

A Multicenter, Randomized, Double-Blind, Placebo-Controlled  
Study to Evaluate the Efficacy and Safety of a New Dilution and  
Injection Volume of AbobotulinumtoxinA for the Treatment of  
Moderate to Severe Glabellar Lines

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**CLINICAL STUDY PROTOCOL**  
**PROTOCOL NUMBER: 43USD1805**

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## TITLE PAGE

A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of a New Dilution and Injection Volume of AbobotulinumtoxinA for the Treatment of Moderate to Severe Glabellar Lines

**CTN: 43USD1805**

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**CONTRACT RESEARCH ORGANIZATION (CRO):**



**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 7.2.2.2.2 and 7.2.2.2.3.

**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 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/>).

 <b>GALDERMA</b>	Title <b>43USD1805 Clinical Study Protocol Dysport New Dilution GL</b>	Doc id <span style="background-color: black; color: black;">XXXXXXXXXX</span>
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## TABLE OF CONTENTS

<b>TITLE PAGE</b>	2
<b>TABLE OF CONTENTS</b>	3
<b>SYNOPSIS</b>	9
<b>CLINICAL STUDY SCHEMATIC AND FLOW CHART</b>	15
<b>SCHEDULE OF ASSESSMENTS</b>	17
<b>LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS</b>	19
<b>1 BACKGROUND AND RATIONALE</b>	21
<b>1.1 Medical Background and Short Rationale for the Clinical Study</b>	21
<b>1.2 Drug Profile</b>	22
<b>1.3 Target Indication</b>	22
<b>1.4 Risk/Benefit Assessment</b>	22
<b>2 CLINICAL STUDY OBJECTIVES, ENDPOINTS, AND CLINICAL HYPOTHESIS</b>	23
<b>2.1 Clinical Study Objectives</b>	23
<b>2.1.1 Primary Efficacy Objectives and Endpoints</b>	23
<b>2.1.2 Secondary Efficacy Objectives and Endpoints</b>	24
<b>2.1.3 Exploratory Efficacy Objectives and Endpoints</b>	24
<b>2.1.4 Safety Objectives and Endpoints</b>	25
<b>2.2 Clinical Hypothesis</b>	26
<b>3 OVERALL CLINICAL STUDY DESCRIPTION</b>	26
<b>4 CLINICAL STUDY DURATION AND TERMINATION</b>	27
<b>5 SELECTION AND DISPOSITION OF CLINICAL STUDY POPULATION</b>	27
<b>5.1 Number of Subjects</b>	27
<b>5.2 Clinical Study Population Characteristics</b>	27
<b>5.2.1 Inclusion Criteria</b>	27
<b>5.2.2 Exclusion Criteria</b>	28
<b>5.3 Medical History</b>	29
<b>5.4 Previous and Concomitant Therapies</b>	30
<b>5.4.1 Definition</b>	30
<b>5.4.2 Categories</b>	30

 <b>GALDERMA</b>	Title <b>43USD1805 Clinical Study Protocol Dysport New Dilution GL</b>	Doc id [REDACTED]
--	---	----------------------

5.4.3	<b>Recording</b> .....	30
5.4.4	<b>Authorized Concomitant Therapies</b> .....	30
5.4.5	<b>Prohibited Concomitant Therapies</b> .....	31
5.5	<b>Procedures/Reasons for Subject Discontinuation</b> .....	31
6	<b>CLINICAL SUPPLIES</b> .....	33
6.1	<b>Clinical Supply Identification and Use</b> .....	33
6.1.1	<b>AbobotulinumtoxinA</b> .....	33
6.1.2	<b>Placebo</b> .....	33
6.1.3	<b>Study Products(s) Description</b> .....	34
6.1.4	<b>Subject Identification Number (SIN)</b> .....	34
6.1.5	<b>Method of Treatment Assignment</b> .....	34
6.1.6	<b>Kit Number/Randomization Number</b> .....	35
6.1.7	<b>Instructions for Use and Administration</b> .....	35
6.1.7.1	<b>Study Products</b> .....	35
6.1.7.1.1	[REDACTED] .....	35
6.1.7.1.2	[REDACTED] .....	35
6.1.7.2	<b>Treatment Preparation</b> .....	35
6.1.7.3	<b>Injection Technique</b> .....	36
6.1.7.4	<b>Treatment Procedure</b> .....	37
6.1.7.5	<b>Post-treatment Care</b> .....	37
6.1.7.6	<b>Treatment Regimen</b> .....	37
6.1.7.7	[REDACTED] .....	38
6.2	<b>Study Products(s) Packaging and Labeling</b> .....	38
6.3	<b>Supplies Management</b> .....	38
6.3.1	<b>Accountability</b> .....	38
6.3.2	<b>Storage of Study Products(s)</b> .....	38
6.3.3	<b>Dispensing and Return</b> .....	38
6.3.4	<b>Treatment Compliance Management and Record</b> .....	39
6.3.5	<b>Dose Modification</b> .....	39
6.3.6	<b>Product Quality Complaints</b> .....	39

	Title <b>43USD1805 Clinical Study Protocol Dysport New Dilution GL</b>	Doc id [REDACTED]
--	---	----------------------

<b>6.4</b>	<b>Blinding</b> .....	<b>39</b>
<b>6.4.1</b>	<b>Verification of Blinding</b> .....	<b>39</b>
<b>6.4.2</b>	<b>Unblinding During the Clinical Study</b> .....	<b>40</b>
<b>7</b>	<b>CLINICAL STUDY ASSESSMENT</b> .....	<b>40</b>
<b>7.1</b>	<b>Efficacy Assessments</b> .....	<b>40</b>
[REDACTED]	[REDACTED]	
<b>7.2</b>	<b>Safety Assessment</b> .....	<b>42</b>
<b>7.2.1</b>	<b>Focused Physical Examination</b> .....	<b>42</b>
<b>7.2.2</b>	<b>Adverse Events</b> .....	<b>43</b>
<b>7.2.2.1</b>	<b>Definitions</b> .....	<b>43</b>
<b>7.2.2.1.1</b>	<i>Adverse Events (AE)</i> .....	<b>43</b>
<b>7.2.2.1.2</b>	<i>Treatment Emergent Adverse Event (TEAE)</i> .....	<b>44</b>
<b>7.2.2.1.3</b>	<i>Serious Adverse Events (SAE)</i> .....	<b>44</b>
<b>7.2.2.1.4</b>	<i>Unexpected Adverse Drug Reaction</i> .....	<b>44</b>
<b>7.2.2.1.5</b>	<i>Adverse Event Reporting Period</i> .....	<b>45</b>
<b>7.2.2.1.6</b>	<i>Severity</i> .....	<b>45</b>
<b>7.2.2.1.7</b>	<i>Relationship to the Study Product and/or Clinical Study Procedure</i> .....	<b>45</b>
<b>7.2.2.2</b>	<b>Reporting Procedures</b> .....	<b>46</b>
<b>7.2.2.2.1</b>	<i>Procedures for Reporting Adverse Events</i> .....	<b>46</b>
<b>7.2.2.2.2</b>	<i>Procedure for Reporting a Serious Adverse Event</i> .....	<b>47</b>
<b>7.2.2.2.3</b>	<i>Procedures for Reporting Pregnancies</i> .....	<b>48</b>
<b>7.3</b>	<b>Other Assessments</b> .....	<b>49</b>
<b>7.3.1</b>	<b>Photography</b> .....	<b>49</b>
<b>7.3.2</b>	<b>Pregnancy Test</b> .....	<b>49</b>
<b>7.4</b>	<b>Appropriateness of Measurements</b> .....	<b>49</b>

 <b>GALDERMA</b>	Title <b>43USD1805 Clinical Study Protocol Dysport New Dilution GL</b>	Doc id [REDACTED]
--	---	----------------------

2019-01-24 15:42

Effective date:

*Effective*

Version: 1.0

<b>8 CLINICAL STUDY VISITS DESCRIPTIONS AND PROCEDURES .....</b>	<b>50</b>
[REDACTED]	[REDACTED]
[REDACTED]	55
<b>8.2 Subject Instructions .....</b>	<b>56</b>
<b>9 STATISTICAL METHODS PLANNED .....</b>	<b>56</b>
<b>9.1 Statistical and Analytical Plans .....</b>	<b>56</b>
<b>9.1.1 Data Transformations .....</b>	<b>56</b>
<b>9.1.2 Populations Analyzed and Evaluability .....</b>	<b>56</b>
<b>9.1.2.1 Intent-to-treat (ITT) Efficacy Population.....</b>	<b>56</b>
<b>9.1.2.2 Per-protocol (PP) Efficacy Population.....</b>	<b>56</b>
<b>9.1.2.3 Safety Population .....</b>	<b>56</b>
<b>9.1.2.4 Imputation of Missing Data .....</b>	<b>57</b>
<b>9.1.3 Data Presentation and Graphics.....</b>	<b>57</b>
<b>9.1.3.1 Safety Analysis .....</b>	<b>57</b>
<b>9.1.4 Withdrawals and Deviations.....</b>	<b>58</b>
<b>9.1.5 Inferential Statistical Analyses .....</b>	<b>58</b>
<b>9.2 Sample Size Determination .....</b>	<b>59</b>
<b>9.2.1 Historical Data .....</b>	<b>59</b>
<b>9.2.2 Assumptions .....</b>	<b>59</b>
<b>9.2.3 Sample Size Calculation .....</b>	<b>59</b>
<b>9.2.4 Interim Analysis.....</b>	<b>59</b>
<b>10 TRAINING / MONITORING / DATA MANAGEMENT / QUALITY ASSURANCE .....</b>	<b>60</b>
<b>10.1 Personnel Training.....</b>	<b>60</b>

Title  
**43USD1805 Clinical Study Protocol Dysport New Dilution GL**

2019-01-24 15:42

Effective date:

## *Effective*

Version: 1.0

 GALDERMA	Title <b>43USD1805 Clinical Study Protocol Dysport New Dilution GL</b>	Doc id [REDACTED]
---	---	----------------------

## List of Tables

Table 1	Clinical Study Schematic.....	15
Table 2	[REDACTED]	
[REDACTED]	[REDACTED]	34

## List of Figures

Figure 1	Study Flow Chart .....	16
Figure 2	Injection Sites for Treating Glabellar Lines.....	37

 <b>GALDERMA</b>	Title <b>43USD1805 Clinical Study Protocol Dysport New Dilution GL</b>	Doc id [REDACTED]
--	---	----------------------

SYNOPSIS	
<b>Clinical Study Title:</b> A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of a New Dilution and Injection Volume of AbobotulinumtoxinA for the Treatment of Moderate to Severe Glabellar Lines	
<b>Short Title:</b> AbobotulinumtoxinA New Dilution and Injection Volume	
<b>Clinical Study Population:</b>	[REDACTED]
<b>Clinical Study Design:</b>	<p>This is a phase 3, multicenter, randomized, double-blind, placebo-controlled, US study to evaluate the efficacy and safety of a new dilution and injection volume of abobotulinumtoxinA for the treatment of moderate to severe glabellar lines.</p> <p>[REDACTED]</p> <p>[REDACTED]</p>
<b>Total Number of Subjects (Planned):</b>	[REDACTED]
<b>Number of Clinical Study Centers (Planned):</b>	[REDACTED]
<b>Region(s) / Country(ies) Involved (Planned):</b>	[REDACTED]
<b>Clinical Study Duration:</b>	<p>[REDACTED]</p> <p>[REDACTED]</p>
<b>Duration of Subject Participation:</b>	[REDACTED]
<b>Key Inclusion Criteria:</b>	<ol style="list-style-type: none"> <li>1. Male or female, 18 to &lt;65 years of age.</li> <li>2. [REDACTED]</li> <li>3. [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 an acceptable, reliable, and approved contraceptive method for the duration of enrollment in the study. Male subjects do not require birth control measures.           <ul style="list-style-type: none"> <li>• Bilateral tubal ligation;</li> <li>• Cervical cap, diaphragm or sponge with spermicide;</li> <li>• Combined (estrogen and progesterone containing) oral, intravaginal or transdermal contraceptives that inhibit ovulation as the primary mode of action, on a stable dose for at least 28 days prior to screening visit;</li> </ul> </li> </ol>



Effective date: 2019-01-24 15:42

## SYNOPSIS

**Clinical Study Title:** A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of a New Dilution and Injection Volume of AbobotulinumtoxinA for the Treatment of Moderate to Severe Glabellar Lines

- Intra uterine device (IUD) inserted at least 28 days prior to screening visit;
  - Intrauterine hormone-releasing system;
  - Partner vasectomized for at least three months prior to screening visit;
  - Progestin-only oral, injectable or implantable contraceptives that inhibit ovulation as the primary mode of action, on a stable dose for at least 28 days prior to screening visit; or
  - Strict abstinence (i.e., refraining from heterosexual intercourse for the entire duration of enrollment in the study).

5. Time and ability to complete the study and comply with site staff instructions.

6. Understands the study requirements and signed the informed consent form (ICF).

### **Key Exclusion Criteria:**

- 1

  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 US Prescribing Information).
    - \* This criterion does not exclude subjects who are lactose intolerant. Lactose intolerance is a gastrointestinal disorder caused by an enzyme deficiency (lactase). An allergy to cow's milk protein is an immunological disorder that results in a systemic reaction, such as anaphylaxis.
  4. Female who is breastfeeding.
  5. Female who intends to conceive a child during the study.

## *Effective*

Version: 1.0

Effective date: 2019-01-24 15:42

Effective

Version: 1.0

	Title <b>43USD1805 Clinical Study Protocol Dysport New Dilution GL</b>	Doc id [REDACTED]
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<b>Clinical Study Title:</b> A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of a New Dilution and Injection Volume of AbobotulinumtoxinA for the Treatment of Moderate to Severe Glabellar Lines	
	[REDACTED]
<b>Investigational Product:</b>	AbobotulinumtoxinA / Dysport®
	[REDACTED]
	[REDACTED]
<b>Location of treated area:</b>	Glabellar region
	[REDACTED]
	[REDACTED]
	[REDACTED]
<b>Placebo Product:</b>	Placebo
	[REDACTED]
	[REDACTED]
<b>Location of treated area:</b>	Glabellar region
	[REDACTED]
<b>Efficacy Assessment:</b>	Efficacy assessments include:
	[REDACTED]
<b>Study Objective:</b>	The objective of this study is to evaluate the efficacy and safety of a single dose of a new dilution and injection volume of abobotulinumtoxinA compared to placebo in the treatment of moderate to severe glabellar lines.
	[REDACTED]
<b>Primary Efficacy Objective and Endpoint:</b>	The primary objective of this study is to evaluate the efficacy of a single dose of 50 U of abobotulinumtoxinA compared to placebo in the treatment of moderate to severe glabellar lines.
	[REDACTED]

Effective date: 2019-01-24 15:42

Effective

Version: 1.0

 GALDERMA	Title <b>43USD1805 Clinical Study Protocol Dysport New Dilution GL</b>	Doc id [REDACTED]
<b>SYNOPSIS</b>		
<b>Clinical Study Title:</b> A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of a New Dilution and Injection Volume of AbobotulinumtoxinA for the Treatment of Moderate to Severe Glabellar Lines		
<b>Secondary Efficacy Objectives and Endpoints:</b>		
<b>Exploratory Efficacy Objectives and Endpoints:</b>		

Effective date: 2019-01-24 15:42

Effective

Version: 1.0

 <b>GALDERMA</b>	Title <b>43USD1805 Clinical Study Protocol Dysport New Dilution GL</b>	Doc id [REDACTED]
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SYNOPSIS	
<b>Clinical Study Title:</b> A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of a New Dilution and Injection Volume of AbobotulinumtoxinA for the Treatment of Moderate to Severe Glabellar Lines	
	[REDACTED]
<b>Safety Assessment:</b>	Safety assessments include: <ul style="list-style-type: none"> <li>Treatment emergent adverse events (TEAEs)</li> <li>Focused physical examination</li> </ul>
<b>Safety Objectives and Endpoints:</b>	To evaluate the safety of a single dose of 50 U of abobotulinumtoxinA compared to placebo in the treatment of moderate to severe glabellar lines.  Endpoints include: <ul style="list-style-type: none"> <li>Incidence and severity of TEAEs</li> <li>Focused physical examination (PE)</li> </ul>
<b>Other Assessments:</b>	Other assessments include: <ul style="list-style-type: none"> <li>Photography</li> <li>Pregnancy test</li> </ul>
<b>Blinding:</b>	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 (i.e., abobotulinumtoxinA or placebo).  An un-blinded statistician will generate the randomization schedule; however, they will not be involved in any other aspect of the study prior to database lock.
<b>Principal Statistical Method:</b>	The primary efficacy endpoint [REDACTED]

Effective date: 2019-01-24 15:42

*Effective*

Version: 1.0

 GALDERMA	Title <b>43USD1805 Clinical Study Protocol Dysport New Dilution GL</b>	Doc id [REDACTED]
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SYNOPSIS	
<b>Clinical Study Title:</b> A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of a New Dilution and Injection Volume of AbobotulinumtoxinA for the Treatment of Moderate to Severe Glabellar Lines	
Sample Size:	[REDACTED]
Interim Analysis (IA):	Not applicable. An interim analysis is not planned for this study.

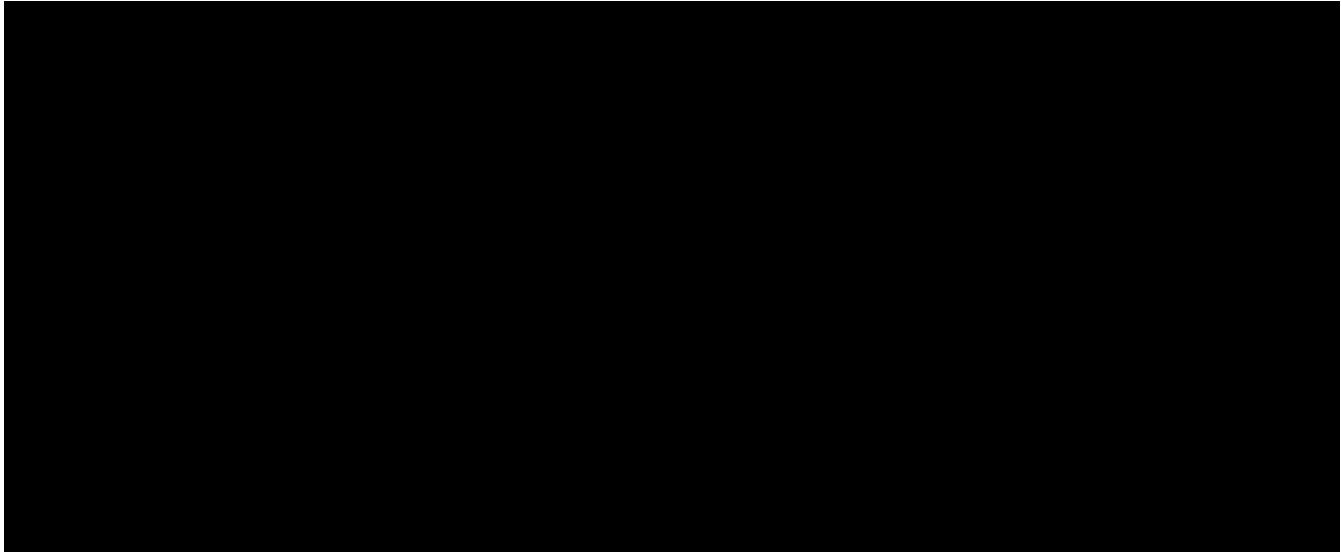
 GALDERMA	Title <b>43USD1805 Clinical Study Protocol Dysport New Dilution GL</b>	Doc id [REDACTED]
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2019-01-24 15:42

Effective date:

*Effective*

Version: 1.0

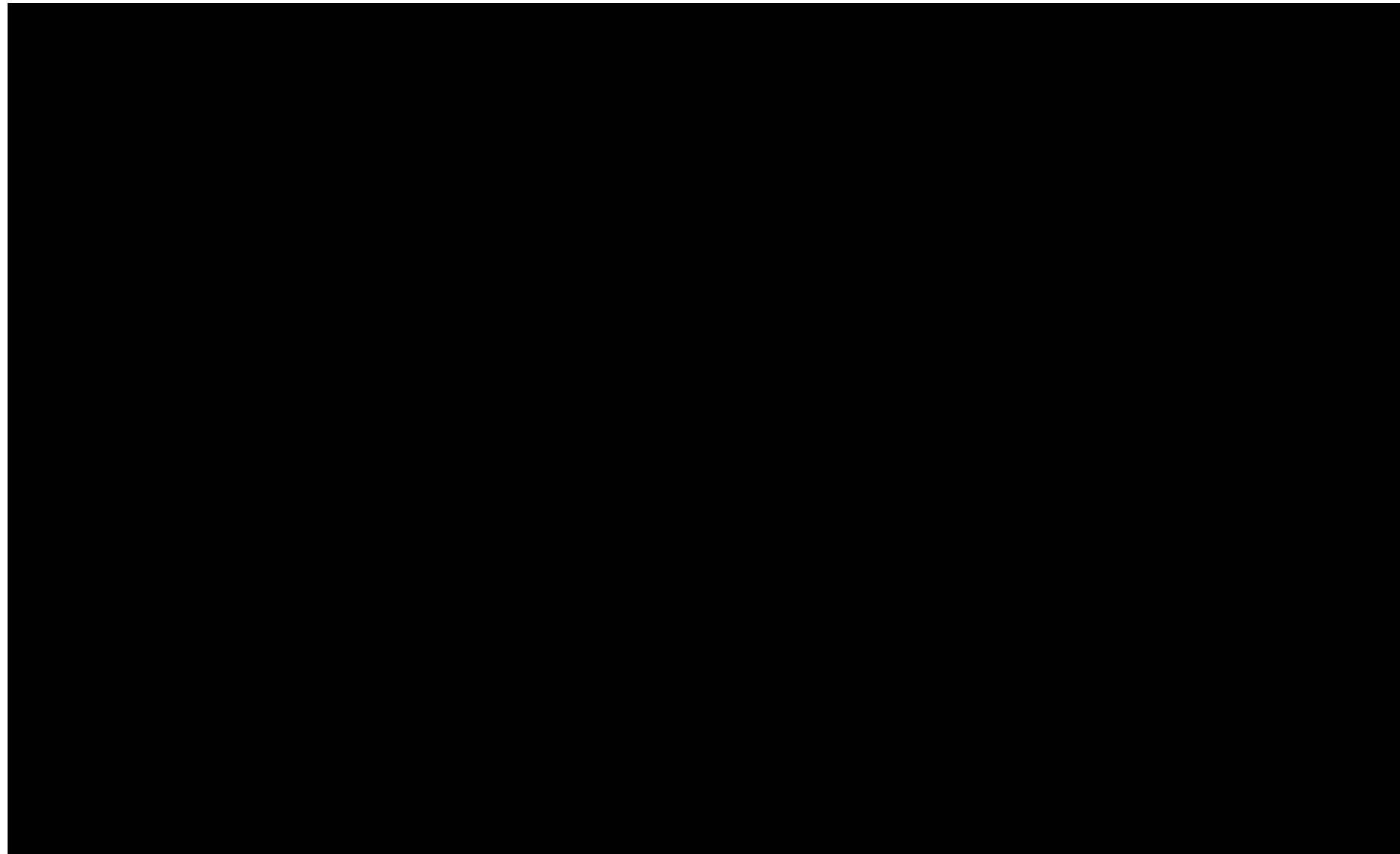
**CLINICAL STUDY SCHEMATIC AND FLOW CHART****Table 1 Clinical Study Schematic**

 GALDERMA	Title <b>43USD1805 Clinical Study Protocol Dysport New Dilution GL</b>	Doc id [REDACTED]
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Effective date: 2019-01-24 15:42

*Effective*

Version: 1.0





Title

43USD1805 Clinical Study Protocol Dysport New Dilution GL

Doc id



 <b>GALDERMA</b>	Title <b>43USD1805 Clinical Study Protocol Dysport New Dilution GL</b>	Doc id [REDACTED]
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## LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

<b>Abbreviation</b>	<b>Term</b>
°C	Degrees Celsius
AE	Adverse Event
ADR	Adverse Reaction
BOCF	Baseline Observation Carried Forward
BoNT	Botulinum Toxin
BoNT-A	Botulinum Toxin Type A
BoNT-A-HAC	Botulinum Toxin Type A-Haemagglutinin Complex
CDMS	Clinical Data Management System
CM	Concomitant Medication
CMH	Cochran-Mantel-Haenszel
CPM	Clinical Project Manager
CRF/eCRF	Case Report Forms/electronic Case Report Forms
CRO	Contract Research Organization
CSP	Clinical Study Protocol
DC	Discontinuation
DMP	Data Management Plan
EDC	Electronic Data Capture
e.g.	For Example (Latin: exempli gratia)
ET	Early Termination
etc	Et cetera
FDA	Food and Drug Administration
FSFV	First Subject First Visit (date of first subject included i.e., informed consent signature)
GAIS	Global Aesthetic Improvement Scale
GCP	Good Clinical Practice
GL	Glabellar Lines
HIPAA	Health Insurance Portability and Accountability Act of 1996
IA	Interim analysis
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
i.e.	That is (Latin: id est)
IEC	Independent Ethics Committee
ILA	Investigator Live Assessment
IND	Investigational New Drug
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITT	Intent-to-treat
IUD	Intrauterine Device
KM	Kaplan-Meier

	Title <b>43USD1805 Clinical Study Protocol Dysport New Dilution GL</b>	Doc id [REDACTED]
--	---	----------------------

2019-01-24 15:42

Effective date:

**Effective**

Version: 1.0

<b><i>Abbreviation</i></b>	<b><i>Term</i></b>
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
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple Imputation
mL	Milliliter
N or n	Number
N/A	Not Applicable
NaCl	Sodium Chloride
OC	Observed Cases
OTC	Over-the-Counter
PE	Physical Examination
PP	Per-Protocol
PQC	Product Quality Complaint
SAE	Serious Adverse Event
SIN	Subject Identification Number
SOC	System Organ Class
SOP	Standard Operating Procedure
SSA	Subject Self-Assessment
SUSAR	Suspected Unexpected Serious Adverse Reaction
TOC	Table of Contents
TEAE	Treatment Emergent Adverse Event
U	Units
UPT	Urine Pregnancy Test
US	United States
USP	United States Pharmacopeia

	Title <b>43USD1805 Clinical Study Protocol Dysport New Dilution GL</b>	Doc id <span style="background-color: black; color: black;">XXXXXXXXXX</span>
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## 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. Botulinum toxins occur in seven known serotypes (A-G) that are produced by different strains of *Clostridium botulinum*. Clinically important biologic activity is limited primarily to the A and B serotypes, of which the type A serotype (BoNT-A) is used widely throughout the world for the treatment of a range of clinical conditions. BoNT-A blocks the release of acetylcholine into the neuromuscular junction (synapse) cleft, thereby prohibiting the activation of acetylcholine receptors. Paresis by chemical denervation thus occurs in the target muscle, leading to inhibition of muscular contraction.

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> In the treatment of facial lines, the effect of BoNT-A injections usually persists for approximately 4-6 months. Facial muscle activity and severity of the facial wrinkles then returns to baseline. Full functionality of facial muscles is usually restored by approximately 6 months post-treatment.<sup>3</sup>

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. To achieve a clinical effect, a total of 50 U is given intramuscularly in five equal aliquots of 10 U each into each of five sites, two in each corrugator muscle and one in the procerus muscle. Re-treatments should be administered no more frequently than every three months.

The rationale of the study is to evaluate the currently approved abobotulinumtoxinA dose of 50 U using a larger injection volume of 0.1 mL per injection site for the treatment of moderate to severe glabellar lines. This injection volume provides better control of the injection, minimized the margin of error, and is comparable to other BoNT-A preparations, (i.e., onabotulinumtoxinA [Botox®] and incobotulinumtoxinA [Xeomin®]). Based on anecdotal experience, it is also reflective of current clinical practice among some physicians and other qualified medical professionals.

	<p>Title <b>43USD1805 Clinical Study Protocol Dysport New Dilution GL</b></p>	<p>Doc id [REDACTED]</p>
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## 1.2 Drug Profile

AbobotulinumtoxinA 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. AbobotulinumtoxinA contains nominally 300 U of BoNT-A-haemagglutinin complex together with 125 µg of human serum albumin (HSA) and 2.5 mg of lactose in a clear glass vial. Further details can be found in the Dysport Aesthetic Investigator's Brochure.<sup>4</sup>

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

## 1.4 Risk/Benefit Assessment

In the Dysport clinical development program for the treatment of glabellar lines the majority of adverse events (AEs) were mild or moderate in severity, transient, and not considered related to study treatment. In clinical trials, the most frequently reported TEAEs considered related to Dysport treatment were headache, injection site reactions and eye disorders, and the adverse reaction (ADR) profile from postmarketing experience is similar to the safety profile observed in the clinical study program. The identified risks associated with treatment of glabellar lines with botulinum toxin type A haemagglutinin complex (BoNT-A-HAC) include eye disorders and spread of effect of the toxin beyond the areas of injection.

In clinical trials in glabellar lines, ocular TEAEs were reported at the following frequencies: common (i.e.  $\geq 1\%$  and  $< 10\%$ ), asthenopia, eyelid ptosis, eyelid edema, increased lacrimation, dry eyes and muscle twitching around the eyes; uncommon (i.e.  $\geq 0.1\%$  and  $< 1\%$ ), blurred vision, diplopia, visual disturbances and eye movement disorders. The most commonly reported eye

 <b>GALDERMA</b>	Title <b>43USD1805 Clinical Study Protocol Dysport New Dilution GL</b>	Doc id [REDACTED]
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disorders from postmarketing data were eyelid ptosis, vision blurred, eyelid edema, eye swelling and diplopia.

Adverse effects resulting from the distribution of the effects of the toxin to sites remote from the site of administration have been reported. The risk of occurrence of such undesirable effects may be reduced by using the lowest effective dose possible and by not exceeding the maximum recommended dose. Very rare cases of death, occasionally in the context of dysphagia, pneumopathy (including but not limited to dyspnea, respiratory failure, respiratory arrest) and/or in patients with significant asthenia have been reported following treatment with botulinum toxin A or B. Patients with disorders resulting in defective neuromuscular transmission, difficulty in swallowing or breathing are more at risk of experiencing these effects.

The potential benefit to subjects participating in the study may be the temporary reduction in the appearance of their glabellar lines. This benefit is expected for all subjects given optional on-label treatment is available to subjects that complete the study through Month 6. Subjects that are randomized to the placebo treatment group at baseline and discontinue the study early are not guaranteed to receive any benefit from participation.



In conclusion, given the anticipated low level of transient and acceptable risks, the risk/benefit assessment of the use of abobotulinumtoxinA for the treatment of moderate to severe glabellar lines appears to offer a substantial clinical benefit at reasonable risk.

## 2 CLINICAL STUDY OBJECTIVES, ENDPOINTS, AND CLINICAL HYPOTHESIS

### 2.1 Clinical Study Objectives

The objective of this study is to evaluate the efficacy and safety of a single dose of a new dilution and injection volume of abobotulinumtoxinA compared to placebo in the treatment of moderate to severe glabellar lines.

#### 2.1.1 Primary Efficacy Objectives and Endpoints

The primary objective of this study is to evaluate the efficacy of a single dose of [REDACTED] of abobotulinumtoxinA compared to placebo in the treatment of moderate to severe glabellar lines.

For the primary endpoint the composite responder rate will be evaluated using the ILA 4-point Photographic Scale and the SSA Static 4-Point Categorical Scale at maximum frown at Month 1.



2019-01-24 15:42

Effective date:

### 2.1.2 Secondary Efficacy Objectives and Endpoints

 GALDERMA	Title 43USD1805 Clinical Study Protocol Dysport New Dilution GL	Doc id [REDACTED]
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Effective date: 2019-01-24 15:42

Effective date:

*Effective*

Version: 1.0

#### 2.1.4 Safety Objectives and Endpoints

The safety objective is to evaluate the safety of a single dose of 50 U of abobotulinumtoxinA compared to placebo in the treatment of moderate to severe glabellar lines.

 GALDERMA	Title <b>43USD1805 Clinical Study Protocol Dysport New Dilution GL</b>	Doc id [REDACTED]
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Effective date: 2019-01-24 15:42

*Effective*

Version: 1.0

Safety endpoints include:

- Incidence and severity of TEAEs
- Focused physical examination (PE)

## 2.2 Clinical Hypothesis



## 3 OVERALL CLINICAL STUDY DESCRIPTION



Safety assessments will include (Section Safety Assessment 7.2):

- TEAEs
- Focused physical examination

Selection criteria for the study population are described in Section 5. Detailed information about study tasks by treatment visit is outlined in Section 8.

 <b>GALDERMA</b>	Title <b>43USD1805 Clinical Study Protocol Dysport New Dilution GL</b>	Doc id [REDACTED]
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## 4 CLINICAL STUDY DURATION AND TERMINATION

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

The planned duration of recruitment (from FSFV to LSFV) is approximately [REDACTED].

Clinical study participation for each subject is up to approximately [REDACTED].

The Sponsor may decide to prematurely terminate or suspend the participation of a particular clinical study center (for example, lack of subject enrollment or non-compliance with clinical study protocol, regulation, or GCP) or prematurely suspend the clinical study (for example, for safety, study products(s) quality, regulatory, efficacy, or logistical reasons) at any time with appropriate notification.

## 5 SELECTION AND DISPOSITION OF CLINICAL STUDY POPULATION

### 5.1 Number of Subjects

[REDACTED]

### 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]

[REDACTED]

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

 <b>GALDERMA</b>	Title <b>43USD1805 Clinical Study Protocol Dysport New Dilution GL</b>	Doc id [REDACTED]
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Effective date: 2019-01-24 15:42

Female of childbearing potential with a negative urine pregnancy test at screening and baseline, and agrees to use an acceptable, reliable, and approved contraceptive method for the duration of enrollment in the study. Male subjects do not require birth control measures.

- Bilateral tubal ligation;
  - Cervical cap, diaphragm or sponge with spermicide;
  - Combined (estrogen and progesterone containing) oral, intravaginal or transdermal contraceptives that inhibit ovulation as the primary mode of action, on a stable dose for at least 28 days prior to screening visit;
  - Intra uterine device (IUD) inserted at least 28 days prior to screening visit;
  - Intrauterine hormone-releasing system;
  - Partner vasectomized for at least three months prior to screening visit;
  - Progestin-only oral, injectable or implantable contraceptives that inhibit ovulation as the primary mode of action, on a stable dose for at least 28 days prior to screening visit; or
  - Strict abstinence (i.e., refraining from heterosexual intercourse for the entire duration of enrollment in the study).
5. Time and ability to complete the study and comply with site staff instructions.
  6. Understands the study requirements and signed the informed consent form (ICF).

### 5.2.2 Exclusion Criteria

1. Botulinum toxin treatment in the face within 6 months prior to study treatment.
2. Anticipated need for treatment with botulinum toxin of any serotype for any reason during the study (other than the investigational product).

4. Female who is breastfeeding.
5. Female who intends to conceive a child during the study.

Version: 1.0

 GALDERMA	Title 43USD1805 Clinical Study Protocol Dysport New Dilution GL	Doc id [REDACTED]
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2019-01-24 15:42

Effective date:

*Effective*

Version: 1.0



### 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.

 <b>GALDERMA</b>	Title <b>43USD1805 Clinical Study Protocol Dysport New Dilution GL</b>	Doc id <span style="background-color: black; color: black;">XXXXXXXXXX</span>
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## 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 Categories

The following two categories are to be considered for previous and concomitant therapies:

- Drugs including but not limited to, prescription, over-the-counter (OTC), birth control pills/patches/hormonal devices, vitamins, herbal medicines/supplements, and homeopathic preparations.
- Medical and surgical procedures including, but not limited to, laser/radiation procedures, dermal fillers (area of treatment should be indicated), X-rays, surgeries, tooth extractions.

### 5.4.3 Recording

Previous and concomitant therapies are to be recorded in the subject's source documents and eCRFs.

Concomitant therapies are to be reviewed at each visit and updated in the source documents and eCRFs as needed.

Any new concomitant therapy or modification of an existing therapy may be linked to an AE. A corresponding AE form should be completed to account for the change in therapy, except in some cases such as therapy used for prophylaxis, dose modification for a chronic condition, etc.

### 5.4.4 Authorized Concomitant Therapies

Unless listed in prohibited concomitant therapies (see Section [5.4.5](#)), all are authorized.

	Title <b>43USD1805 Clinical Study Protocol Dysport New Dilution GL</b>	Doc id [REDACTED]
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#### 5.4.5 Prohibited Concomitant Therapies

The following therapies are prohibited because they may interfere with the efficacy and/or safety assessment of the study products(s):

- Botulinum toxin of any serotype.
- Any other investigational new drug or device.
- Any absorbable (temporary) or non-absorbable (permanent) material above the lower orbital rim.
- Facial aesthetic procedures (e.g ablative skin resurfacing, chemical peel, photorejuvenation or skin/vascular laser intervention) above the lower orbital rim.
- Planned facial surgery or eye surgery (including LASIK procedure).
- Medications that affect neuromuscular transmission such as curare-like depolarizing agents, lincosamides, polymyxins, anticholinesterases and aminoglycoside antibiotics.

If a prohibited therapy becomes a necessary treatment for best clinical interest of the subject or due to safety reason, the Medical Monitor (Section 11.9) should be notified, if time permits, to discuss possible alternatives prior to administration of a prohibited therapy.

If a subject receives a prohibited therapy during the clinical study, the Medical Monitor (Section 11.9) should be notified to discuss the subject's continuation in the clinical study..

#### 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.

When a subject does not complete the clinical study, he/she will be fully assessed, if such assessment is possible. The procedures designated for the Month 6/ ET visit should be completed for all subjects discontinuing the clinical study and the appropriate eCRF should be completed.

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.

Potential reasons for discontinuation, as listed on the exit form, are defined below:

- Adverse Event: Complete an AE form.

	Title <b>43USD1805 Clinical Study Protocol Dysport New Dilution GL</b>	Doc id [REDACTED]
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2019-01-24 15:42

Effective date:

- Withdrawal by Subject: Includes consent withdrawal, subject relocation, schedule conflicts, etc. Explain the reason for withdrawal in the comment section of the eCRF exit form.
- Lost to Follow-up: Confirmed with two documented phone calls and a certified letter (delivery receipt requested) without answer. Explain in the comment section of the eCRF exit form.
- Other: This category is to be used for a subject who discontinues due to a reason other than as specified in the predefined categories above. Explain the reason for discontinuation in the comment section of the eCRF exit form.

A subject who has been randomized and assigned a kit number/randomization number cannot be replaced by another subject if he/she discontinues the clinical study for any reason. Additional subjects could be enrolled (randomized/assigned to treatment) in order to attain the number of evaluable subjects.

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 7.2.2.3. 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.

Effective

Version: 1.0

 GALDERMA	Title <b>43USD1805 Clinical Study Protocol Dysport New Dilution GL</b>	Doc id [REDACTED]
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## 6 CLINICAL SUPPLIES

Details of the drug composition and excipients are provided in the current Dysport Aesthetic Indications Investigator's Brochure.<sup>4</sup>

### 6.1 Clinical Supply Identification and Use

#### 6.1.1 AbobotulinumtoxinA

[REDACTED]

[REDACTED]

#### 6.1.2 Placebo

[REDACTED]

The placebo product should be stored at the recommended temperature (between 2°C and 8°C). The product does not contain any antimicrobial agent; therefore, it is recommended that the product is used immediately after reconstitution. The placebo product should not be frozen and should be protected from light.

 <b>GALDERMA</b>	Title <b>43USD1805 Clinical Study Protocol Dysport New Dilution GL</b>	Doc id [REDACTED]
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### 6.1.3 Study Products(s) Description

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

	Investigational product	Placebo product
<b>Trade Name</b>	Dysport	N/A
<b>Name of Drug Substance</b>	abobotulinumtoxinA	N/A
<b>Internal Code</b>	N/A	Placebo
<b>Pharmaceutical Form</b>	Lyophilized powder	Lyophilized powder
<b>Location of treated area</b>	Glabellar region	Glabellar 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. For the duration of the study, the subject will be identified using the subject number for all documentation and discussion.

Subject numbers will consist of the study center number followed by a consecutive number starting with 001 at each center. The subject numbers shall be allocated in ascending sequential order within each center. If a subject is deemed not eligible for the study participation, the reason for screen failure should be specified. A screen failure cannot be re-screened.

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 allocated a study product by the Electronic Data Capture (EDC) system.

 <b>GALDERMA</b>	Title <b>43USD1805 Clinical Study Protocol Dysport New Dilution GL</b>	Doc id [REDACTED]
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### 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 at baseline.

Kit number/randomization number will be allocated in ascending sequential order to each eligible subject.

### 6.1.7 Instructions for Use and Administration

Placebo is identical in appearance to abobotulinumtoxinA but contains no active drug substance. AbobotulinumtoxinA and placebo are administered in exactly the same way. All treating Investigators in this study will be trained in the administration technique prior to the study start.

Basic reconstitution information for the study products are included in Sections [6.1.7.1.1](#), and [6.1.7.1.2](#) below. Additional information regarding the reconstitution/administration procedures is included in Sections [6.1.7.2](#), [6.1.7.3](#), [6.1.7.4](#) and, [6.1.7.5](#). Handling of damaged or spilled study product is described in the Material Safety Data Sheet.

#### 6.1.7.1 *Study Products*

[REDACTED]

[REDACTED]

[REDACTED]

#### 6.1.7.1.2 *Placebo*

[REDACTED]

#### 6.1.7.2 *Treatment Preparation*

[REDACTED]

 <b>GALDERMA</b>	Title <b>43USD1805 Clinical Study Protocol Dysport New Dilution GL</b>	Doc id
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The Investigator or designee will be responsible for preparing each dose. Each kit (including the vial) will be numbered; no indication will be given as to whether the vial contains active drug or placebo.






#### ***6.1.7.3 Injection Technique***

Glabellar facial lines arise from the activity of the lateral corrugator and vertical procerus muscles. These can be readily identified by palpating the tensed muscle mass while having the subject frown. The corrugator depresses the skin creating a “furrowed” vertical line surrounded by tensed muscle (i.e., frown lines). The location, size, and use of the muscles vary markedly among individuals. Investigators must understand the relevant neuromuscular and/or orbital anatomy of the area involved and any alterations to the anatomy due to prior surgical procedures.

Risk of ptosis can be mitigated by careful examination of the upper lid for separation or weakness of the levator palpebrae muscle (true ptosis), identification of lash ptosis, and evaluation of the range of lid excursion while manually depressing the frontalis to assess compensation.

In order to reduce the complication of ptosis, the following steps should be taken:

- Avoid injection near the levator palpebrae superioris, particularly in subjects with larger brow depressor complexes.

 GALDERMA	Title <b>43USD1805 Clinical Study Protocol Dysport New Dilution GL</b>	Doc id [REDACTED]
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2019-01-24 15:42

Effective date:

*Effective*

Version: 1.0

#### **6.1.7.5 Post-treatment Care**

Following treatment administration at baseline, subjects will be monitored at the study center for 30 minutes.

Subjects will be instructed to avoid rubbing and massaging the treated area for 4 hours after treatment.

#### **6.1.7.6 Treatment Regimen**

Each subject will receive a single treatment with abobotulinumtoxinA or placebo at the baseline visit.

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[REDACTED]  
[REDACTED]

2019-01-24 15:42

Effective date:

Effective

Version: 1.0

	Title <b>43USD1805 Clinical Study Protocol Dysport New Dilution GL</b>	Doc id [REDACTED]
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[REDACTED]

[REDACTED]

[REDACTED]

[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.

	Title <b>43USD1805 Clinical Study Protocol Dysport New Dilution GL</b>	Doc id <span style="background-color: black; color: black;">[REDACTED]</span>
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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 Product Quality Complaints**

Product Quality complaints (PQCs) should be reported to the Sponsor Contact or designee (Section 11.9). A PQC is an external judgement presuming a quality defect of a product; quality issue for a product relating to its presentation or use, identified by a subject, a practitioner or investigator site personnel, a distributor, or anyone else involved in clinical supplies handling. Examples may include but are not limited to appearance issues, odor, damaged stoppers, low fills, and foreign matter in the product. These complaints may or may not represent a potential risk to the subject. A PQC form must be completed by the study center personnel and forwarded to the Sponsor or designee within 24 hours of awareness. Affected study product should be quarantined, and not used, until further notice by the Sponsor.

Additional contact details are provided in the Investigator's site file.

### **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.

An un-blinded statistician will generate the randomization schedule; however, they will not be involved in any other aspect of the study prior to database lock.

#### **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.

	Title <b>43USD1805 Clinical Study Protocol Dysport New Dilution GL</b>	Doc id [REDACTED]
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#### 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 7.2.2.2.2). 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, and inform the Sponsor immediately. .

### 7 CLINICAL STUDY ASSESSMENT

#### 7.1 Efficacy Assessments

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]	[REDACTED]	[REDACTED]	



2019-01-24 15:42

Effective date:

*Effective*

#### 7.1.4 Subject Satisfaction Questionnaire

At baseline (prior to treatment), Months 1, 3, and 6/ET (prior to optional on-label treatment, if applicable), subjects will be asked to complete the Subject Satisfaction Questionnaire (Appendix 3).



Version: 1.0

 GALDERMA	Title <b>43USD1805 Clinical Study Protocol Dysport New Dilution GL</b>	Doc id [REDACTED]
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[REDACTED]

#### 7.1.6 Diary Card

[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 TEAEs, and focused physical examination findings.

#### 7.2.1 Focused Physical Examination

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

 <b>GALDERMA</b>	Title <b>43USD1805 Clinical Study Protocol Dysport New Dilution GL</b>	Doc id <span style="background-color: black; color: black;">XXXXXXXXXX</span>
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## 7.2.2 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.

### 7.2.2.1 *Definitions*

#### 7.2.2.1.1 *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 [7.2.2.3](#).
- The effects of Dysport and all BoNT products may spread from the area of injection to produce symptoms consistent with BoNT effects. These symptoms have been reported hours to weeks after injection. Remote spread of toxin that affects swallowing and breathing can be life threatening, and there have been reports of death. The risk of symptoms is increased in subjects who have underlying conditions (e.g. disorders of the neuromuscular junction) that would predispose them to these symptoms. Dysport is contraindicated in individuals with known hypersensitivity to any BoNT preparation or to any of the components in the formulation.

 <b>GALDERMA</b>	Title <b>43USD1805 Clinical Study Protocol Dysport New Dilution GL</b>	Doc id <span style="background-color: black; color: black;">XXXXXXXXXX</span>
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#### 7.2.2.1.2 *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.

#### 7.2.2.1.3 *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).

#### 7.2.2.1.4 *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).

 <b>GALDERMA</b>	Title <b>43USD1805 Clinical Study Protocol Dysport New Dilution GL</b>	Doc id <span style="background-color: black; color: black;">XXXXXXXXXX</span>
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#### 7.2.2.1.5 *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.

#### 7.2.2.1.6 *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.

#### 7.2.2.1.7 *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.

 <b>GALDERMA</b>	Title <b>43USD1805 Clinical Study Protocol Dysport New Dilution GL</b>	Doc id [REDACTED]
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2019-01-24 15:42

Effective date:

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.

#### **7.2.2.2 Reporting Procedures**

##### **7.2.2.2.1 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 [7.2.2.2.2](#)) and pregnancies (see Section [7.2.2.2.3](#)), 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 [7.2.2.2.2](#)).

Effective

Version: 1.0

 <b>GALDERMA</b>	Title <b>43USD1805 Clinical Study Protocol Dysport New Dilution GL</b>	Doc id [REDACTED]
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#### 7.2.2.2.2 *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 [7.2.2.1.3](#)).
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.



Additional contact details are provided in the Investigator's site file.

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

	<p>Title <b>43USD1805 Clinical Study Protocol Dysport New Dilution GL</b></p>	<p>Doc id [REDACTED]</p>
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Effective date: 2019-01-24 15:42

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.

#### 7.2.2.2.3 *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.

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Effective

Version: 1.0

 GALDERMA	Title <b>43USD1805 Clinical Study Protocol Dysport New Dilution GL</b>	Doc id [REDACTED]
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### **7.3 Other Assessments**

#### **7.3.1 Photography**

[REDACTED]

#### **7.3.2 Pregnancy Test**

For all women of childbearing potential a urine pregnancy test will be performed prior to treatment at screening/baseline and Month 6 (if optional on-label treatment is performed). A negative pregnancy test is required for study inclusion. The result will be documented.

### **7.4 Appropriateness of Measurements**

[REDACTED]

The subject satisfaction questionnaire is a tool that has been developed in order for the Sponsor to better understand the subject's needs and expectations with respect to abobotulinumtoxinA treatment.



2019-01-24 15:42

Effective date:

## *Effective*

Version: 1.0

## 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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 GALDERMA	Title <b>43USD1805 Clinical Study Protocol Dysport New Dilution GL</b>	Doc id [REDACTED]
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2019-01-24 15:42

Effective date:

*Effective*

Version: 1.0



2019-01-24 15:42

Effective date:

## *Effective*

Version: 1.0

Effective date: 2019-01-24 15:42

Effective date:

*Effective*

Version: 1.0

 GALDERMA	Title <b>43USD1805 Clinical Study Protocol Dysport New Dilution GL</b>	Doc id [REDACTED]
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2019-01-24 15:42

Effective date:

*Effective*

Version: 1.0





2019-01-24 15:42

Effective date:

## *Effective*

Version: 1.0

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	Title <b>43USD1805 Clinical Study Protocol Dysport New Dilution GL</b>	Doc id [REDACTED]
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## 9 STATISTICAL METHODS PLANNED

### 9.1 Statistical and Analytical Plans

A Statistical Analysis Plan (SAP) will be developed as a separate document. The SAP will contain a more detailed and technical description of specific data conventions, calculations and of statistical procedures for executing the analyses that are specified in the sections of the clinical study protocol below. The SAP will be finalized prior to database lock.

Any change made to the finalized SAP will be documented in the Clinical Study Report (CSR).

#### 9.1.1 Data Transformations

#### 9.1.2 Populations Analyzed and Evaluability

The statistical analyses will be performed based on the following subject populations.

##### 9.1.2.1 *Intent-to-treat (ITT) Efficacy Population*

The Intention-to-treat (ITT) population includes all subjects who are randomized and dispensed the investigational product, and will be analyzed according to the randomization scheme. All primary efficacy variables, secondary efficacy, and exploratory variables will be analyzed based on the ITT population.

##### 9.1.2.2 *Per-protocol (PP) Efficacy Population*

##### 9.1.2.3 *Safety Population*

The safety population includes all subjects who were administered the study product, and will be analyzed according to as-treated principle. All safety data will be summarized descriptively based on the safety population.

 <b>GALDERMA</b>	Title <b>43USD1805 Clinical Study Protocol Dysport New Dilution GL</b>	Doc id [REDACTED]
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Effective date: 2019-01-24 15:42

Effective

Version: 1.0

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

### 9.1.3 **Data Presentation and Graphics**

All statistical analyses, including summary tables and data listings, will be performed using the SAS® system (version 9).

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. The categorical variables will be summarized by number of subjects and percentage for each response category (N, %). The continuous variables will be summarized using n (number of observations), mean, median, minimum, maximum, and standard deviation for the data collected at each visit.

For analysis of duration of effect and time to onset of treatment response, Kaplan-Meier plots and estimates of the median event times will be used. Responder rates over time will be presented in graphs.

All study data will also be listed in subject data listings. Graphs will be utilized as appropriate.

### 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. 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. 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.

 Title **43USD1805 Clinical Study Protocol Dysport New Dilution GL** Doc id XXXXXXXXXX

Effective date: 2019-01-24 15:42

## *Effective*

Version: 1.0

### 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.

Subjects with CSP deviations will be listed individually, including subject number and observed deviation. They will also be summarized by study center and in total (by treatment group and overall). Depending on the seriousness of the deviation, the subject might be excluded from the PP population, which shall be documented prior to database lock.

### 9.1.5 Inferential Statistical Analyses

the first time in the history of the world, the people of the United States have been called upon to determine whether they will submit to the law of force, and give up the God-given right of self-government, or whether they will, in the language of their ancestors, stand by their principles and "die freemen rather than live slaves."

188

For more information, contact the Office of the Vice President for Research and Economic Development at 319-273-2500 or [research@uiowa.edu](mailto:research@uiowa.edu).

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2019-01-24 15:42

Effective date:

*Effective*

Version: 1.0

 GALDERMA	<small>Title</small> <b>43USD1805 Clinical Study Protocol Dysport New Dilution GL</b>	<small>Doc id</small> [REDACTED]
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## 9.2 Sample Size Determination

### 9.2.1 Historical Data

[REDACTED]

### 9.2.2 Assumptions

[REDACTED]

### 9.2.3 Sample Size Calculation

[REDACTED]

[REDACTED]

[REDACTED]

### 9.2.4 Interim Analysis

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

 <b>GALDERMA</b>	Title <b>43USD1805 Clinical Study Protocol Dysport New Dilution GL</b>	Doc id <span style="background-color: black; color: black;">XXXXXXXXXX</span>
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## 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).

	Title <b>43USD1805 Clinical Study Protocol Dysport New Dilution GL</b>	Doc id [REDACTED]
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Effective date: 2019-01-24 15:42

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 Changes in Clinical Study Conduct/Amendments**

### **10.5.1 Clinical Study Conduct**

With the exception of eliminating an immediate hazard to a subject, the Investigator should not deviate from the clinical study protocol or implement any changes without written approval from the Sponsor and prior review and documented approval/favorable opinion from the IRB/IEC of a protocol amendment.

Changes that involve only logistical or administrative changes to the clinical study protocol are authorized. The Investigator should document and explain any deviation from the clinical study protocol.

### **10.5.2 Amendments**

The Sponsor may modify the clinical study protocol at any time for ethical, medical, or scientific reasons. Any amendments will be handled according to applicable local regulations.

The Sponsor does not have to notify non-substantial amendments to the competent authorities or the Ethics Committees. However, non-substantial amendments should be recorded and detailed in subsequent submissions e.g., in the subsequent notification of a substantial amendment.

## **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.

Effective

Version: 1.0

	Title <b>43USD1805 Clinical Study Protocol Dysport New Dilution GL</b>	Doc id [REDACTED]
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Effective date: 2019-01-24 15:42

*Effective*

## 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.

Version: 1.0

	Title <b>43USD1805 Clinical Study Protocol Dysport New Dilution GL</b>	Doc id [REDACTED]
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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

 <b>GALDERMA</b>	Title <b>43USD1805 Clinical Study Protocol Dysport New Dilution GL</b>	Doc id [REDACTED]
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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.

## 11.8 Publication Policy

The Institution/PI's and the Sponsor's obligations regarding intellectual property rights, confidentiality, and publications are described in detail in the CTA.



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

 GALDERMA	Title <b>43USD1805 Clinical Study Protocol Dysport New Dilution GL</b>	Doc id [REDACTED]
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Effective date: 2019-01-24 15:42

*Effective*

Version: 1.0

 GALDERMA	Title <b>43USD1805 Clinical Study Protocol Dysport New Dilution GL</b>	Doc id [REDACTED]
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2019-01-24 15:42

Effective date:

*Effective*

Version: 1.0



 <b>GALDERMA</b>	Title <b>43USD1805 Clinical Study Protocol Dysport New Dilution GL</b>	Doc id [REDACTED]
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Effective date: 2019-01-24 15:42

## 12 LITERATURE REFERENCE LIST

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2. Carruthers, J. and A. Carruthers (2007). "The evolution of botulinum neurotoxin type A for cosmetic applications." *J Cosmet Laser Ther* 9(3): 186-192.
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7. Klassen, AF., SJ Cano, AM. Scott, AL. Pusic (2014) "Measuring outcomes that matter to face-lift patients: development and validation of FACE-Q appearance appraisal scales and adverse effects checklist for the lower face and neck." *Plast Reconstr Surg.* Jan;133(1):21-30.

Effective

Version: 1.0

 GALDERMA	<small>Title</small> <b>43USD1805 Clinical Study Protocol Dysport New Dilution GL</b>	Doc id [REDACTED]
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Effective date: 2019-01-24 15:42

*Effective*

Version: 1.0

 GALDERMA	Title <b>43USD1805 Clinical Study Protocol Dysport New Dilution GL</b>	Doc id [REDACTED]
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Effective date: 2019-01-24 15:42

*Effective*

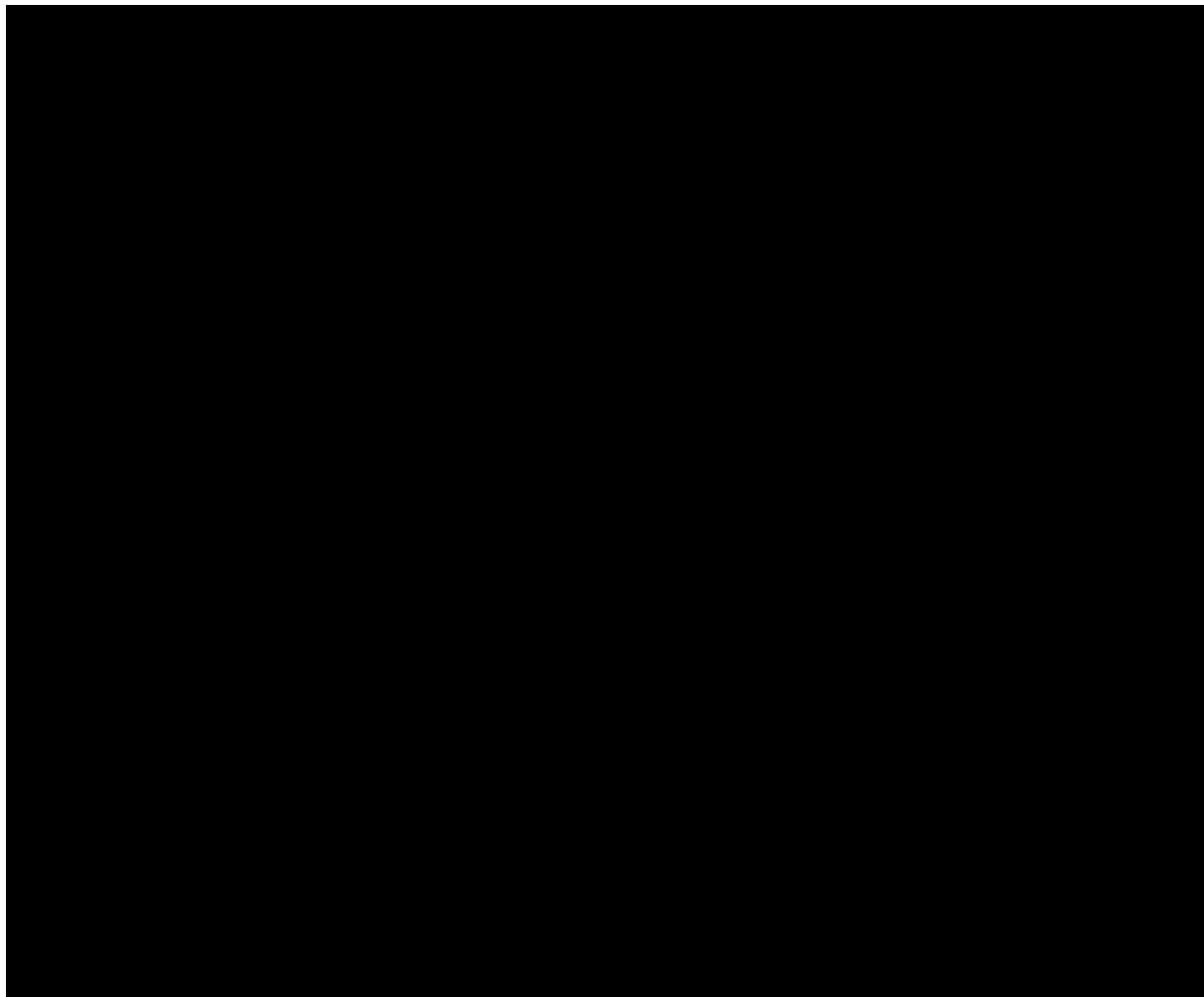
Version: 1.0

 GALDERMA	Title <b>43USD1805 Clinical Study Protocol Dysport New Dilution GL</b>	Doc id [REDACTED]
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Effective date: 2019-01-24 15:42

*Effective*

Version: 1.0



 GALDERMA	Title <b>43USD1805 Clinical Study Protocol Dysport New Dilution GL</b>	Doc id [REDACTED]
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Effective date: 2019-01-24 15:42

*Effective*

Version: 1.0

 GALDERMA	Title <b>43USD1805 Clinical Study Protocol Dysport New Dilution GL</b>	Doc id [REDACTED]
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Effective date: 2019-01-24 15:42

*Effective*

Version: 1.0

 GALDERMA	Title <b>43USD1805 Clinical Study Protocol Dysport New Dilution GL</b>	Doc id [REDACTED]
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Effective date: 2019-01-24 15:42

*Effective*

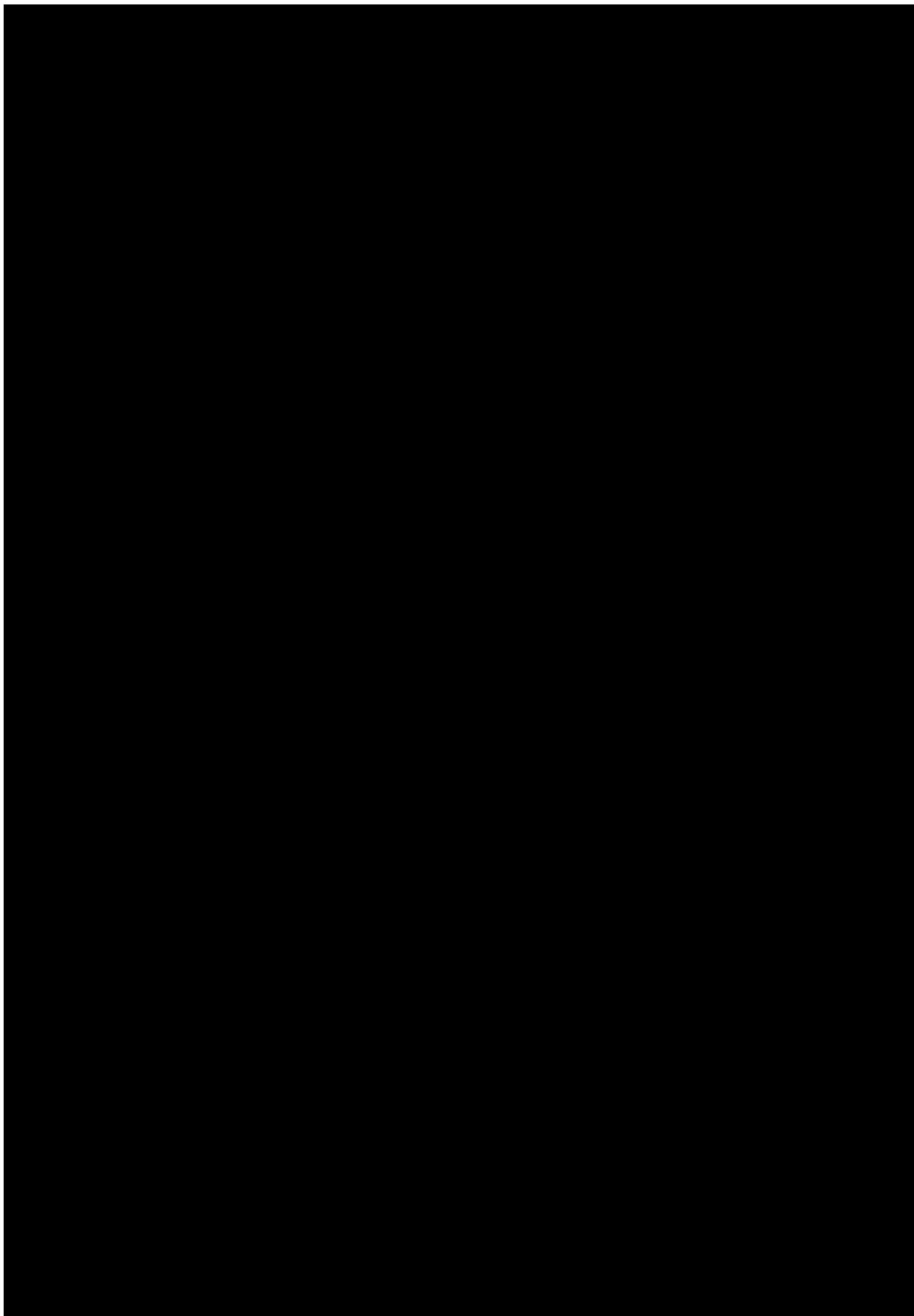
Version: 1.0

 GALDERMA	Title <b>43USD1805 Clinical Study Protocol Dysport New Dilution GL</b>	Doc id [REDACTED]
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Effective date: 2019-01-24 15:42

*Effective*

Version: 1.0



 GALDERMA	<small>Title</small> <b>43USD1805 Clinical Study Protocol Dysport New Dilution GL</b>	<small>Doc id</small> [REDACTED]
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Effective date: 2019-01-24 15:42

Effective date:

*Effective*

Version: 1.0



Title

43USD1805 Clinical Study Protocol Dysport New Dilution GL

Doc id

[REDACTED]

Effective date: 2019-01-24 15:42

*Effective*

Version: 1.0

 GALDERMA	Title <b>43USD1805 Clinical Study Protocol Dysport New Dilution GL</b>	Doc id [REDACTED]
---	---	----------------------

Effective date: 2019-01-24 15:42

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Version: 1.0

 GALDERMA	Title <b>43USD1805 Clinical Study Protocol Dysport New Dilution GL</b>	Doc id [REDACTED]
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Effective date: 2019-01-24 15:42

*Effective*

Version: 1.0

	Title <b>43USD1805 Clinical Study Protocol Dysport New Dilution GL</b>	Doc id [REDACTED]
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2019-01-24 15:42

Effective date:

## 14 SIGNED AGREEMENT OF THE CLINICAL STUDY PROTOCOL

CTN: 43USD1805

CSP title: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of a New Dilution and Injection Volume of AbobotulinumtoxinA for the Treatment of Moderate to Severe Glabellar Lines

I, the undersigned, have read and understand the CSP specified above, and agree on the contents. The CSP, the clinical trial agreement (CTA) and the additional information given in the Investigator's Brochure (IB) will serve as a basis for co-operation in this study.

### Principal Investigator

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Printed name

---

Signature

---

Date

---

Study center

Effective  
Version: 1.0

 <b>GALDERMA</b>	<small>Title</small> <b>43USD1805 Clinical Study Protocol Dysport New Dilution GL</b>	<small>Doc id</small> <span style="background-color: black; color: black;">[REDACTED]</span>
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2019-01-24 15:42

Effective date:

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Version: 1.0

## SIGNATURES PAGE

Date	Signed by
2019-01-24 00:57	<span style="background-color: black; color: black;">[REDACTED]</span>
<b>Justification</b>	Approved by Technical Expert
2019-01-24 07:58	<span style="background-color: black; color: black;">[REDACTED]</span>
<b>Justification</b>	Approved by Technical Expert
2019-01-24 08:49	<span style="background-color: black; color: black;">[REDACTED]</span>
<b>Justification</b>	Approved by Owner
2019-01-24 15:42	<span style="background-color: black; color: black;">[REDACTED]</span>
<b>Justification</b>	Compiled by