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CLINICAL STUDY PROTOCOL

Clinical Trial Number (CTN): 05PF2009

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TITLE PAGE

A Prospective, Non-interventional Study to Collect Subject and Physician Satisfaction During Long Term Treatment of Glabellar Lines with *Dysport*® in Subjects of Chinese Origin in Real Clinical Practice

CTN: 05PF2009

SPONSOR
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This clinical study shall be performed in compliance with the clinical trial agreement (CTA), the clinical study protocol (CSP), International Council for Harmonisation Good Clinical Practice (ICH 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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INVESTIGATOR AND ADMINISTRATIVE STRUCTURE

Role	Contact Information
PPD	
Investigators:	Approximately 10 study centers.
PPD	

Note: Further details on all participating Investigators and the complete administrative structure of the study are found in the study files. Note that administrative changes are to be documented in the study files without requiring a CSP amendment.

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SYNOPSIS

Clinical Study Title: A Prospective, Non-interventional Study to Collect Subject and Physician Satisfaction During Long Term Treatment of Glabellar Lines with *Dysport* in Subjects of Chinese Origin in Real Clinical Practice	
Clinical Study Phase:	Post-marketing study
Clinical Study Population:	Male and female adult subjects up to 65 years of age with moderate to severe glabellar lines (GL).
Clinical Study Design:	This is a prospective, longitudinal, non-interventional, multi-center study to collect subject and physician satisfaction, and treatment experience with *Dysport* in real clinical practice in subjects of Chinese origin. Approximately 250 subjects are planned to be included in the study to receive three injection cycles with *Dysport* in the GL. The decision by the physician to treat the subject with *Dysport* on a long term basis must be made before including the subject in the study, and has to be clearly separated and independent of the decision to include the subject in the study. Given the non-interventional nature of the study, subject visits, treatment regimen, and the administration of *Dysport* to treat GL will be carried out according to the physician's real clinical practice and the approved leaflet in China. The study consists of three injection cycles. Each injection cycle includes an injection visit and a follow up visit three weeks later (± 7 days). Following the 1st injection at Visit 1, subsequent injections, i.e., 2nd injection and 3rd injection, will be scheduled three to six months apart. The final follow up visit will be held three to six months after the subject's 3rd injection. The screening visit and the 1st injection visit may be conducted on the same day. Data will be collected at all visits, if held. Subjects and physicians, independent of each other, will assess the subject's GL severity, and will complete a questionnaire about satisfaction with treatment outcomes at all visits. Injection practice details for each injection visit, including muscle(s) injected, total dose and volume, dose and volume per injection point, and number of injection points will be collected per the study objectives. Adverse events (AEs) will be collected during the study.
Total Number of Subjects (Planned):	Approximately 250 subjects will be included in the study. To avoid bias in the recruitment of subjects, physician will be asked to include all consecutive subjects during Botulinum toxin A (BoNT-A) consultations to achieve the recruitment target of 20-30 subjects during a restricted and defined period. If consecutive inclusions are not feasible (e.g., administrative constraints), and in order not to disturb the medical activities in the physician's clinic, physician will be authorized to space the inclusions (e.g. inclusion of one subject after every two, or three, etc.), and will follow the same recruitment frequency until achievement of the recruitment target. The modalities for recruitment will have to be determined prior to recruitment start.
Number of Clinical Study Centers (Planned):	10 study centers

Region(s) / Country Involved (Planned):	China
Clinical Study Duration:	The planned clinical study duration is approximately 24 months. The planned duration of recruitment is approximately six months.
Duration of Subject Participation:	In accordance with the treatment regimen and the physician's real clinical practice, study participation for each subject is anticipated to be approximately nine to 18 months.
Inclusion Criteria:	1. Adult male or female up to 65 years of age, and of Chinese origin. 2. Moderate (grade 2) or severe (grade 3) glabellar lines at max frown as assessed by the physician using the CCI [redacted] 3. Prior to and independent of study, subject is seeking long term treatment of their glabellar lines. 4. Prior to and independent of the study participation, physician intended to treat the subject with *Dysport*. 5. Time and ability to complete the study and comply with instructions. 6. Understands the study requirements and signed the informed consent form (ICF).
Exclusion Criteria	1. Hypersensitive to *Dysport* or its excipients. 2. Presence of contraindications to *Dysport* treatment as specified in the approved leaflet in China. 3. Subject is at risk for precautions, warnings, and/or contraindications to *Dysport* as specified in the approved leaflet in China 4. Subject has an infection in the proposed treatment area. 5. Subjects has had treatment failure experience with other toxins. 6. Pregnant or breast feeding female, or female intending to get pregnant during the study. 7. Participation in a clinical study, interventional or non-interventional, within 30 days prior to study entry (signature of informed consent).
Treatment:	This is a non-interventional study (NIS). The decision by the physician to treat the subject with *Dysport* on a long term basis must be made before including the subject in the study, and has to be clearly separated and independent of the decision to include the subject in the study. Commercially available *Dysport* will be used in the study but will not be supplied by the study Sponsor. The physician is free to choose *Dysport* modalities of administration in accordance with the local SmPC and the approved leaflet in China.

Product:	Commercially available *Dysport*, a BoNT-A product.
Strength/Concentration:	300 units (U) per vial
Reconstitution Volume:	1.5 milliliter (mL)
Dosage (total dose per treatment):	50 U total (0.25 mL total) 10 U per injection site (0.05 mL per injection site)
Route:	Intramuscular injection
Treatment Regimen:	Three injection cycles, 3-6 months apart
Location of Treated Area:	Glabellar region
Efficacy Assessments:	Efficacy assessments include: • Subject Satisfaction Questionnaire • Subject assessment of GL severity at max frown using the 4-point Categorical Scale • Physician Satisfaction Questionnaire • Physician assessment of GL severity at rest and max frown using the Investigator's 4-point Photographic Scale • Injection practice details
Primary Objective and Endpoint:	The primary objective of the study is to evaluate subject satisfaction after three injection cycles with *Dysport* in the GL. At Visit 6 (i.e., three weeks, ± 7 days, after the 3rd injection) subjects will be asked "What is your overall satisfaction after three treatment cycles with *Dysport*?" See Appendix 1 Question 17. Response options: • Very Satisfied • Satisfied • Dissatisfied • Very Dissatisfied The primary endpoint will evaluate the proportion of subjects in each response category.
Secondary Objectives and Endpoints:	The secondary efficacy objectives and endpoints of the study are: 1. Objective: To evaluate physician satisfaction after three injection cycles with *Dysport* in the GL. Endpoint: Proportion of subjects in each response category for the physician's overall satisfaction with *Dysport* after three injection cycles will be evaluated at Visit 6 (i.e., three weeks, ± 7 days, after the 3rd injection). See Appendix 2, Question 7. 2. Objective: To evaluate subject CCI [redacted] after each injection cycle with *Dysport* in the GL. Endpoints: a. Proportion of subjects in each response category per question answered on the Subject Satisfaction Questionnaire complete at all visits. See Appendix 1. CCI [redacted]

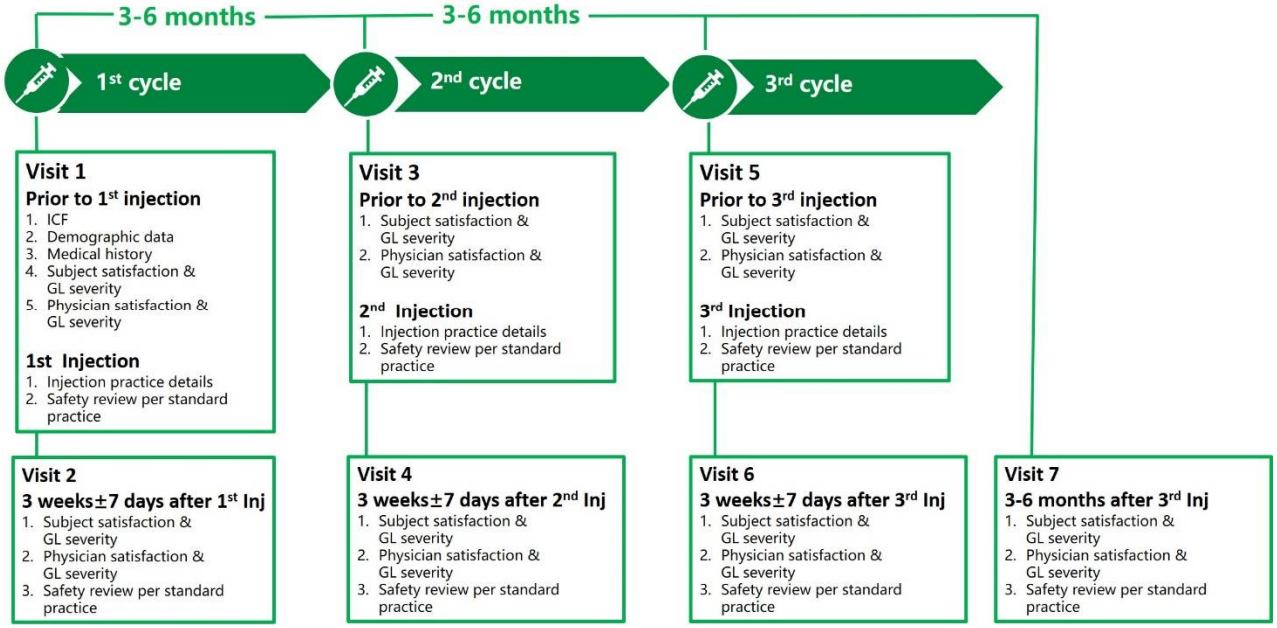
	CCI [redacted]
Safety Assessment:	AEs will be collected during the study. AE data will be recorded in the electronic case report form (eCRF) for inclusion in the clinical database. In addition to AEs, physicians will report any Adverse Drug Reaction (ADR), Unexpected ADR (UADR), Serious Adverse Event (SAE), Special Situation (SS) and pregnancy events to CCI [redacted] in accordance with regulatory requirements and timelines. The data will be included in the global drug safety database.
Statistical Methods:	In general, efficacy, safety, and baseline characteristics variables will be presented using descriptive statistics and graphs, as appropriate. Continuous endpoints will be summarized using descriptive statistics (e.g., mean, median, standard deviation, minimum and maximum values). Categorical endpoints will be presented in frequency tables with number and percentage of observations for each level. 95% confidence intervals (CIs) will be calculated whenever appropriate.
Sample Size:	The sample size of approximately 250 subjects is not based on a statistical calculation. The selected number of subjects is regarded as sufficient for an evaluation of the studied endpoints by using descriptive statistics.
Analysis:	Since this is an open non-interventional study, available data may be analyzed prior to study completion.

CLINICAL STUDY SCHEMATIC AND FLOW CHART

Table 1 Clinical Study Schematic

	Physician decision to treat the subject with *Dysport* on a long term basis
	↓
	Screening/Baseline/1st Injection ↓
Treatment	Commercially available *Dysport*
Treatment Frequency	Three injection visits, three to six months apart (Visits 1, 3, 5) ↓
Follow up Visits	A follow up visit occurs three weeks (± 7 days) after each injection visit (Visits 2, 4, 6) Final follow up visit occurs three to six months after the 3rd injection (Visit 7)

Figure 1 Study Flow Chart



SCHEDULE OF ASSESSMENTS

Table 2 Schedule of Assessments

	Injection Cycle 1		Injection Cycle 2		Injection Cycle 3		
Visit Number	Visit 1[1]	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7
Visit Name	Screening Baseline/ Injection 1[1]	Follow up 1	Injection 2	Follow up 2	Injection 3	Follow up 3	Follow up 4
Visit Window	≤ 30 days of Baseline/Injection 1	3 weeks (± 7 days) from Injection 1	3-6 months from Injection 1	3 weeks (± 7 days) from Injection 2	3-6 months from Injection 2	3 weeks (± 7 days) from Injection 3	3-6 months from Injection 3
Informed Consent	X						
Demographic Data	X						
Medical History	X						
Safety Review	X	X	X	X	X	X	X
Injection Practice Details	X		X		X		
Physician GL Severity Assessment	X[2]	X	X[2]	X	X[2]	X	X
Physician Satisfaction Questionnaire	X[2]	X	X[2]	X	X[2]	X	X
Subject assessments							
Subject GL Severity Assessment	X[2]	X	X[2]	X	X[2]	X	X
Subject Satisfaction Questionnaire	X[2]	X	X[2]	X	X[2]	X	X

Definitions:

- 1 month = 4 weeks

1. Screening and Baseline/Visit 1 (i.e., Injection 1) may be performed on the same day. If performed as separate visits, informed consent, demographic data, and medical history should be complete at Screening, and all other remaining visit procedures and confirmation of subject medical history should be performed at Baseline /Visit 1 (i.e., Injection 1).
2. Prior to injection.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	*Term*
°C	Degrees Celsius
ADR	Adverse Drug Reaction
AE	Adverse Event
BoNT	Botulinum toxin
BoNT-A	Botulinum toxin serotype A
CI	Confidence interval
eCRF	electronic Case Report Forms
CRO	Contract Research Organization
CSP	Clinical Study Protocol
CTA	Clinical Trial Agreement
e.g.	For Example (Latin: exempli gratia)
etc.	Et cetera
G	Gauge
GL	Glabellar lines
GCP	Good Clinical Practice
HSA	human serum albumin
ICH	International Council for Harmonisation
i.e.	That is (Latin: id est)
IEC	Independent Ethics Committee
ICF	Informed Consent Form
mL	Milliliter
N/A	Not Applicable
NIS	Non-interventional study
NMPA	National Medical Products Administration
p	Page(s)
PP	Per-Protocol
PQC	Product Quality Complaint
QA	Quality Assurance
RA	Regulatory Authority
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SS	Special Situation
U	Units
UADR	Unexpected Adverse Drug Reaction

Note: Physician and Investigator are synonymous and used interchangeably throughout the CSP.

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,[1, 2] 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.[1] 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.[3]

Ipsen is the marketing holder of *Dysport*, a BoNT-A product, which is currently licensed in over 75 countries worldwide, and it was approved by the National Medical Products Administration of China (NMPA) in 2020. It is indicated for the temporary improvement in the appearance of moderate to severe glabellar lines (GL) caused by the activity of corrugator or musculus procerus in adult patients not more than 65 years of age. To achieve a clinical effect, a total of 50 units (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.

Controlled clinical trials in China demonstrated the short and long term efficacy and safety of *Dysport* in the treatment of the GL; however, there is a lack of scientific data related to subject and physician reported outcomes. The rationale for the current study is to collect subject and physician satisfaction, and long term treatment experience with *Dysport* in the GL in subjects of Chinese origin in a real-life clinical setting.

1.2 Drug Profile

Dysport contains a neurotoxin complex that is produced by fermentation of Clostridium botulinum bacteria toxin type A, Hall strain. This haemagglutinin complex is composed of a number of proteins naturally produced along with the toxin which is believed to stabilize it but which has no apparent therapeutic effect in its own right. *Dysport* 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 approved leaflet in China.[4]

Dysport is labelled for a dose of 50 U to be injected 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. Retreatment is permitted every three months.[4]

1.3 Risk/Benefit Assessment

In placebo-controlled clinical trials of *Dysport*, very common adverse reactions (> 1/10) following injection were injection site reactions (e.g. erythema, oedema, irritation, rash, pruritus, paraesthesia, pain, discomfort, stinging and haematoma), and headache. Common reactions (> 1/100) included eye disorders (e.g., asthenopia, eyelid ptosis, eyelid oedema, lacrimation increased, dry eye, muscle twitching (twitching of muscles around the eyes), and facial paresis (due to temporary paresis of facial muscles proximal to injection sites, it is predominantly manifested as brow paresis).[4]

Side effects related to spread of toxin distant from the site of administration have been reported, such as dry mouth, excessive muscle weakness, dysphagia, aspiration pneumonia, with fatal outcome in some very rare cases. Hypersensitivity reactions have also been reported post-marketing.[4]

The dose administered and the minimum time between treatments are according to the approved leaflet in China. Steps to reduce complications of ptosis are outlined in Section 6.1.5. Subject will be provided with information on the benefits and risks of their treatment by the physician in accordance with their real clinical practice.

The risks associated with participation in this study are considered acceptable compared to the anticipated high degree of subject and physician satisfaction with treatment and the treatment regimen.

2 CLINICAL STUDY OBJECTIVES

2.1 Clinical Study Objectives

The objectives of this study are to collect subject and physician satisfaction, and long term treatment experience with *Dysport* in the GL in subjects of Chinese origin in a real-life clinical setting.

2.1.1 Primary Efficacy Objectives and Endpoints

The primary objective of the study is to evaluate subject satisfaction after three injection cycles with *Dysport* in the GL.

At Visit 6 (i.e., three weeks, ± 7 days, after the 3rd injection) subjects will be asked "What is your overall satisfaction after three treatments cycles with *Dysport*?" See Appendix 1, Question 17.

Response options:

- Very Satisfied
- Satisfied
- Dissatisfied
- Very Dissatisfied

The primary endpoint will evaluate the proportion of subjects in each response category.

2.1.2 Secondary Efficacy Objectives and Endpoints

The secondary efficacy objectives and endpoints of the study are:

1. Objective: To evaluate physician satisfaction after three injection cycles with *Dysport* in the GL.

   Endpoint: Proportion of subjects in each response category for the physician's overall satisfaction with *Dysport* after three injection cycles will be evaluated at Visit 6 (i.e., three weeks, ± 7 days, after the 3rd injection). See Appendix 2, Question 7.

2. Objective: To evaluate subject CCI [redacted] after each injection cycle with *Dysport* in the GL.

   Endpoints:

   a. Proportion of subjects in each response category per question answered on the Subject Satisfaction Questionnaire complete at all visits. See Appendix 1

CCI [redacted]

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3 OVERALL CLINICAL STUDY DESCRIPTION

This is a prospective, longitudinal, non-interventional, multi-center study to collect subject and physician satisfaction, and treatment experience with *Dysport* in real clinical practice in subjects of Chinese origin.

Approximately 250 subjects are planned to be included in the study to receive three injection cycles with *Dysport* in the GL. The decision by the physician to treat the subject with *Dysport* on a long term basis must be made before including the subject in the study, and has to be clearly separated and independent of the decision to include the subject in the study.

Given the non-interventional nature of the study, subject visits, treatment regimen, and the administration of *Dysport* to treat GL will be carried out according to the physician's real clinical practice and the approved leaflet in China.

The study consists of three injection cycles. Each injection cycle includes an injection visit and a follow up visit three weeks later (± 7 days). Following the 1st injection at Visit 1, subsequent injections, i.e., 2nd injection and 3rd injection, will be scheduled three to six months apart. The final follow up visit will be held three to six months after the subject's 3rd injection.

The screening visit and the 1st injection visit may be conducted on the same day. Data will be collected at all visits, if held. Subjects and physicians, independent of each other, will assess the subject's GL severity, and will complete a questionnaire about satisfaction with treatment outcomes at all visits.

Injection practice details for each injection visit, including muscle(s) injected, total dose and volume, dose and volume per injection point, and number of injection points will be collected per the study objectives.

Adverse events (AEs) will be collected during the study.

4 CLINICAL STUDY DURATION AND TERMINATION

The planned clinical study duration is approximately 24 months. The date of end of the clinical study is defined as the date of the last visit of the last subject.

The planned duration of recruitment is approximately six months.

In accordance with the treatment regimen and the physician's real clinical practice, study participation for each subject is anticipated to be approximately nine to 18 months.

The Sponsor may decide to prematurely terminate or suspend the participation of a particular clinical study center (for example, for 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 drug(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

Approximately 250 subjects will be included in the study.

To avoid bias in the recruitment of subjects, physician will be asked to include all consecutive subjects during Botulinum toxin A (BoNT-A) consultations to achieve the recruitment target of 20-30 subjects during a restricted and defined period. If consecutive inclusions are not feasible (e.g., administrative constraints), and in order not to disturb the medical activities in the physician's clinic, physician will be authorized to space the inclusions (e.g. inclusion of one subject after every two, or three, etc.), and will follow the same recruitment frequency until achievement of the recruitment target. The modalities for recruitment will have to be determined prior to recruitment start.

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 screening/baseline.

5.2.1 Inclusion Criteria

1. Adult male or female up to 65 years of age, and of Chinese origin.
2. Moderate (grade 2) or severe (grade 3) glabellar lines at max frown as assessed by the physician CCI [redacted]
3. Prior to and independent of study, subject is seeking long term treatment of their glabellar lines.
4. Prior to and independent of the study participation, physician intended to treat the subject with *Dysport*.
5. Time and ability to complete the study and comply with instructions.
6. Understands the study requirements and signed the informed consent form (ICF).

5.2.2 Exclusion Criteria

1. Hypersensitive to *Dysport* or its excipients.
2. Presence of contraindications to *Dysport* treatment as specified in the approved leaflet in China.
3. Subject is at risk for precautions, warnings, and/or contraindications to *Dysport* as specified in the approved leaflet in China.
4. Subject has an infection in the proposed treatment area.

5. Subjects has had treatment failure experience with other toxins.

6. Pregnant or breast feeding female, or female intending to get pregnant during the study.

7. Participation in a clinical trial, interventional or non-interventional, within 30 days prior to study entry (signature of informed consent).

5.3 Medical History

Relevant history of surgical events and medical conditions shall be documented using medical terminology according to the physician's real clinical practice.

5.4 Previous and Concomitant Medications and Therapies

Previous and concomitant medications and therapies shall be documented using medical terminology according to the physician's real clinical practice.

5.5 Procedures/Reasons for Subject Discontinuation

The importance of completing the entire clinical study should be explained to the subject by the clinical study personnel; however, 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.

6 CLINICAL SUPPLIES

Commercially available *Dysport* will be used in the study but will not be supplied by the study Sponsor per the non-interventional nature of the study.

6.1 Clinical Supply Identification and Use

Dysport is a white lyophilised powder provided in a vial containing 300 U botulinum toxin type A hemagglutinin complex, 125 µg human serum albumin, and 2.5 mg of lactose. Each vial will be reconstituted with 0.9% sodium chloride for injection to yield a solution containing 200 U per mL. A total volume of 0.25 mL of reconstituted *Dysport* will be administered in 5 equal aliquots of 0.05 mL each.

The 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. It should not be frozen and should be protected from light.

6.1.1 Product Description

Table 3 Description and Usage of the Study Drug

	Product
Trade Name	*Dysport*
Name of Drug Substance	abobotulinumtoxinA
Internal Code	N/A
Pharmaceutical Form	Lyophilised powder
Strength	300 U per vial
Packaging	Single-use vial for reconstitution with 1.5 mL 0.9% Sodium Chloride Injection
Storage conditions	2-8ºC
Reconstitution volume	1.5 mL
Dosage	50 U total (0.25 mL total) 10 U per injection site (0.05 mL per injection site)
Route	Intramuscular injection
Dose regimen	Up to three treatment cycles, 3-6 months apart
Location of treated area	Glabellar region

6.1.2 Subject Identification Number (SIN)

Each study participant who has signed the ICF will be entered into the electronic Case Report Forms (eCRF) system and a subject number will be assigned via the eCRF system. 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. The reason for excluding a consenting subject from entering the study should be specified in each case. A screen failure should not be re-screened in the study.

All subjects who have signed the ICF should be listed. Sufficient information to link the eCRF to the medical records should be recorded in the source documentation.

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

6.1.3 Method of Treatment Assignment

Not applicable; this is a non-interventional study.

6.1.4 Randomization Number

Not applicable; this is a non-interventional study.

6.1.5 Dosage and Administration

This is a non-interventional study. The decision by the physician to treat the subject with *Dysport* on a long term bases must be made before including the subject in the study. The physician is free to choose *Dysport* modalities of administration in accordance with the approved leaflet in China.[4]

The units of Botulinum Toxin Type A are specific to the preparation and are not interchangeable with other preparations of botulinum toxin.

Botulinum Toxin Type A must be administered by appropriately qualified physicians with relevant professional knowledge and skills.

When preparing and handling Botulinum Toxin Type A solutions, the use of gloves is recommended. If Botulinum Toxin Type A dry powder or reconstituted solution should come into contact with the skin or mucous membranes, they should be washed thoroughly with water.

Dysport is supplied as a single-use vial. Each vial is intended for one treatment administration session for a single subject. When reconstituting the product, the exposed central portion of the rubber stopper should be cleaned with alcohol immediately prior to piercing the septum. A sterile 23 gauge (G) or 25 G needle should be used. The product should be reconstituted with 1.5 mL of sodium chloride injection (0.9%) to yield a solution containing 200 U per mL. Appearance of product after reconstitution: A clear, colorless solution, free from particulate matter.

Prior to injection, remove any make-up and disinfect the skin with a local antiseptic.

Before injection, place the thumb or index finger firmly below the orbital rim in order to prevent extravasation below the orbital rim. The needle should be pointed upward and medially during the injection.

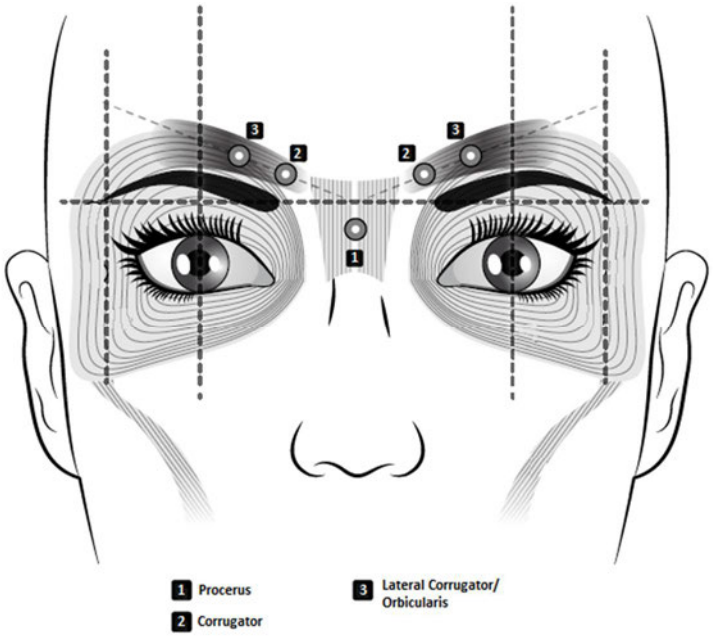
In order to reduce the complication of ptosis, the following steps should be taken:

- Avoid injections near the *levator palpebrae superioris* muscle, particularly in patients with larger *depressor supercilii*.

- Injections in the *corrugator* muscle must be made into the central part of that muscle, at least 1 cm above the orbital rim.

The recommended dose is 50 U (0.25 mL of reconstituted solution) of *Dysport* divided into five injection sites, 10 U (0.05 mL of reconstituted solution) administered intramuscularly, at right angles to the skin, into each of the five sites: two injections into each *corrugator* muscle and one into the *procerus* muscle near the nasofrontal angle as shown in Figure 2. Intramuscular injections performed with a sterile 29-30 G needle.

Figure 2 Injection Sites for Treating Glabellar Lines



1. Procerus 2. Corrugator 3. Lateral Corrugator/Orbicularis

Immediately after treatment of the patient, any residual *Dysport* which may be present in either vial or syringe should be inactivated with dilute hypochlorite solution (1% available chlorine).

Spillage of *Dysport* should be wiped up with an absorbent cloth soaked in dilute hypochlorite solution.

Any unused product or waste material should be disposed of in accordance with local requirements.

Discard needle and syringe in accordance with local regulations.

6.1.5.1 Post-treatment Care

Subjects should be provided with post-treatment care instructions per the physician's real clinical practice.

6.1.5.2 Treatment Regimen

The treatment regimen will be performed according to the approved leaflet in China and the physician's real clinical practice. Each enrolled subject will receive treatment with *Dysport* in the GL at Visits 1, 3, and 5, scheduled three to six months apart.

6.2 Product Packaging and Labeling

Commercially available *Dysport* will be used in the study.

6.3 Supplies Management

6.3.1 Accountability

Commercially available *Dysport* will be used in the study. The physician is responsible for suppling the product used in the study, and accountability should be documented according to the physician's real clinical practice.

6.3.2 Storage of Study Drug(s)

Dysport should be stored in accordance with the approved leaflet in China.

6.3.3 Dispensing and Return

Not applicable; this is a non-interventional study.

6.3.4 Treatment Compliance Management and Record

This is a non-interventional study. The decision by the physician to treat the subject with *Dysport* on a long term bases must be made before including the subject in the study. The physician is free to choose *Dysport* modalities of administration in accordance with the approved leaflet in China.

The treatment is an injection administered by the physician. Injection practice details for each injection visit, including muscle(s) injected, total dose and volume, dose and volume per injection point, and number of injection points will be collected per the study objectives.

6.3.5 Product Quality Complaints

Product Quality Complaints (PQCs) should be reported to CCI [redacted] 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, physician, or study center 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 should be clearly

described in an email submitted by the study center personnel to CCI within 24 hours of awareness. Affected study product should be quarantined, and not used, until further notice by the CCI

CCI	

See Investigator and Administrative Structure for additional contact details.

In addition to submitting the PQC, any subject reaction associated with a PQC should be documented and evaluated by the physician according to Section 8.

6.4 Dose Modification

Per real clinical practice, the physician is to administration *Dysport* in accordance with the approved leaflet in China.[4]

6.5 Blinding

Not applicable; this is a non-interventional study.

7 EFFICACY ASSESSMENTS

7.1 Subject Satisfaction Questionnaire

Subjects will be asked to complete the Subject Satisfaction Questionnaire, all or in part as specified, at all study visits, prior to treatment, as applicable (Appendix 1). The subject should complete the questionnaire independent of the physician.

7.2 Physician Satisfaction Questionnaire

Physicians will complete the Physician Satisfaction Questionnaire, all or in part as specified, at all study visits, prior to treatment, as applicable (Appendix 2). The physician should complete the questionnaire independent of the subject.

7.3 Subject Self-Assessment of GL Severity

Subjects will evaluate the appearance of their glabellar lines at max frown using a 4-point Categorical Scale. The 4-point Categorical Scale represents the severity of glabellar lines from no wrinkles (grade 0) to severe wrinkles (grade 3) as represented in Table 4.

The subject self-assessment of GL severity will be complete at all study visits, prior to treatment, as applicable, and should be made independently of the physician's assessment. See Appendix 3 for additional details and subject instructions.

Table 4 4-point Categorical Scale of GL Severity

Grade	Severity of Glabellar Lines
0	No wrinkles
1	Mild wrinkles
2	Moderate wrinkles
3	Severe wrinkles

With guidance from the physician, subjects may also reference the CCI [redacted]) when completing their self-assessment.

7.4 Physician Live Assessment of GL Severity

Physicians will use the CCI [redacted] for direct, live comparison of the severity of the subject's glabellar lines at rest and max frown at all study visits, prior to treatment, as applicable.

The CCI [redacted] includes two grading systems: one for the assessments at rest, and one for the assessments at max frown. The scale represents the severity of glabellar lines from none (grade 0), mild (grade 1), moderate (grade 2) to severe (grade 3). Each grade is also depicted by an individual photograph and a descriptive text.

Physicians will be trained on the use of the scale, and the assessment of GL severity at rest should be performed before the assessment at max frown. See Appendix 4 for physician instructions and CCI [redacted]

8 SAFETY ASSESSMENTS

AEs will be recorded in the eCRF for inclusion in the clinical database.

In addition, physicians will report all AEs non-serious, serious, and/or unexpected ADRs, and SS events to CCI in accordance with regulatory reporting requirements and timelines. The data will be included in the global drug safety database.

8.1 Definitions

8.1.1 Adverse Event (AE)

Any untoward medical occurrence in a patient or 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 product, whether or not related to the medicinal 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) compared to the condition at the first visit, should be considered as an AE.

8.1.2 Adverse Drug Reaction (ADR)

For marketed medicinal products, an ADR is a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of diseases or for modifications of physiological function.

8.1.3 Unexpected Adverse Drug Reaction (UADR)

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

8.1.4 Serious Adverse Event (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 a 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.

In-patient hospitalization is considered to have occurred if the subject 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 solely for the purpose of a diagnostic test, even if related to an AE, elective hospitalization for an intervention which 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 an administrative admission (e.g., for an annual physical examination) may not itself constitutes sufficient grounds to be considered as SAE.

8.1.5 Special Situation (SS) Events

A Special Situation (SS) event is an incidence of overdose, off-label use, medication error, occupational exposure, abuse, misuse or lack of therapeutic efficacy while using the medicinal product, or any instance of drug exposure during pregnancy or breast-feeding. A SS should be reported even if it is not associated with an adverse event.

8.2 Severity

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

The physician is to classify the intensity of AEs using the following definitions as a guideline. For this classification, the physician 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.

8.3 Relationship to the Product and/or Procedure

The physician is to determine whether there is a reasonable causal relationship between the occurrence of the reaction and exposure to the product and/or the injection 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 a reaction is to be completed using the following definitions as a guidelines.

Reasonable Possibility:

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

- The product and the reaction.
- The injection procedure (injection related trauma, etc.) and the reaction.

A two-point scale (Yes or No response) shall be used for the causality assessment.

- “Do you consider that there is a reasonable possibility that the reaction may have been caused by the product?”, and
- “Do you consider that there is a reasonable possibility that the reaction may have been caused by the injection procedure?”

If either of these questions is answered Yes, the reaction is considered related, and should be reported according to the procedures outlined in Section 8.4.

No Reasonable Possibility:

No suggestive evidence or arguments can be identified regarding a causal relationship between the product or the procedure and the reaction.

8.4 Reporting Procedures

AE data will be recorded in the eCRF for inclusion in the clinical database and will be reported to CCI .

In addition, any ADR/UADR/SAE/SS and pregnancy must be reported immediately (within 24 hours of the physician’s knowledge of the event) to the following:

CCI

See Investigator and Administrative Structure for additional contact information.

In order to facilitate this reporting, the physicians will be provided with Adverse Event and Special Situation Reporting Form If the immediate report is submitted by telephone, this must be followed by detailed written reports using the Adverse Event and Special Situation Reporting Form .

8.4.1 Minimum Reporting Criteria

The following information is the minimum that must be provided to the pharmacovigilance contact within 24 hours of being aware of such adverse reactions:

- Subject identifier
- Product
- AE term and description
- Physician name and contact details

Any additional information included in the Adverse Event and Special Situation Reporting Form must be provided as soon as it is available.

The physician should report a diagnosis or a syndrome rather than individual signs or symptoms. The physician should also try to separate a primary AE considered as the foremost untoward medical occurrence from secondary AE which occurred as complications.

8.5 Pregnancy

Pregnancy itself is not regarded as an adverse reaction unless there is a suspicion that the product has interfered with a contraceptive method. If pregnancy occurs while using the product, the outcome of the pregnancy will then need to be collected. This applies to whether or not the pregnancy is considered to be related to interference of the product with a contraceptive method.

Any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.

Abnormal pregnancy outcomes (e.g. spontaneous abortion, foetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.

Information regarding pregnancies must be manually collected on the Drug Exposure for Pregnancy Form, item 1 to 19.

Outcome information should also be collected on the Drug Exposure for Pregnancy Form, item 20 to 29. Drug Exposure for Pregnancy Form must be reported to CCI immediately (within 24 hours of the physician's knowledge of the event).

The physician must instruct all female subjects to inform them immediately should they become pregnant while using the product. The physician should counsel the subject, discussing the risks of continuing with the pregnancy and the possible effects on the fetus.

8.6 Appropriateness of Measurements

The satisfaction questionnaires are tools that have been developed in order for the Sponsor to better understand the subject and physician needs and expectations with respect to *Dysport* treatment and the treatment regimen.

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

9 CLINICAL STUDY VISITS DESCRIPTIONS AND PROCEDURES

9.1 Description of Clinical Study Visits

Please refer to the schedule of assessment table (Table 2).

The decision to administer *Dysport* must be made by the treating physician before including the subject in the study and has to be clearly separated and independent of the decision to include the subject in the study.

The treatment regimen will be performed according to the approved leaflet in China and the physician's real clinical practice.

9.1.1 Screening (≤ 30 days of Baseline/Injection 1)

NOTE: Screening and Baseline/Visit 1 (i.e., Injection 1) may be performed on the same day. If performed as separate visits, informed consent, demographic data, and medical history should be complete at Screening, and all other remaining visit procedures and confirmation of subject medical history should be performed at Baseline/Visit 1 (i.e., Injection 1).

1. Review and explain the nature of the study to the subject.
2. Obtain the signed and dated ICF prior to performing any study-related evaluations and/or procedures. Provide a fully completed dated and signed copy to the subject.
3. Collect information regarding demographics, relevant medical history, previous therapies and procedures, and concomitant medications and procedures in accordance with the physician's real clinical practice.

9.1.2 Injection Visits / Visits 1, 3 and 5 (3-6 months apart)

1. If Screening is performed as a separate visit, confirm subject medical history.
2. Subject to complete self-assessment of glabellar line severity at max frown using the 4-point Categorical Scale. See Section 7.3 and Appendix 3.
3. Subject to complete the Subject Satisfaction Questionnaire. See Appendix 1.
4. Physician to complete assessment of the subject's glabellar line severity at rest and max frown using CCI [redacted]
5. Physician to complete the CCI [redacted]. See Appendix 2.
6. Physician or designee to prepare *Dysport* treatment for the subject. See Section 6.1.5.
7. Prior to injection, clean the subject's treatment area with a suitable antiseptic solution. See Section 6.1.5.
8. The physician will administer *Dysport* treatment. See Section 6.1.5.

9. The physician will document injection practice details including muscle(s) injected, total dose and volume, dose and volume per injection point, and number of injection points.
10. Physician or designee will ask the subject about reactions, and document in accordance with the physician's real clinical practice.
11. Schedule the subject's follow up visit three weeks (± 7 days) from the date of injection.

9.1.3 Follow up Visits / Visits 2, 4, and 6 (three weeks (± 7 days) from last injection visit)

1. Subject to complete self-assessment of glabellar line severity at max frown using the Static 4-point Categorical Scale. See 7.3 and Appendix 3.
2. Subject to complete the Subject Satisfaction Questionnaire. See Appendix 1.
3. Physician to complete assessment of the subject's glabellar line severity at rest and max frown CCI [redacted]
4. Physician to complete the Physician Satisfaction Questionnaire. See Appendix 2.
5. Physician or designee will ask the subject about reactions, and document in accordance with the physician's real clinical practice.
6. Schedule the subject's next visit three to six months from the date of the injection visit.

9.1.4 Final Follow up Visit / Visit 7 (3-6 months from Visit 5)

1. Subject to complete self-assessment of glabellar line severity at max frown using the Static 4-point Categorical Scale. See 7.3 and Appendix 3.
2. Subject to complete the Subject Satisfaction Questionnaire. See Appendix 1.
3. Physician to complete assessment of the subject's glabellar line severity at rest and max frown CCI [redacted]
4. Physician to complete the CCI [redacted] See Appendix 2.
5. Physician or designee will ask the subject about reactions, and document in accordance with the physician's real clinical practice.
6. Exit the subject from the study.

10 STATISTICAL METHODS PLANNED

10.1 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 FSFV.

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

10.1.1 Data Transformations

Not applicable.

10.1.2 Populations Analyzed and Evaluability

The primary analysis will be performed on the enrolled population. Analysis on the per-protocol (PP) population maybe performed, if needed.

The rules for the allocation of subjects to each of the analysis populations will be defined and documented during a data review meeting held prior to database lock.

During the data review meeting, based on minor or major protocol deviations recorded, subjects may be excluded from the PP population.

Subjects may be excluded from the analyses if one or more of the following deviations occur.

- Subject did not complete the study
- Violation of inclusion/exclusion criteria

10.1.2.1 Enrolled Population

The enrolled population includes all subjects who are enrolled in the study treated at least once with *Dysport*.

10.1.2.2 Per-protocol (PP) Population

The Per Protocol (PP) population is a subset of the enrolled subjects who have no major protocol deviations, as outlined above.

10.1.3 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. Depending on the seriousness of the deviation, the subject might be excluded from the PP population, which shall be documented prior to database lock.

10.1.4 Statistical Methods

In general, efficacy, safety, and baseline characteristics variables will be presented using descriptive statistics and graphs, as appropriate. Continuous endpoints will be summarized using descriptive statistics (e.g., mean, median, standard deviation, minimum and maximum values). Categorical endpoints will be presented in frequency tables with number and percentage of observations for each level.

95% confidence intervals (CIs) will be calculated whenever appropriate.

10.1.5 Subgroup Analysis

Subgroup analysis may be performed as determined and identified during the data review meeting.

10.2 Sample Size Determination

The sample size of approximately 250 subjects is not based on a statistical calculation. The selected number of subjects is regarded as sufficient for an evaluation of the studied endpoints by using descriptive statistics.

10.3 Analysis

Since this is an open non-interventional study, available data may be analyzed prior to study completion.

11 TRAINING / MONITORING / DATA MANAGEMENT / QUALITY ASSURANCE

11.1 Personnel Training

Investigators (i.e., physicians) and other responsible persons should be listed together with their function on the signature and delegation log. Study staff shall provide a curriculum vitae or equivalent, as appropriate.

It is the responsibility of the Investigator 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.

11.2 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, national regulations, and applicable SOPs.

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

The Investigator also agrees to assist the representative if required.

11.3 Data Management

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

11.4 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, applicable ICH guidelines, and SOPs for clinical study conduct and monitoring from the Sponsor and/or the CRO.

Audits of clinical study centers may be conducted by the Sponsor/CRO representatives, and inspection may be performed by Regulatory Authority (RA) inspectorates or Independent Ethics Committees (IECs) before, during, or after the clinical study.

The Investigator will allow and assist the CRO/Sponsor's representatives, 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.

11.5 Changes in Clinical Study Conduct / Amendments

11.5.1 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 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.

11.5.2 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 IEC. However, non-substantial amendments should be recorded and detailed in subsequent submissions e.g., in the subsequent notification of a substantial amendment.

12 ETHICS AND GENERAL CLINICAL TRIAL CONDUCT CONSIDERATIONS

12.1 Independent Ethics Committee (IEC)

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

This CSP and all applicable amendments will be reviewed and approved by the appropriate IEC. It is the responsibility of the Investigator to obtain approval of the CSP/CSP amendment(s) from the IEC. The study shall not begin until the required favorable opinion from the IEC has been obtained. The Investigator shall file all correspondence with the IEC in the Investigator file and provide copies of IEC approvals to the Sponsor as required. Any additional requirements imposed by the IEC or RA shall be followed.

12.2 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 national regulatory requirements.

12.3 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, and guidelines and in accordance with local requirements.

The ICF approved by an IEC, will be fully explained to the subject.

Prior to enrollment into the clinical study, the subject and the Investigator 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).

12.4 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 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 Investigator are responsible for complying with all requirements pursuant to national legislation in the country in which the Institution and Investigator are located.

The Sponsor shall, to the extent feasible, protect study subject identifier information.

The Institution and 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 China.

The Institution and 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.

Authorized representatives from the Sponsor or a RA may visit the study center to perform audits/inspections, including source data verification, i.e., comparing data in the subjects' medical records and the eCRF. Data and information shall be handled strictly confidential.

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.

12.5 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.

12.6 Data Collection and Archiving

12.6.1 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.

12.6.2 Source Documentation

The eCRF is considered a data entry form and does not constitute the original (or source) medical records unless otherwise specified. Source documents are all documents used by the Investigator or hospital that relate to the subject's medical history, verifying the existence of the subject, the inclusion and exclusion criteria, and all records covering the subject's participation in the study. Source documents may include a subject's medical records, hospital charts, clinic charts, the physician's subject study files, as well as the results of diagnostic tests such as laboratory tests, electrocardiograms, etc.

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.

Source documents shall be made available for inspection by the monitor at each monitoring visit, as well as during audits and/or inspections.

12.6.3 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 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.

12.7 Insurance

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

12.8 Publication Policy

The Institution/Investigator and the Sponsor's obligations regarding intellectual property rights, confidentiality, and publications are described in detail in the Clinical Trial Agreement.

The aim is to submit the results of this study for publication in a public database (e.g., www.ClinicalTrials.gov) and to a medical journal for publication of the results. Everyone who is to be listed as an author of the results of this multicenter study shall have made a substantial, direct, intellectual contribution to the work. Authorship will be based on (1) substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; and (2) drafting the work or revising it critically for important intellectual content; and (3) final approval of the version to be published; and (4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.[a] Conditions 1, 2, 3, and 4 must all be met in order to be

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

designated as author. Those who do not meet all four criteria will be acknowledged. Among the authors that fulfil the above mentioned criteria, one author will be appointed by the Sponsor to take primary responsibility for the overall work as primary author.

13 LITERATURE REFERENCE LIST

1. Monheit GD, Pickett A. AbobotulinumtoxinA: A 25-Year History. Aesthet Surg J. 2017 May 1;37(suppl_1):S4-S1.
2. Carruthers J, Carruthers A. The evolution of botulinum neurotoxin type A for cosmetic applications. J Cosmet Laser Ther. 2007 Sep;9(3):186-92.
3. Rzany B, Dill-Müller D, Grablowitz D, et al. Repeated botulinum toxin A injections for the treatment of lines in the upper face: a retrospective study of 4,103 treatments in 945 patients. Dermatol Surg. 2007 Jan;33(1 Spec No.):S18-25.
4. Botulinum Toxin Type A for Injection Leaflet Dysport®. Berkshire, UK: Ipsen Biopharm Ltd: 17 Jun 2020.

14 APPENDICES

Appendix 1: Subject Satisfaction Questionnaire

Appendix 2: Physician Satisfaction Questionnaire

Appendix 3: Subject Self-Assessment of GL Severity Using The 4-point Categorical Scale

[redacted]

Appendix 1 Subject Satisfaction Questionnaire

Subject #:

Visit #:

Date of questionnaire completion (DD/MM/YYYY):

Please tick the box corresponding to your preferred answer (only one box should be ticked by question unless otherwise specified).

Complete at Visit 1 ONLY

CCI

[redacted]

4. **How satisfied have you been with the aesthetic outcome in the injected area after treatment?**
   - ❒ Very satisfied
   - ❒ Satisfied
   - ❒ Dissatisfied
   - ❒ Very dissatisfied

5. **How satisfied were you with the comfort of the injection?**
   - ❒ Very satisfied
   - ❒ Satisfied
   - ❒ Dissatisfied
   - ❒ Very dissatisfied

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CCI

[redacted]

Complete at Visit 6 ONLY

17. What is your overall satisfaction after three treatment cycles with *Dysport*?

- ❒ Very satisfied
- ❒ Satisfied
- ❒ Dissatisfied
- ❒ Very dissatisfied

Appendix 2 Physician Satisfaction Questionnaire

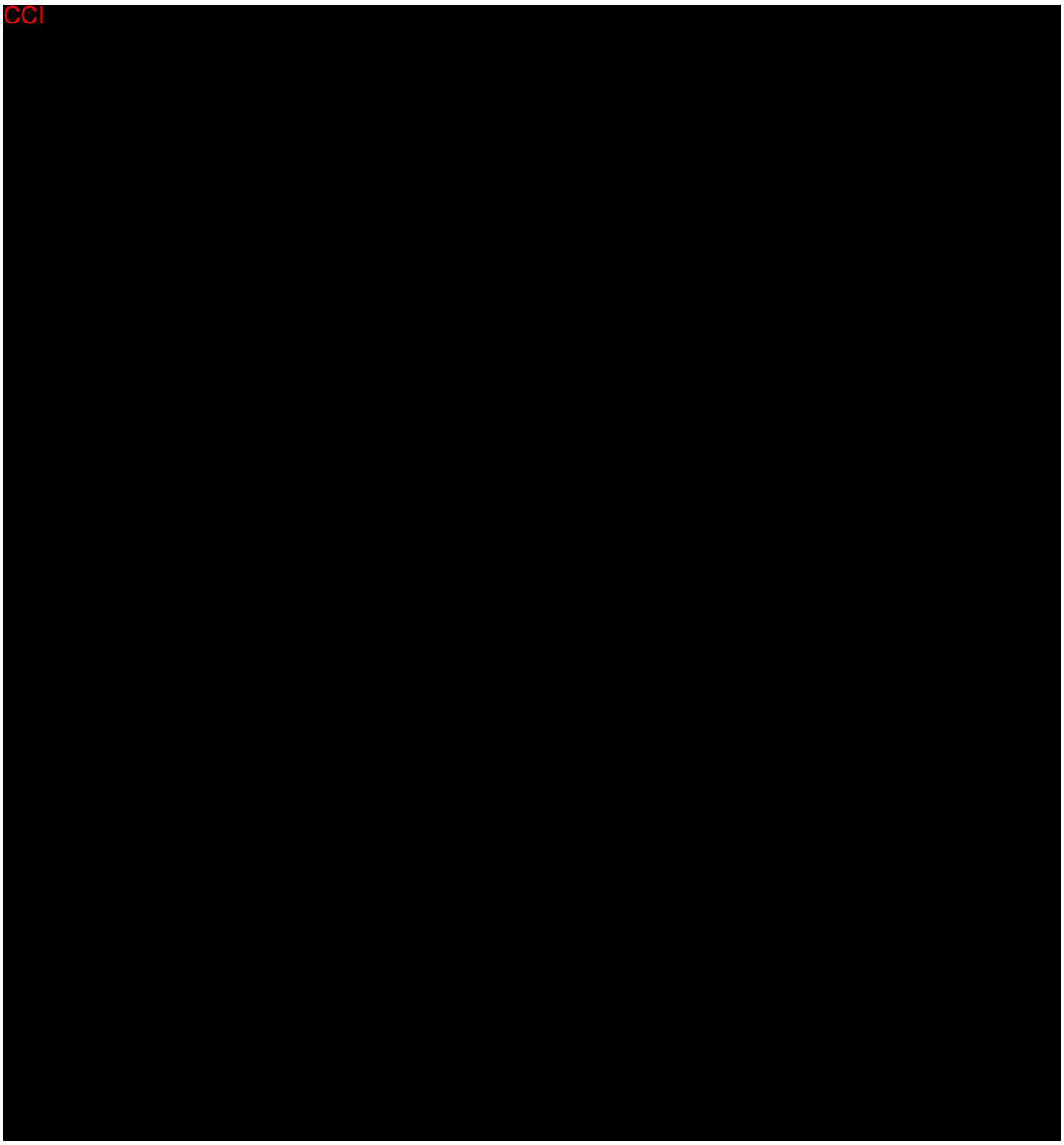
Subject#:

Visit #:

Date of questionnaire completion (DD/MM/YYYY):

Please tick the box corresponding to your preferred answer (only one box should be ticked by question unless otherwise specified).

CCI



Complete at Visits 6 ONLY

7. What is your overall satisfaction after three treatment cycles with *Dysport*?

- ❒ Very satisfied
- ❒ Satisfied
- ❒ Dissatisfied
- ❒ Very dissatisfied

Appendix 3 Subject Self-Assessment of GL Severity using the 4-point Categorical Scale

Subject#:

Visit #:

Date of completion (DD/MM/YYYY):

Subject Instructions: Using a mirror, evaluate your 'glabellar lines' (the lines between your eyebrows) while you are frowning. To produce a 'max frown' you are to raise your eyebrows, then bring them together as strongly as you can. You may repeat this until you are comfortable with frowning. Evaluate your lines at max frown according to these four categories shown below.

These assessments will be repeated at each visit in the study center and we will ask that you make the max frown in exactly the same way on each occasion. Please place a mark (X) in the box that best describes how you think the lines between your eyebrows look when frowning today.

At max frown:

No wrinkles (smooth skin)	Mild wrinkles (fairly smooth skin)	Moderate wrinkles (glabellar lines)	Severe wrinkles (severe glabellar lines)

Please be advised that you will be using the same scale to rate the appearance of your glabellar lines at every visit.

Note: The subject should perform their self-assessment independently of the physician's assessment.

Note: With guidance from the physician, subjects may also reference the CCI [redacted] CCI when completing their self-assessment.

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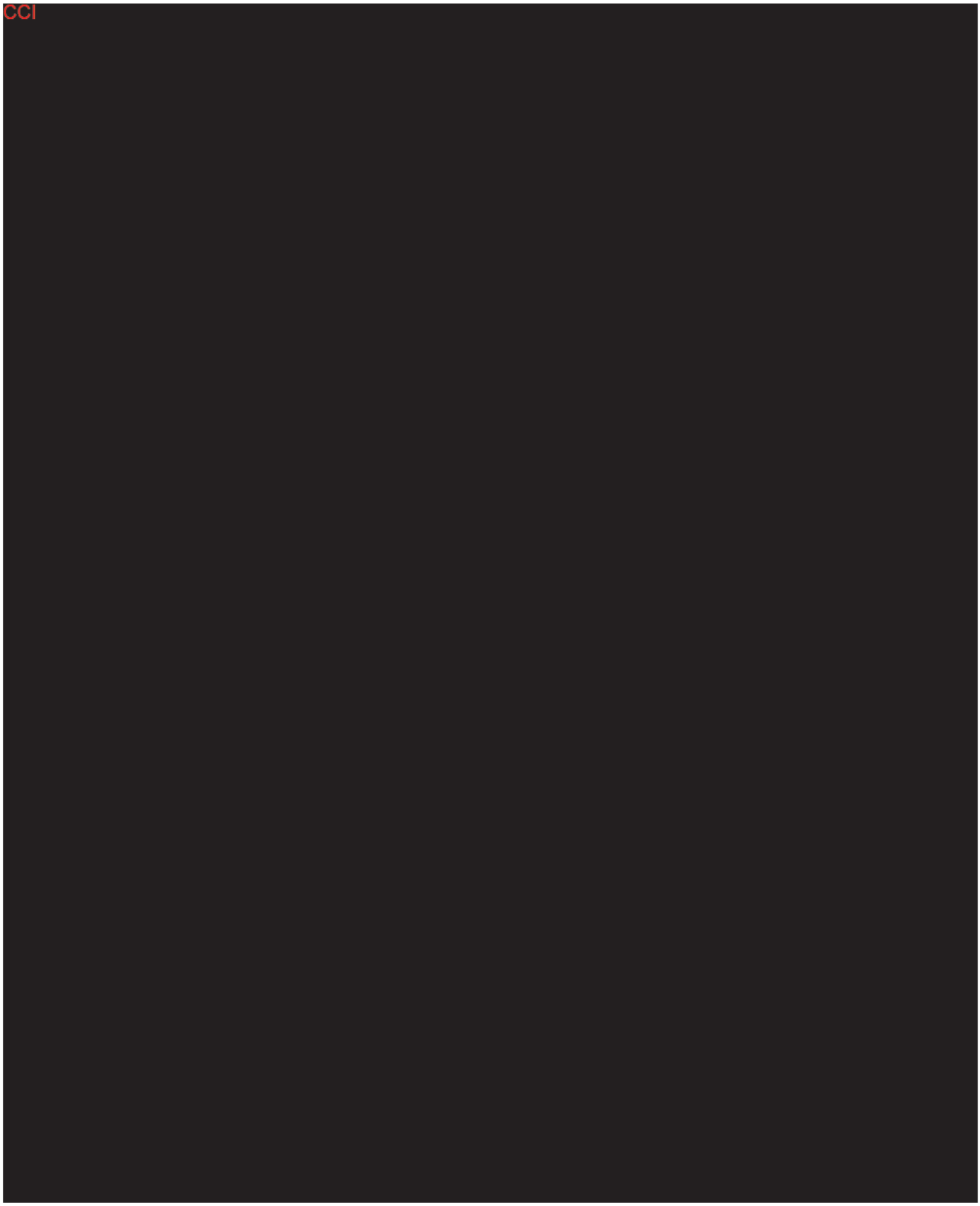
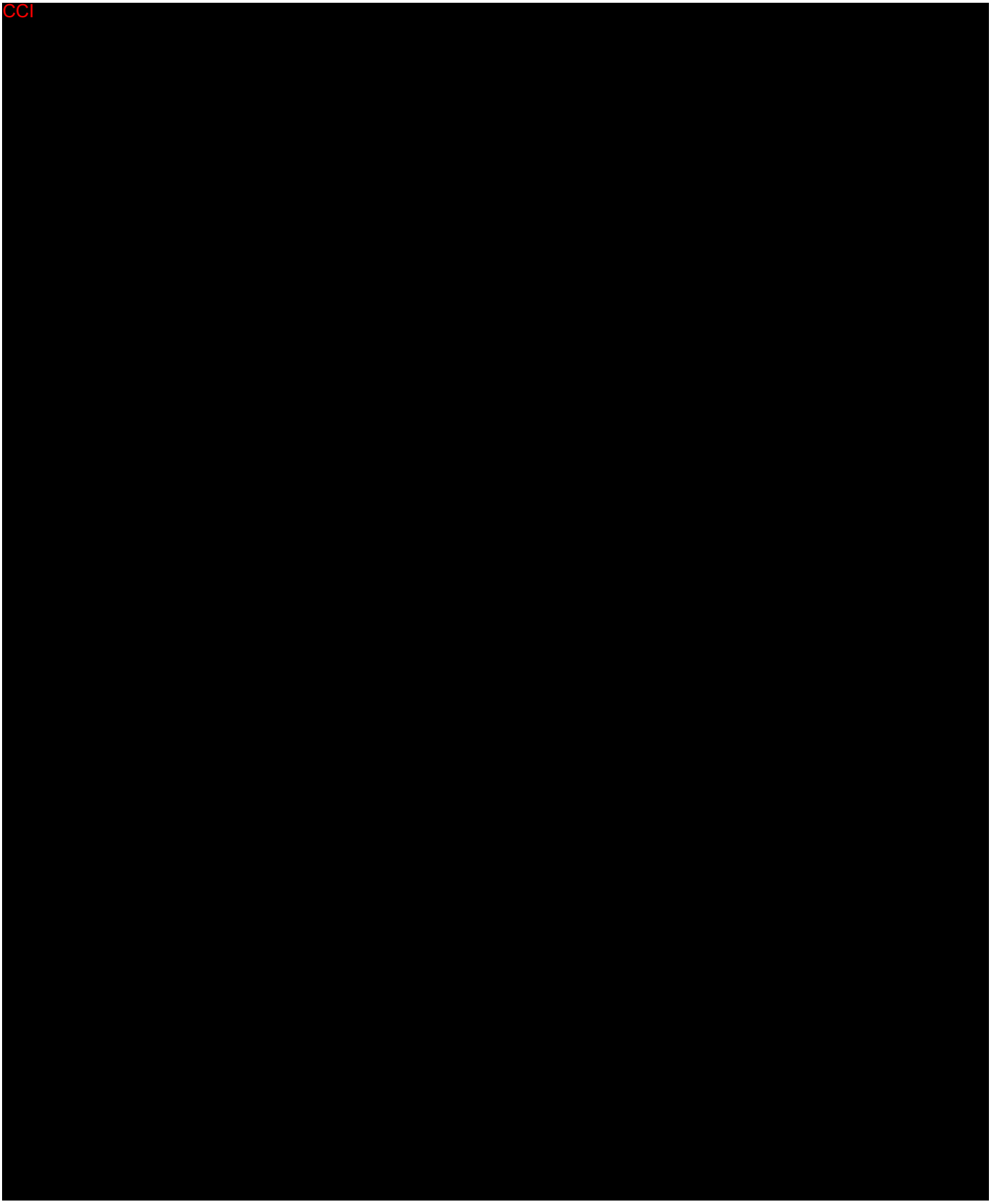


GALDERMA		

CCI

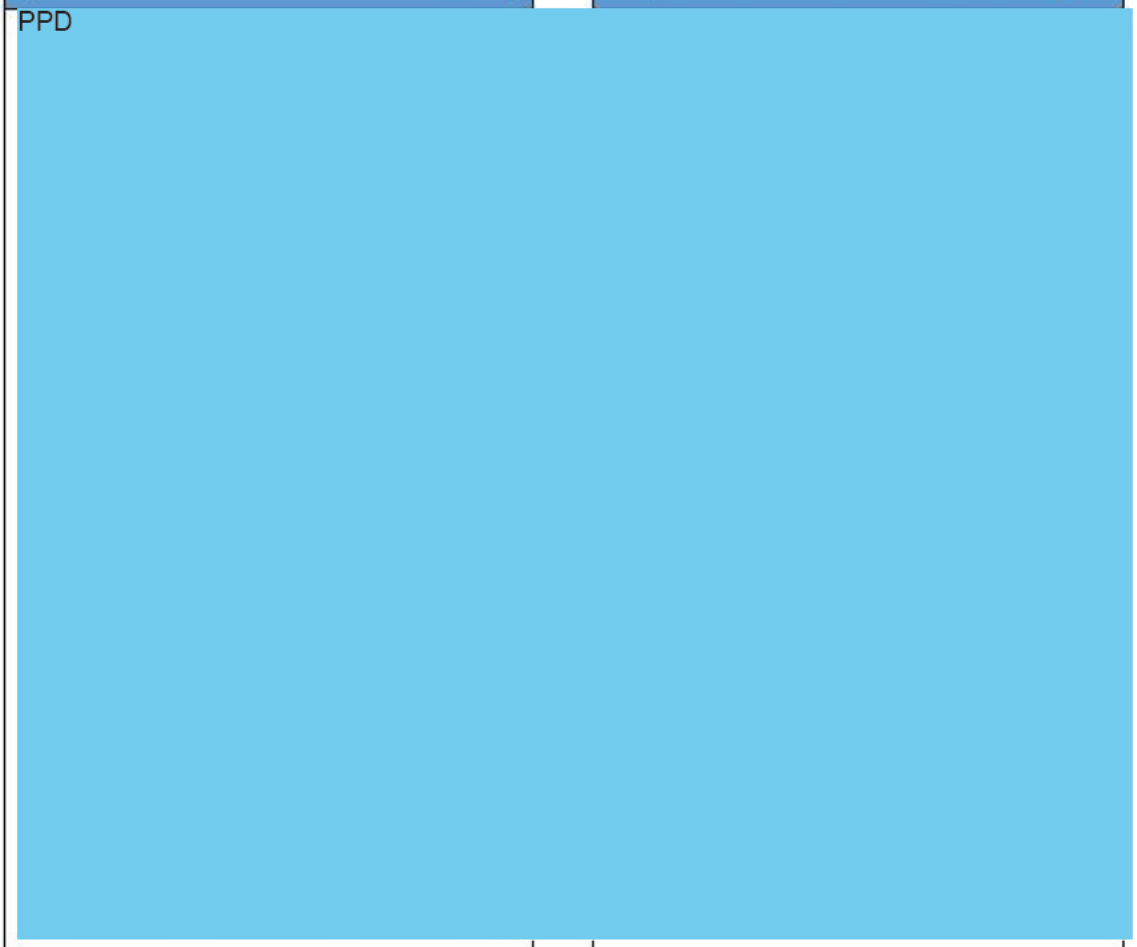


IPSEN
Innovation for patient care

Investigator's Validated 4-point Photographic Scale

At Rest

Characterized by muscle activity at the time of evaluation having limited impact on their presence or absence

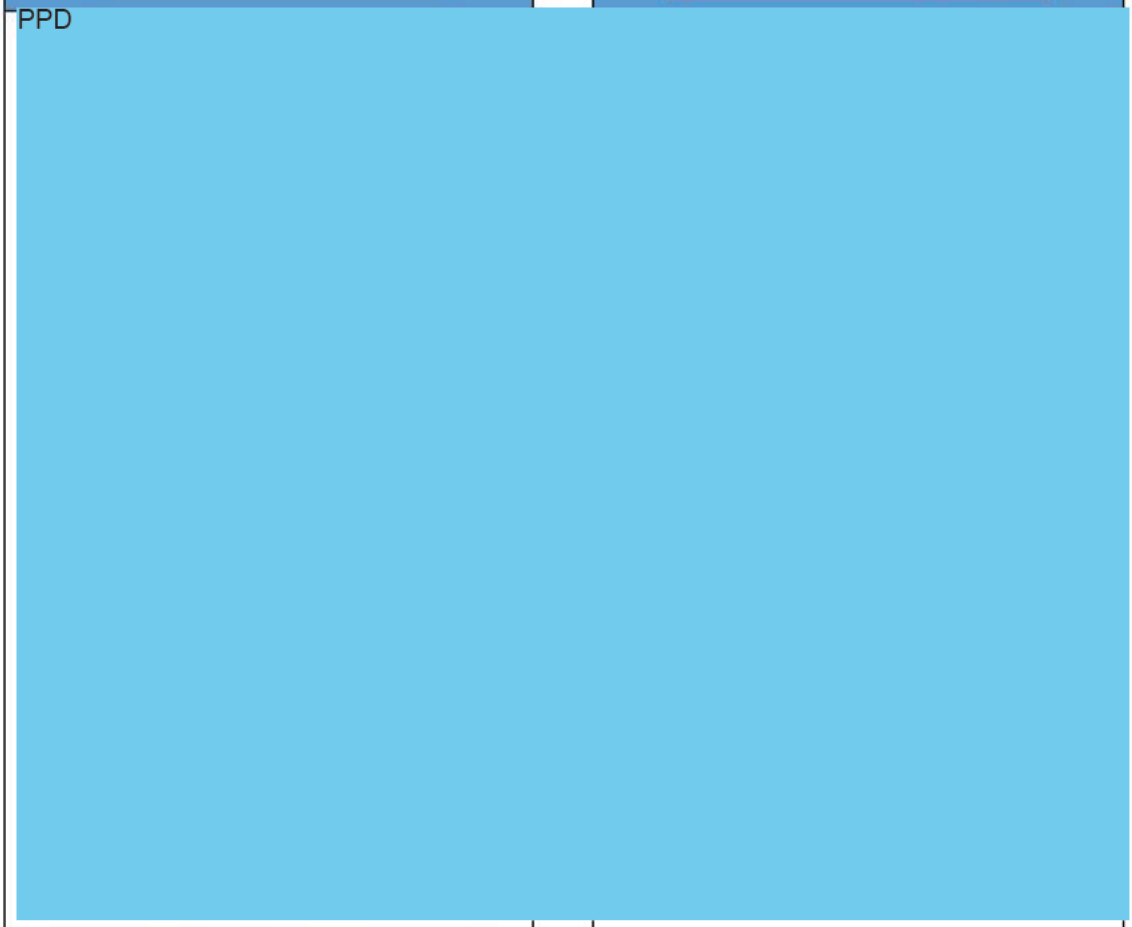
GRADE 2: MODERATE / 中度	GRADE 3: SEVERE / 重度
PPD 	
Dermal crease – A deep linear depression in the skin surface that is deeper and/or wider than a fine wrinkle distinguishable from a dermal groove by the absence of muscle contractions at rest.	Dermal groove – A deep linear depression in the skin surface distinguishable from a dermal crease by the presence of persistent muscle contraction or spasm visible when the patient is "at rest".

IPSEN
Innovation for patient care

Investigator's Validated 4-point Photographic Scale

At Max Frown

Glabellar lines produced by maximal voluntary muscular activity contributing to the presence of the lines

GRADE 0: NONE / 无	GRADE 1: MILD / 轻度
	
Relaxed skin tension line; no wrinkles	Glabellar depression(s) – A mild depression(s) in the glabellar area (inter-brow space) surrounded by mild bulging of the glabellar muscles.

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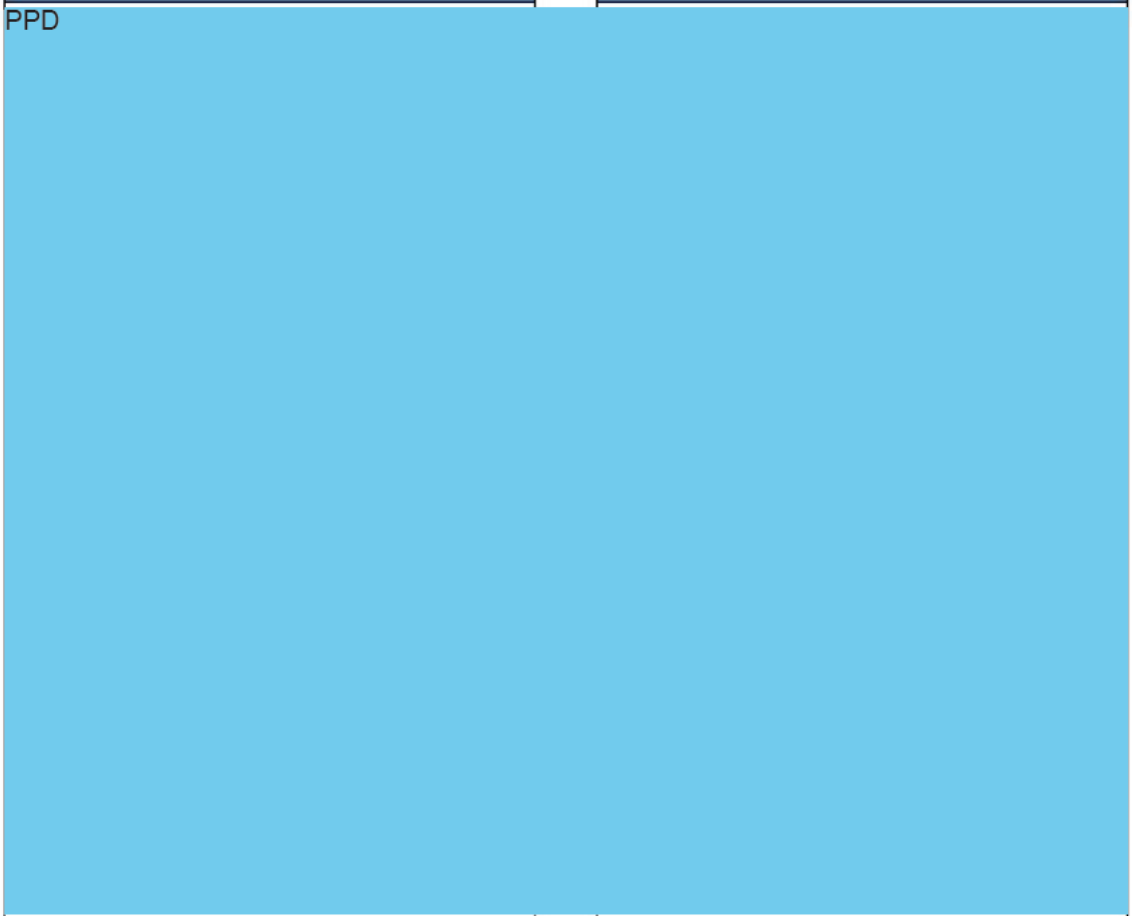
At Max Frown

Glabellar lines produced by maximal voluntary muscular activity contributing to the presence of the lines

GRADE 2: MODERATE / 中度	GRADE 3: SEVERE / 重度
PPD 	
Glabellar groove – Moderate depression(s) of the inter-brow space surrounded by moderate to significant muscle contraction and bulging.	Glabellar furrow – Deep groove(s) in the glabellar area (inter-brow space) surrounded by profound muscle contraction and bulging.

15 SIGNED AGREEMENT OF THE CLINCAL STUDY PROTOCOL

CTN:	05PF2009
CSP Title:	A Prospective, Non-interventional Study to Collect Subject and Physician Satisfaction During Long Term Treatment of Glabellar Lines with *Dysport*® in Subjects of Chinese Origin in Real Clinical Practice

I, the undersigned, have read and understand the CSP specified above, and agree on the contents. The CSP, the CTA, and the additional information given in the prescribing information will serve as a basis for cooperation in this study.

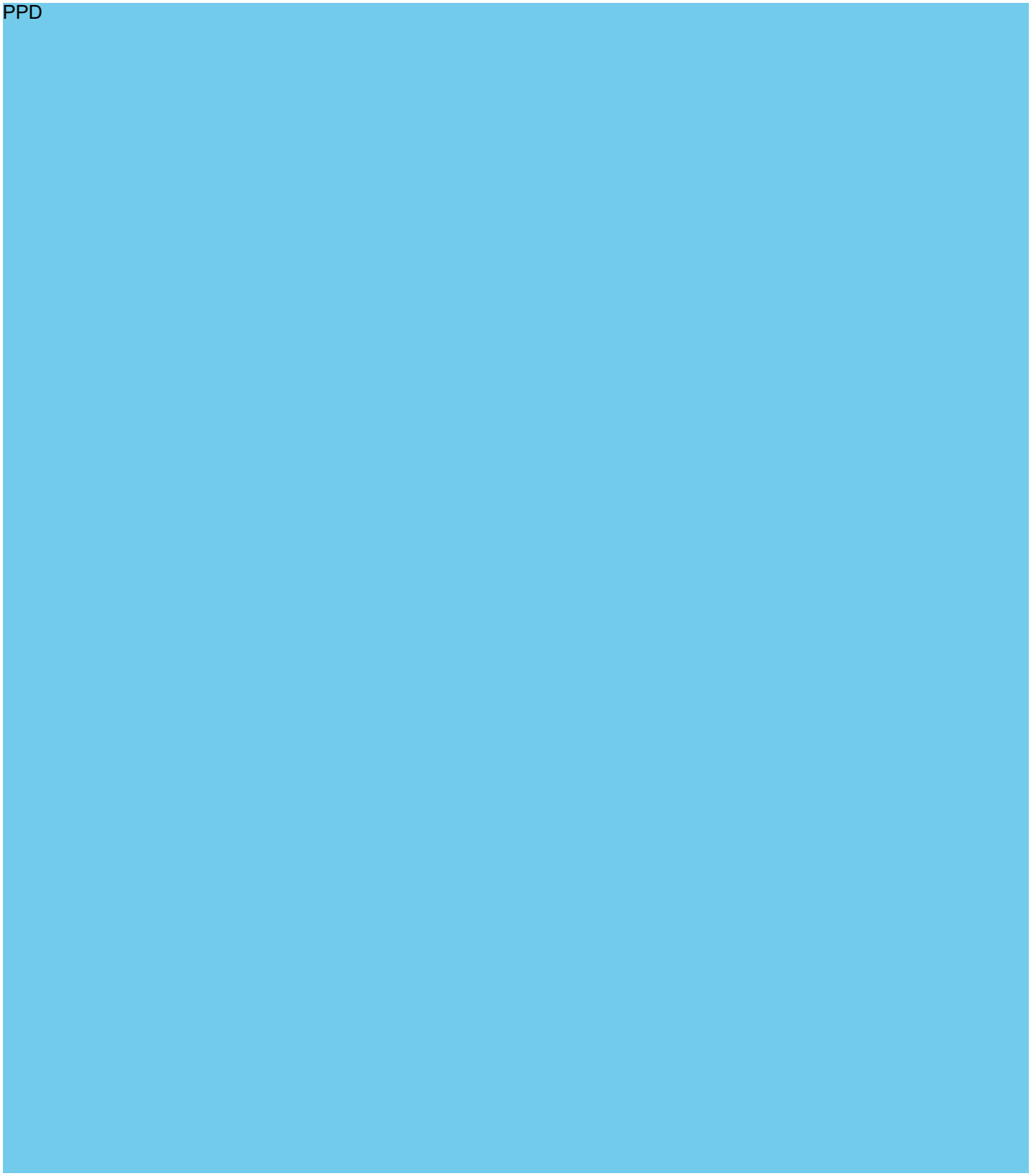
Investigator

Printed name	Signature	Date

Study center

GALDERMA		

Effective date: 2021-06-28 08:30



Effective

2.0