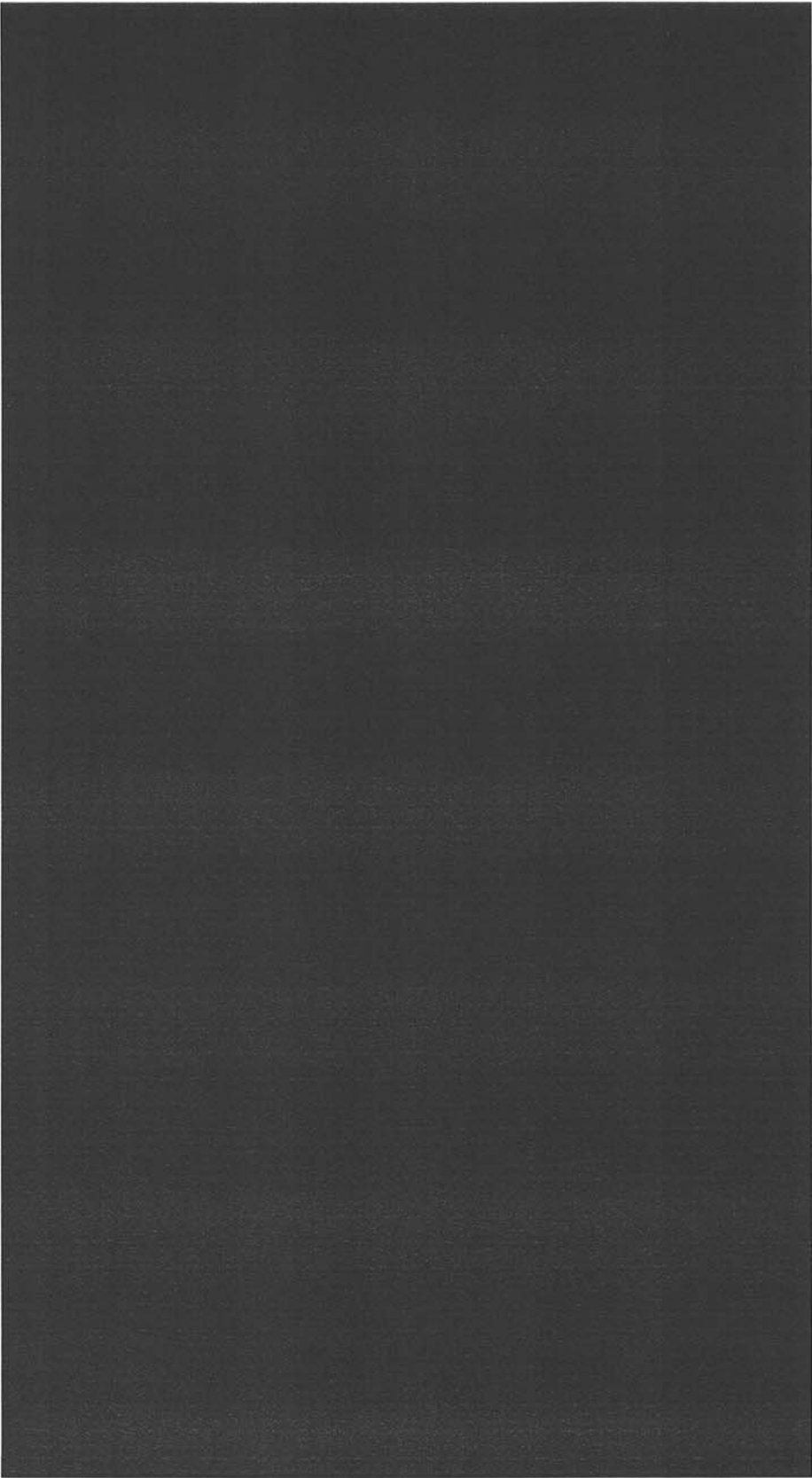
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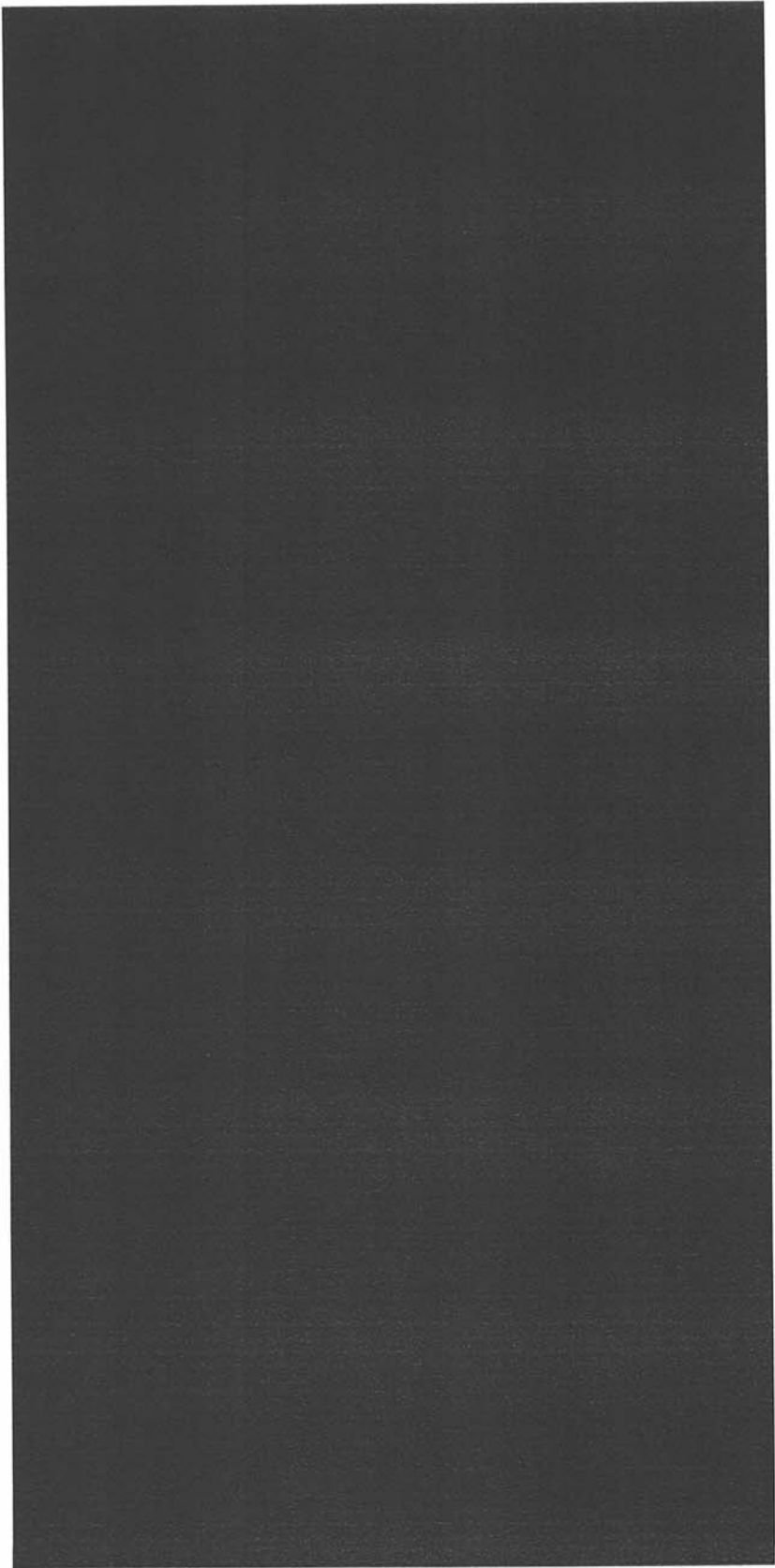
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## LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS


<i>Abbreviation</i>	<i>Term</i>
°C	Degrees Celsius
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT/ALAT (SGPT)	Alanine Aminotransferase (Serum Glutamic Pyruvic Transaminase)
approx	Approximately (or use 'about', not C. or ca.)
AST/ASAT (SGOT)	Aspartate Aminotransferase (Serum Glutamic Oxaloacetic Transaminase)
BP	Blood Pressure
bpm	Beats per Minute
BoNT	Botulinum Toxin
BoNT-A	Botulinum Toxin Type A
CA	Competent Authorities
CDMS	Clinical Data Management System
CI	Coordinating Investigator
CM	Concomitant Medication
CPM	Clinical Project Manager
CRA	Clinical Research Associate
CRF/eCRF	Case Report Forms/electronic Case Report Forms
CRO	Contract Research Organization
DC	Discontinuation
DMP	Data Management Plan
DSMC	Data Safety Monitoring Committee
e.g.	For Example (Latin: exempli gratia)
ET	Early Termination
etc	Et cetera
FDA	Food and Drug Administration
FL	Forehead Lines
FSFV	First Subject First Visit (date of first subject included i.e., informed consent signature)
GCP	Good Clinical Practice
GL	Glabellar Lines
GGT	Gamma Glutamyl Transferase
Hb	Hemoglobin
Hct	Hematocrit
HIPAA	Health Insurance Portability and Accountability Act of 1996
HR	Heart Rate
IA	Interim analysis
IB	Investigator's Brochure

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<i>Abbreviation</i>	<i>Term</i>
ICF	Informed Consent Form
ICH	International Council for Harmonisation
ID	Identity
i.e.	That is (Latin: id est)
IEC	Independent Ethics Committee
IND	Investigational New Drug
IRB	Institutional Review Board
ITT	Intent-to-treat
IUD	Intrauterine Device
LCL	Lateral Canthal Lines
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)
MD	Medical Doctor
ME	Medical Expert
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple Imputations
mL	Milliliter
N or n	Number
N/A	Not Applicable
NaCl	Sodium Chloride
OTC	Over-the-Counter
p	Page(s)
PE	Physical Examination
PP	Per-Protocol
PR	Pulse Rate
PQC	Product Quality Complaint
RBC	Red blood cell
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SIN	Subject Identification Number
SOC	System Organ Class
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TOC	Table of Contents
TEAE	Treatment-emergent Adverse Event
U	Units

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<i>Abbreviation</i>	<i>Term</i>
UPT	Urine Pregnancy Test
US	United States
USP	United States Pharmacopeia
WBC	White Blood Cell

## 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, many of which are characterized by increased muscle activity. [REDACTED]

In the early 1990s, patients treated with BoNT-A for blepharospasm were observed to lose their frown lines,<sup>1,2</sup> 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, especially in the facial region.<sup>1</sup> [REDACTED]

AbobotulinumtoxinA (Dysport) was approved by the United States Food and Drug Administration (FDA) in 2009. AbobotulinumtoxinA is indicated for the temporary improvement in the appearance of moderate to severe GL associated with procerus and corrugator muscle activity in adult patients less than 65 years of age. [REDACTED]

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[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

The rational for the current study is to evaluate efficacy and safety of [REDACTED] abobotulinumtoxinA compared to placebo. In addition, the aim is for a prolonged duration of effect, which is a key unmet need in current BoNT-A therapy that would reduce the frequency of injections and may be a significant advantage likely to enhance patient satisfaction.

## 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 stabilise it but which has no apparent therapeutic effect in its own right. [REDACTED]

[REDACTED]

[REDACTED]

## 1.3 Risk/Benefit Assessment

[REDACTED]

[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 of [REDACTED] abobotulinumtoxinA, respectively, compared to placebo in the treatment of moderate to severe glabellar lines.

#### 2.1.1 Primary Efficacy Objectives and Endpoints

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 glabellar lines.

For the primary endpoint, the [REDACTED] responder rate will be evaluated using the ILA [REDACTED] Photographic Scale and the SSA Static [REDACTED] Categorical Scale at maximum frown at Month 1.

[REDACTED]

#### 2.1.2 [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

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[REDACTED]

- [REDACTED]
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[REDACTED]

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[REDACTED]


- [REDACTED]
- [REDACTED]

[REDACTED]

- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]

[REDACTED]

- [REDACTED]
- [REDACTED]

 GALDERMA	Title <b>43USD1801 Clinical Study Protocol Dysport</b> [REDACTED]	Doc id [REDACTED]
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[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

### 2.1.3 Safety Objectives and Endpoints

The safety objective is to evaluate a single dose of [REDACTED] abobotulinumtoxinA compared to placebo in the treatment of glabellar lines.

Safety endpoints include:

- Incidence and severity of TEAEs
- New and unexpected serious adverse reactions
- Neutralizing antibody production

### 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 glabellar lines, 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 assess the safety and efficacy of abobotulinumtoxinA in the treatment of moderate to severe glabellar lines. Approximately 400 subjects, 18-65 years of age will be enrolled at up to 15 centers in the US.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

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[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

#### 4 CLINICAL STUDY DURATION AND TERMINATION

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 visit of the last subject.

[REDACTED]

[REDACTED]

[REDACTED]

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- [REDACTED]
19. Receipt of any investigational drug or device within 30 days prior to study treatment, from a previous clinical study.
- [REDACTED]
- [REDACTED]
- [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

#### 5.4.2 [REDACTED]

- [REDACTED]
- [REDACTED]

- [REDACTED]

#### 5.4.3

[REDACTED]

[REDACTED]

[REDACTED]

#### 5.4.4

[REDACTED]


#### 5.4.5

[REDACTED]

- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]

[REDACTED]

[REDACTED]

 GALDERMA	Title <b>43USD1801 Clinical Study Protocol Dysport</b>	Doc id [REDACTED]
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## 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]

- [REDACTED] [REDACTED]
- [REDACTED] [REDACTED]
- [REDACTED] [REDACTED]
- [REDACTED] [REDACTED]

[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 7.2.6.2.3. 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

### 6.1 Clinical Supply Identification and Use

Details of the drug composition and excipients are provided in the current Dysport Aesthetic Indications Investigator's Brochure.<sup>10</sup>

#### 6.1.1 [REDACTED]

[REDACTED]

[REDACTED]

#### 6.1.2 [REDACTED]

[REDACTED]

[REDACTED]

### 6.1.3 Study Products(s) Description


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

	Investigational product	Investigational product	Investigational product	Investigational product	Placebo product
Trade Name	Dysport	Dysport	Dysport	Dysport	N/A
Name of Drug Substance	abobotulinumtoxinA	abobotulinumtoxinA	abobotulinumtoxinA	abobotulinumtoxinA	N/A
Internal Code	N/A	N/A	N/A	N/A	Placebo
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Location of treated area	Glabella region	Glabella region	Glabella region	Glabella region	Glabella region

### 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]

[REDACTED]

 GALDERMA	Title 43USD1801 Clinical Study Protocol Dysport [REDACTED]	Doc id [REDACTED]
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All subjects who have signed the ICF should be listed. Sufficient information to link the eCRF to the medical records should be recorded on the Subject Identification Log. The Subject Identification Log shall only be available at the center, both throughout and after the study.

For the duration of the entire study, the subject will be identified using the subject number for all documentation and discussion.

**6.1.5 Method of Treatment Assignment**

Before starting the study, a randomization list stratified by gender will be generated. Female subjects will be further stratified by center; male subjects will not be further stratified by center due to the small number of males expected in the study. When the Investigator has confirmed that all inclusion criteria and no exclusion criteria are met, each subject will be allocated a study product by the Integrated Response Technology (IRT) system.

**6.1.6 Kit Number/Randomization Number**

Each kit will have a unique number on the label of the study product, and will have accompanying instructions as to how many units are to be administered to the subject [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

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## 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 designated staff member (see Section 6.4) 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 used and 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 by the designated staff member (see Section 6.4). 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.

**6.3.6** [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

**6.4 Blinding**

This is a double-blind study in which neither the Investigator, sub-Investigator, study center staff, nor the subject will know the subject's study product assignment (i.e., abobotulinumtoxinA or placebo).

All treatments will be prepared by a staff member at each study center (other than the Investigator administering the study medication) who will not take part in the treatments or assessments in the study.

[REDACTED]

[REDACTED]

[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 7.2.6.2.2). 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 on the appropriate form (provided by the Sponsor) and e-mail the completed form to the Safety Mailbox immediately.

7 CLINICAL STUDY ASSESSMENT

7.1 Efficacy Assessments

7.1.1 [REDACTED] Photographic Scale of Glabellar Line Severity

[REDACTED]

[REDACTED]

7.1.2 Static [REDACTED] Categorical Scale

[REDACTED]

[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]

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[REDACTED]	

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

## 7.2 Safety Assessment

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 DSMC, TEAEs, laboratory testing (chemistry and hematology), focused physical examination findings, vital signs, and neutralizing antibody production.

### 7.2.1 Data 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.

Evaluation of safety data will include [REDACTED] the following stopping criteria:

- [REDACTED]
- [REDACTED]

The study will discontinue enrollment if evaluation of the safety data by the DSMC meets 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) and advise the Sponsor of safety finding that may result in discontinuation of study enrollment. [REDACTED]

[REDACTED]

[REDACTED]

### 7.2.2 Focused Physical Examination

[REDACTED]  
Investigator or designee will perform a physical examination of the subject that includes the face, head, and neck. Further details are provided in Appendix 4.

[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.

Clinically significant abnormal findings at the screening visit and baseline visits are exclusionary, and the subject should not be enrolled in the study. If the abnormality is not clinically significant, capture it as medical history.

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 [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. Vital signs are to be taken prior to any blood draw, excluding baseline post-treatment measurements.

All abnormal values at the screening visit identified as clinically significant by the Investigator, will be recorded in the medical history.

For any clinically significant changes from the screening visit, an AE is to be recorded.

### 7.2.4 Laboratory Safety Tests

The following laboratory safety tests shall be performed [REDACTED]  
[REDACTED]

- Hematology: White blood cell (WBC) count with differential, red blood cell (RBC) count, haemoglobin (Hb), hematocrit (hct), and platelet count (Plt)
- Blood chemistry: Creatinine, urea nitrogen, gamma glutamyl transferase (GGT), alkaline phosphatase (ALP), aspartate aminotransferase (AST=SGOT), alanine aminotransferase (ALT=SGPT), and bilirubin (total and conjugated)

The Investigator or a medically qualified sub-Investigator must review and evaluate laboratory values for each subject in a timely manner. The Investigator or designee will initial and date all laboratory reports and note directly on the report whether or not each out of range laboratory value is clinically significant. An out of range laboratory value should be considered as clinically significant if either of the following conditions is met:

- The abnormality suggests a disease and/or organ toxicity.
- The abnormality is of a degree that requires additional active management, e.g. close observation, more frequent follow-up assessments, or further diagnostic investigation.

For each out of range laboratory result, the Investigator or designee will assess for clinical significance.

All clinically significant out-of-range laboratory values for blood samples collected at baseline will be recorded in the medical history. All clinically significant out of range laboratory values for blood samples collected after baseline are to be reported as an AE if this abnormality was not present at the baseline visit or is assessed as having worsened since the baseline visit (i.e., there is a significant change from baseline). In instances when a laboratory abnormality is reported, the Investigator is to provide a diagnosis rather than reporting individual laboratory abnormalities, whenever possible. See Section 7.2.6.1.1 for additional details.

A summary of sample volumes and the number of blood samples will be included in a Laboratory Manual.

#### 7.2.5 Neutralizing Antibody Testing

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

#### 7.2.6 Adverse Events

AEs are to be monitored throughout the course of the clinical study from the time the informed consent form has been signed. 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 study center personnel for reporting AEs and medical emergencies.

### 7.2.6.1 Definitions

#### 7.2.6.1.1 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 an important medical event that must be monitored as described in Section 7.2.6.2.3.

#### 7.2.6.1.2 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.

#### 7.2.6.1.3 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).

#### 7.2.6.1.4 *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).

#### 7.2.6.1.5 *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.

#### 7.2.6.1.6 *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.

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

#### 7.2.6.1.7 *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.

### 7.2.6.2 *Reporting Procedures*

#### 7.2.6.2.1 *Procedures 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, and outcome, without omitting any requested and known information. Additional information will 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 7.2.6.2.2) and pregnancies (see Section 7.2.6.2.3), the Sponsor is to be informed immediately by e-mail. The event must be reported by e-mail to the Safety Mailbox within 24 hours of receipt of the information (contact details in Section 7.2.6.2.2).

#### 7.2.6.2.2 *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 7.2.6.1.3).
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 Mailbox 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 Mailbox via e-mail and discuss further actions to be taken.

[REDACTED]

[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 Mailbox 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 in his/her files all pertinent medical records, information, and medical judgments from colleagues who assisted in the treatment and follow-up of the subject. If necessary, contact the subject's personal physician or hospital staff to obtain further details.
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 Mailbox.
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.

#### 7.2.6.2.3 *Procedures 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 (e.g. no sample taken for lab test).
2. Complete the Pregnancy Surveillance form – Part I: History and Start of Pregnancy as fully as possible. Send by e-mail this pregnancy form along with the exit form (if applicable) within 24 hours of receipt of the information to the Safety Mailbox listed above (and in Section 11.9).
3. Monitor and record the progress of the pregnancy until its outcome. Contact the subject's regular physician (general practitioner or gynecologist) or hospital staff to obtain further details and ask regular follow-up information.
4. Inform the Sponsor of the progress by tri-monthly updates until the final outcome of the pregnancy by completing the Pregnancy Surveillance form – Part I. For all the additional evaluations, send by e-mail the additional follow-up information to the Safety Mailbox 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. At the outcome of the pregnancy, complete the Pregnancy Surveillance form – Part II: Course and Outcome of Pregnancy, as fully as possible. Inform the Sponsor by sending this pregnancy form to the Safety Mailbox within 24 hours of receipt of the information.
6. 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 7.2.6.2.2).

### 7.3 Other Assessments

[REDACTED]

#### 7.3.2 Pregnancy Test

For all women of childbearing potential, a urine pregnancy test will be performed at screening, baseline (prior to treatment), and at the Month 9/early termination visit. 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]

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## 9 STATISTICAL METHODS PLANNED

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### 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 safety analyses as well as the exploratory analyses. The primary and secondary efficacy ITT analysis will be performed using baseline observation carried forward (BOCF), and repeated using multiple imputation (MI) for missing values. If deemed necessary, any analyses may be repeated using OC, BOCF, or MI as appropriate.

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### 9.1.3 Data Presentation and Graphics

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]

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#### **9.1.3.1 Safety Analysis**

A summary of all AEs will be provided, which will include:

- number of subjects who did not have an AE
- number of subjects with at least one AE and number of events
- number of subjects with at least one TEAE and number of events
- number of subjects with at least one related TEAE and number of events
- number of subjects with at least one TEAE by causality
- number of subjects with at least one TEAE by maximum intensity
- number of subjects with at least one TEAE leading to discontinuation
- number of subjects with at least one serious TEAE.

All TEAEs, treatment emergent SAEs, TEAEs by maximum intensity, TEAEs by causality, TEAEs by maximum intensity and causality, and TEAEs leading to discontinuation will be summarized by SOC and PT including number of subjects with at least one event, percentages, and number of events. All related TEAEs will also be summarized by time to onset and duration.

Data for hematology, blood chemistry, antibodies, and vital signs will be summarized by descriptive statistics with the value at each visit as well as the change from baseline. Shift tables for out of normal ranges results will be presented for hematology, blood chemistry and antibodies. The numbers and percentages of subjects with abnormalities in physical examination and vital signs will also be summarized. The results of the urine pregnancy tests will be listed.

#### **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.

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## 9.2 Sample Size Determination

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The study is planned to include approximately 400 subjects; 80 will be treated in each dose group [REDACTED]

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Thus, a sample size of 80 in each group is planned to be sufficient to explore the safety and responder rates over time.

#### 9.2.4 Interim Analysis

[REDACTED]

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[REDACTED]

[REDACTED]

## 10 TRAINING / MONITORING / DATA MANAGEMENT / QUALITY ASSURANCE

### 10.1 Personnel Training

Investigators and other responsible persons should be listed together with their function on the study on the signature and delegation log. 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

All data management procedures will be detailed in a Data Management Plan (DMP).

The DMP will describe the Clinical Data Management System (CDMS) that will be used to collect data (either EDC or paper CRF), and whether the data management activities are performed internally or outsourced. Computerized edit checks and review processes will be performed on an ongoing basis as outlined in the DMP until all data clarifications are resolved. The data will be exported to be stored in SAS datasets. After all data clarifications are resolved, coding is approved, SAE/pregnancy reconciliation has been completed (if applicable) and subject's evaluability is determined, the database will be locked.

### 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.

## 10.5 [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

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[REDACTED]

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## 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 amendments will be reviewed and approved by the appropriate IECs/IRBs.

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## 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.

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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. 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.

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.

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<sup>a</sup> 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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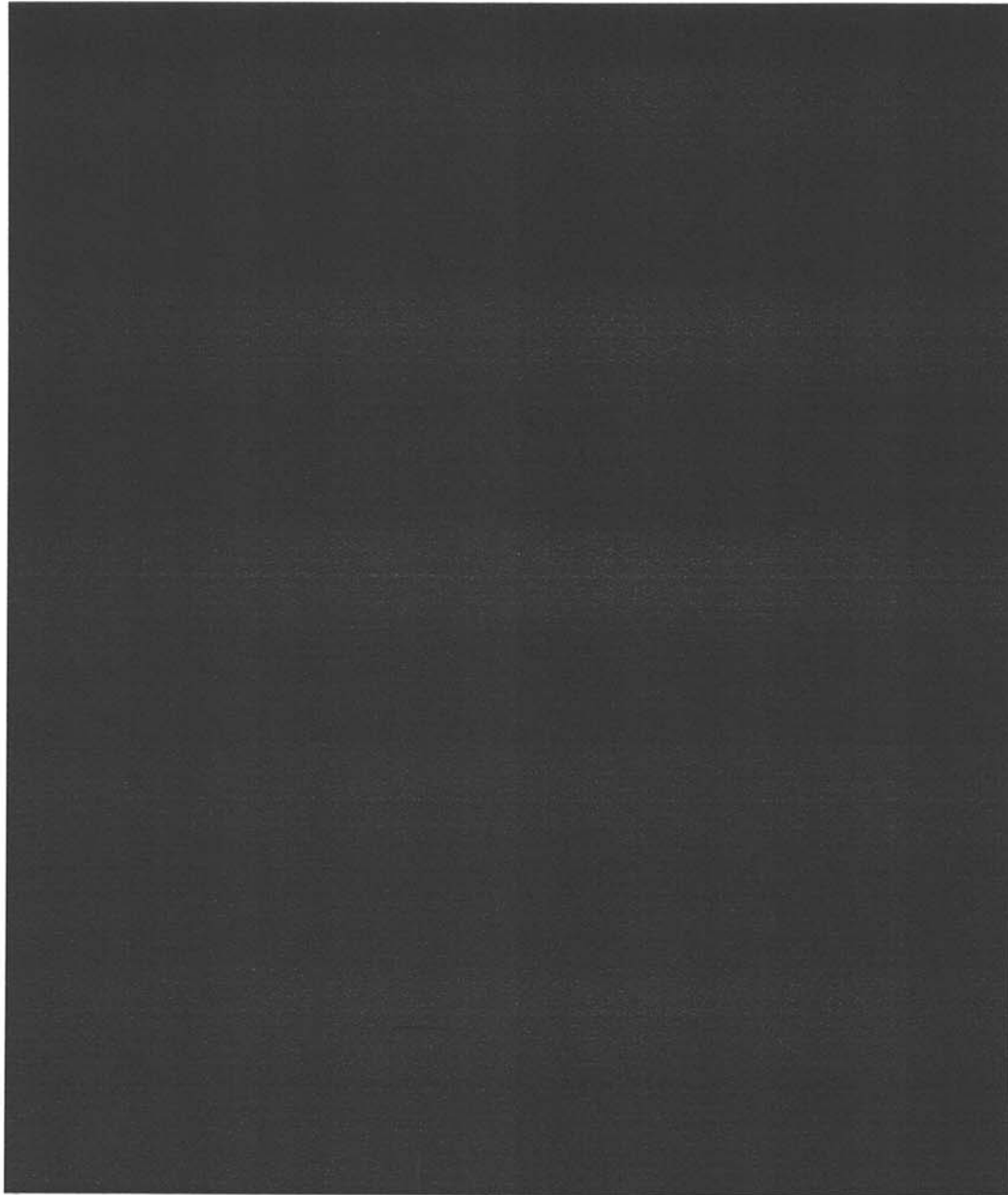
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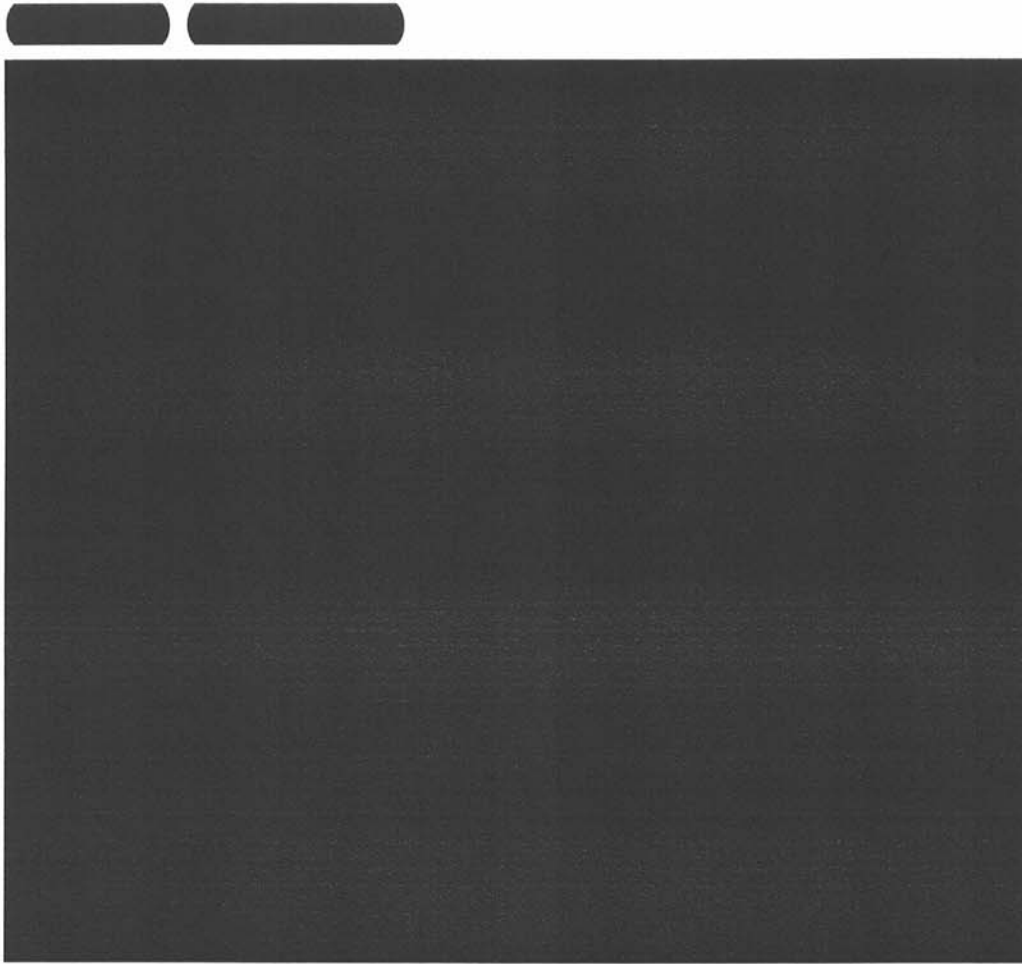
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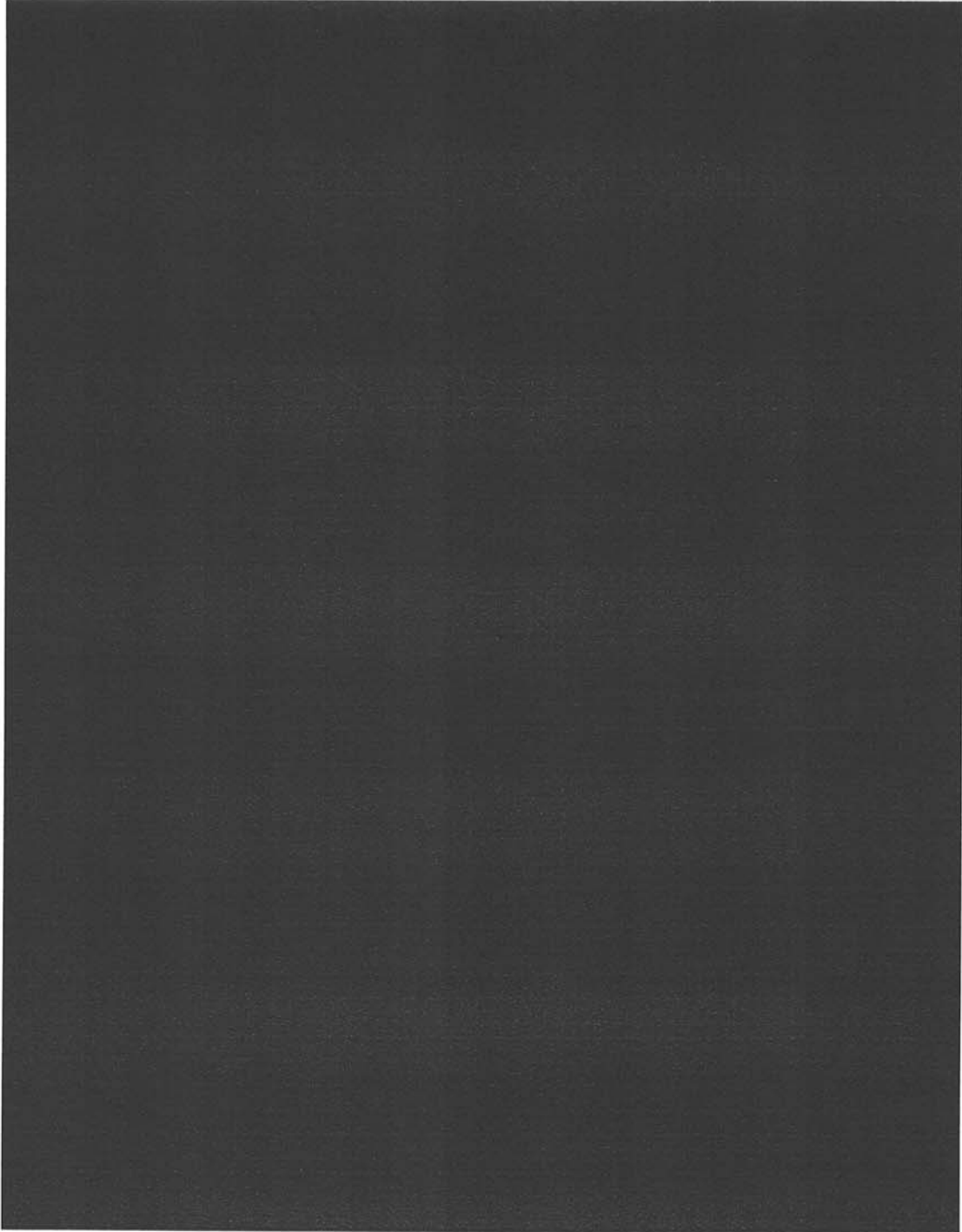
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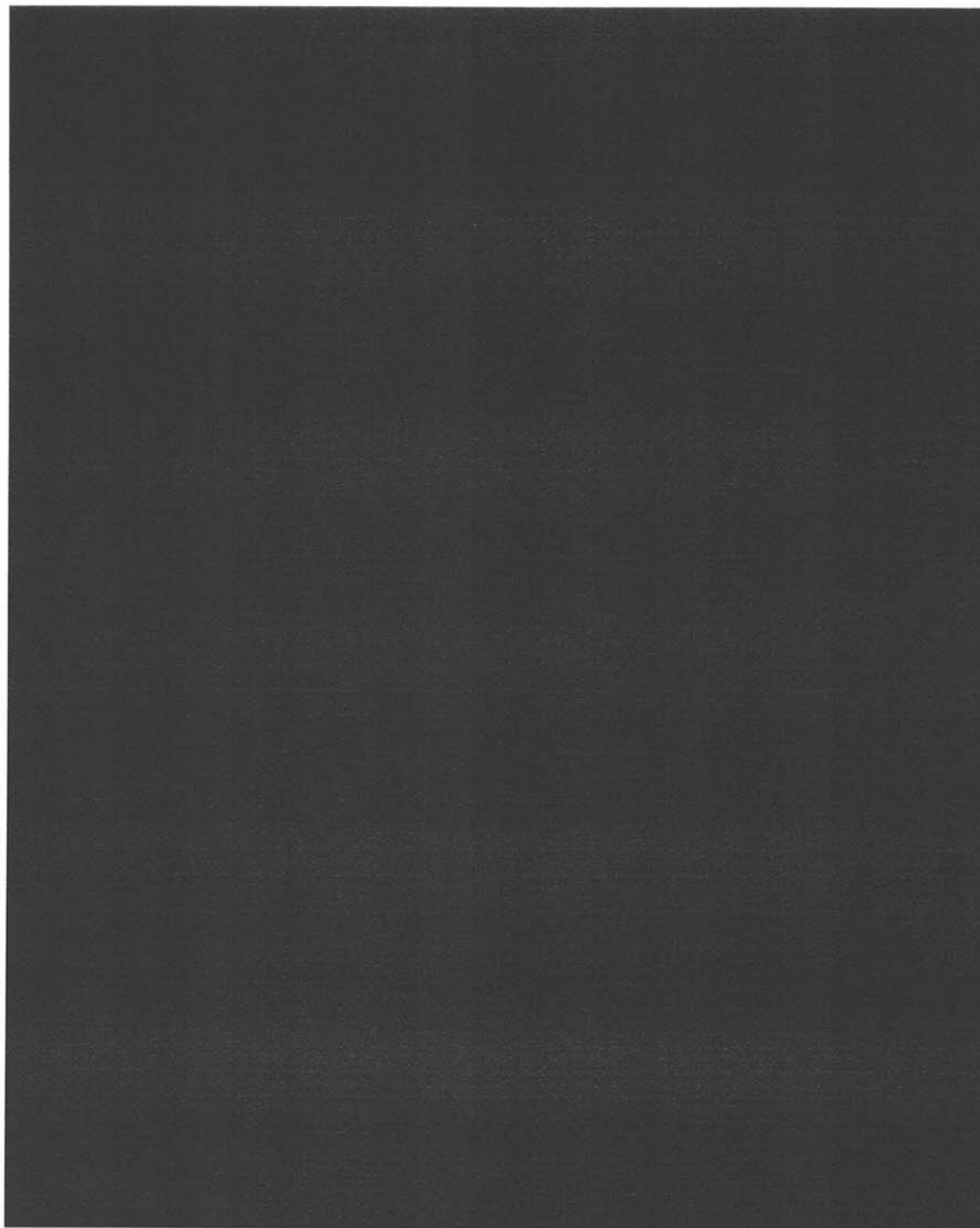
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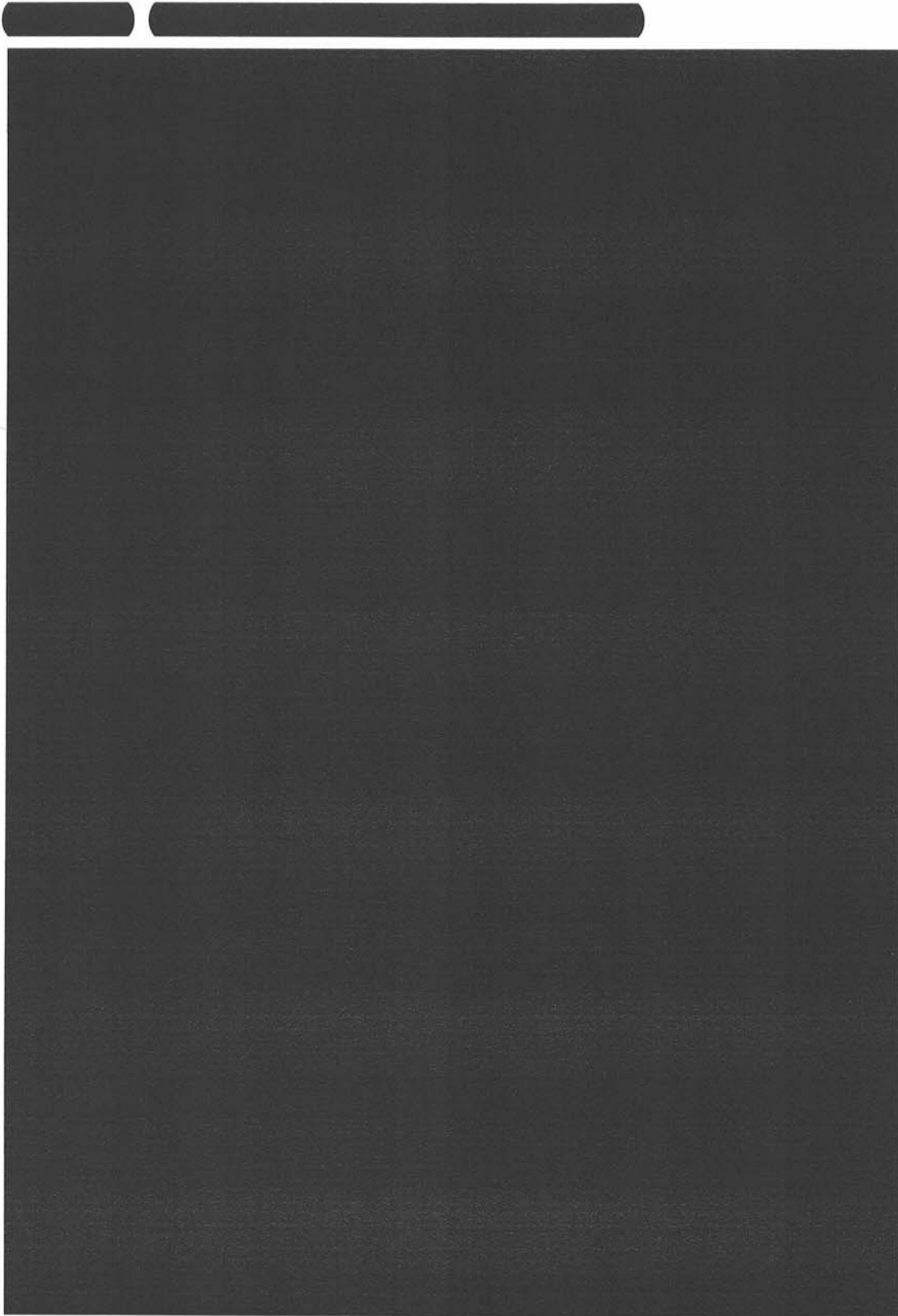
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