CLINICAL STUDY PROTOCOL

PROTOCOL NUMBER: 05PF2005

CONFIDENTIAL

This document contains confidential, proprietary information

TITLE PAGE

A Phase IV, Randomized, Interventional, Study to Assess Subject Treatment Session Perception and Investigator Treatment Experience of Alluzience and Vacuum-Dried Botulinum Neurotoxin Type A for Aesthetic Use

Short title:

Study comparing **T**reatment with **A**lluzience vs **R**econstituted toxin
STAR

Clinical Trial Number (CTN): 05PF2005

Phase: Phase IV, post-market study

SPONSOR:
Q-Med AB, part of the Galderma Group
Seminariegatan 21
SE-752 28 Uppsala, Sweden
Telephone: +46 18 474 90 00

SAFETY:
For safety questions, the Safety e-mail (drugsafetypv@advancedclinical.com) or Medical Monitor should be contacted using the contact information provided in the Investigator's site file. Serious adverse events (SAEs) and pregnancy report forms should be submitted as described in Sections 7.2.1.2.2 and 7.2.1.2.3.

MEDICAL MONITOR:
For any medical questions related to the clinical study protocol (CSP), the Medical Monitor should be contacted using the contact information provided in the Investigator's site file.

This clinical study shall be performed in compliance with the clinical trial agreement (CTA), the clinical study protocol, International Council for Harmonization (ICH)-Good Clinical Practice (GCP),[1] 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.

STUDY ADMINISTRATIVE STRUCTURE

Sponsor contact:	PPD , Sr. Clinical Project Manager PPD Telephone: PPD E-mail: PPD
Medical Monitor:	Contact details provided in the Investigator's site file
E-mail for SAE and Pregnancy Reporting:	drugsafetypv@advancedclinical.com
E-mail for PQC Reporting:	drugsafetypv@advancedclinical.com

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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STUDY SYNOPSIS	
Clinical Study Title:	A Phase IV, Randomized, Interventional, Study to Assess Subject Treatment Session Perception and Investigator Treatment Experience of Alluzience and Vacuum-Dried Botulinum Neurotoxin Type A for Aesthetic Use
Short Title:	**S**tudy comparing **T**reatment with **A**lluzience vs **R**econstituted toxin **(STAR)**
Clinical Trial Number:	05PF2005
Countries Involved and Planned Number of Study Sites:	Countries: Germany and the United Kingdom No. of study sites: up to 10 sites
Clinical Study Design:	This is a Phase IV, open-label, randomized, interventional, two-armed, multi-centre study to investigate subject treatment perception and Investigator treatment experience when using Alluzience or vacuum-dried botulinum neurotoxin type A (powder BoNT-A) for treatment of glabellar lines (GL). Approximately 150 subjects will be randomized to either Alluzience or powder BoNT-A treatment in a CCI ratio. It is estimated that around 170 subjects will be screened to obtain the number of randomized subjects needed for the study. Randomization will be stratified by study site. The study consists of six visits; screening, treatment and four follow-up visits 1, 3, 5 and 6 months after treatment, subjects randomized to be treated with powder BoNT-A will only be followed for 1month. The screening visit and the treatment visit might be conducted at the same day. The Investigator and subject will after the treatment fill in questionnaires about how they perceived the treatment session and the Investigator will also answer questionnaires regarding treatment details, reconstitution CCI [redacted] CCI [redacted] of the used study product. CCI [redacted] Adverse events (AEs) will be collected from treatment until the end of the subject's participation. Any related, unresolved AE will be followed until resolution for up to 3 months after the study or until considered stable.
Total Number of Subjects (Planned):	Approximately 150 subjects will be randomized to either Alluzience or powder BoNT-A treatment in a CCI ratio,

	giving a total of 100 subjects randomized to Alluzience and 50 subjects to powder BoNT-A treatment groups.
Primary Objective and Endpoint	To evaluate time needed to prepare Alluzience and powder BoNT-A. o Time to prepare study product according to protocol (Appendix 1).
Secondary Efficacy Objectives and Endpoints:	1. To evaluate preparation/reconstitution experience of Alluzience and powder BoNT-A. o Proportion of study products prepared by the investigators in front of the patients. o Proportion of answers within each answer option (strongly agree, agree, neither agree nor disagree, disagree and strongly disagree) to question comparing Alluzience preparation vs. powder BoNT-A reconstitution with regards to technical issues/problems. o Proportion of treatment sessions where the Investigator answers that he/she have experienced issues with powder BoNT-A reconstitution. Questionnaire to be used is available in Appendix 1. 2. To describe Investigator treatment experience when using Alluzience for the treatment of GL. o Proportion of answers within each answer option (strongly agree, agree, neither agree nor disagree, disagree and strongly disagree) for each question specified in the Investigator Treatment Session Questionnaire (Appendix 2) CCI [redacted]

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Safety Objectives and Endpoints:	The safety objective is to evaluate the safety of a single dose of Alluzience for the treatment of moderate to severe GL. o Incidence, causality, severity, and duration of AEs collected during the study.
Clinical Study Duration:	The planned duration of recruitment (from first subject first visit [FSFV] to last subject first visit [LSFV]) is approximately 3 months. The planned clinical study duration from FSFV to last subject last visit [LSLV] is approximately 9 months.
Inclusion Criteria:	1. Female 18 to < 65 years of age. 2. Moderate to severe GL at maximum frown as assessed by the Investigator. 3. Female of non-childbearing potential (i.e., postmenopausal [absence of menstrual bleeding for 1 year prior to screening, without any other medical reason], or has undergone hysterectomy or bilateral oophorectomy). OR Female of childbearing potential

	with a negative urine pregnancy test at screening and baseline, and agrees to use a highly effective and approved contraceptive method for the duration of the study. A highly effective method of contraception is defined as: • Bilateral tubal ligation; • 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; • Hormonal or copper intra uterine device (IUD) inserted at least 28 days prior to Day 1; • Partner vasectomized for at least three months prior to screening visit; • Progestogen-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 the subject's participation in the study). 4. Time and ability to complete the study and comply with instructions. 5. Understands the study requirements and signed the informed consent form (ICF). 6. Subjects who have planned to undergo aesthetic facial treatment with powder toxin at the study site. 7. Previous use of any approved botulinum toxin in facial areas.
Exclusion Criteria:	1. Previous use of any botulinum toxin in facial area within 6 months prior to study treatment. 2. Female who is pregnant, breast feeding, or intends to conceive a child during the study. 3. Known allergy or hypersensitivity to any component of the study product or any botulinum toxin serotype. 4. Any known contraindication such as subject with bleeding disorder or subject currently using anticoagulants.

	5. Previous use of any hyaluronic acid soft tissue augmentation therapy in the treated area within 3 months before baseline. 6. Previous soft tissue augmentation with any permanent (non-biodegradable such as silicone, polyacrylamide, etc) or semi-permanent (i.e., calcium hydroxylapatite, poly-L-Lactic acid or polymethyl-methacrylate) product; lifting threads, or autologous fat in the treatment area. 7. Subject has any prior or current psychiatric illness (e.g. Psychosis, depression, anxiety), alcohol or drug abuse, or is taking antidepressant, anxiolytic, or antipsychotic medication that, in the Investigator's opinion, could affect the subject's safety and/or participation in the study. 8. Other concurrent medical conditions, therapy, or other condition that, in the Investigator's opinion, would interfere with the evaluation of the study medication, safety or efficacy, and/or put the subject at risk if he/she participates in the study. 9. Participation in an investigational device or drug study within 30 days prior to study treatment or plans to enroll in any other investigational study during participation in this study. 10. Study site personnel, close relatives of the study site personnel (e.g. parents, children, siblings, or spouse), employees or close relatives of employees at the Sponsor company.
Treatment groups	• Alluzience • powder BoNT-A (BOTOX®/Vistabel®) 150 subjects will be randomized to either Alluzience or powder BoNT-A treatment in a [redacted] ratio.
Alluzience: **Strength/Concentration:**	Alluzience is an abobotulinum neurotoxin type A, supplied as a sterile, buffered solution for injection. Each vial contains 125 Speywood units (s.U) in 0.625 mL of solution, i.e. 200 s.U/mL. 10 U/0.05 mL per injection point. In total 50 s.U in 0.25 mL for 5 injection points.
BOTOX®/Vistabel®:	BOTOX®/Vistabel® is a botulinum toxin type A, supplied in a sterile, vacuum-dried form. The vial, containing 50 U, is reconstituted with 1.25 mL of sterile, 0.9% sodium chloride before study treatment.

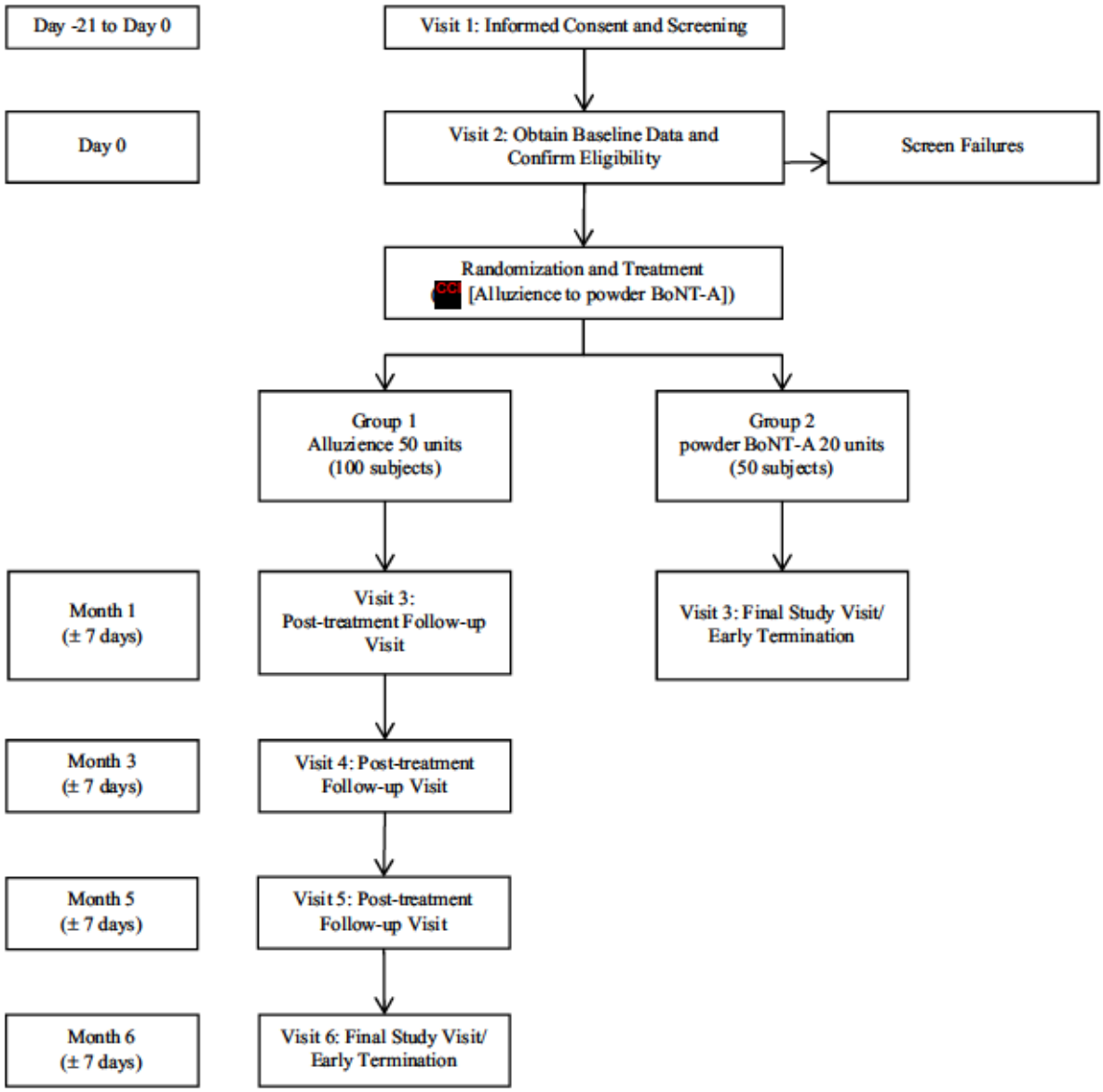
Strength/Concentration:	4 U/0.1 mL per injection point. In total 20 U in 0.5 mL for 5 injection points.
Treatment area/Indication:	Glabellar lines
Treatment regimen and injection procedure:	Single treatment at the baseline visit, with either Alluzience or powder BoNT-A administered according to each products SmPC.
Statistical Method:	CCI [redacted]
Sample Size:	The sample size of approximately 150 subjects, 100 subjects in the Alluzience treatment group and 50 in the powder BoNT-A treatment group, 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.
Interim Analysis:	No interim analysis will be performed.

CLINICAL STUDY SCHEMATIC AND FLOW CHART

Table 1 Clinical Study Schematic

	Screening ↓ Baseline/Randomization to Treatment ↓	
	Group 1	Group 2
	n=100	n=50
Treatment	50 s.U of Alluzience in GL	20 U of powder BoNT-A in GL
Treatment Frequency	Single treatment at Baseline	
	↓ Follow-Up Visits	
	Group 1 1, 3, 5- and 6-months FU visits	Group 2 1-month FU visit

Figure 1 Study Flow Chart



SCHEDULE OF ASSESSMENTS

Table 2 Schedule of Assessments

1 month = 4 weeks/28 days Visit windows are calculated from Baseline/Visit 2 if not otherwise specified.	**Visit 1** Group 1 and 2 Screening[1]	**Visit 2** Group 1 and 2 Treatment/ Baseline[1] (within 3 weeks after screening)	**Visit 3/** Group 1 EoS Group 2 1-Month Follow-up (±7 days)	**Visit 4** Group 1 3-Month Follow-up (±7 days)	**Visit 5** Group 1 5-Month Follow-up (±7 days)	**Visit 6/ET** EoS Group 1 6-Month Follow-up (±7 days)
Informed Consent	X	(X)[2]				
Demographic Data including, medical history & con-current diseases, previous facial treatments/ procedures	X	(X)[2]				
Inclusion /Exclusion Criteria	X	X				
Adverse Events[3]		X	X	X	X	X
Concomitant Medication/ Procedures	X	X	X	X	X	X
Urine Pregnancy Test[4]	X	X				
Photography		X	X	X		X
Randomization		X				
Treatment		X				
End of study[5]			X Group 2, powder BoNT-A			X Group 1, Alluzience
Investigator Assessments						
Reconstitution/Preparation Questionnaire		X				
Investigator Treatment Session Questionnaire[6]		X				
CCI [redacted]						

1. Screening and treatment/baseline visits can be performed at the same day
2. Only to be conducted if no screening visit has been performed. Changes to medical history should be asked for if the screening and baseline visits are not performed on the same day.
3. AEs are collected from treatment to the end of the subject's participation, for details how to follow-up ongoing AEs at the last visit see section 7.2.1.1.5.
4. Only for women of childbearing potential
5. Subjects in the powder BoNT-A treatment group will be followed 1 month and subjects in the Alluzience treatment group will be followed for 6months.
6. Only for Alluzience-treated subjects
7. Only to be completed once for each Treating Investigator, per study product, after all enrolled subjects have completed Visit 2.
8. Performed pre-treatment

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation/Term	*Definition*
AE	Adverse Event
Alluzience	Botulinum Neurotoxin Type A haemagglutinin complex solution ready for injection (investigational product)
BoNT	Botulinum Neurotoxin
BoNT-A	Botulinum Neurotoxin Type A
BoNT-A-HAC	Botulinum Neurotoxin Type A haemagglutinin complex
°C	Degrees Celsius
CRA	Clinical Research Associate
CSP	Clinical Study Protocol
CTA	Clinical Trial Agreement
CTN	Clinical Trial Number
DMP	Data Management Plan
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
e.g.	For Example (Latin: exempli gratia)
ET	Early Termination
EU	European Union
FAS	Full Analysis Set
FSFV	First Subject First Visit (first subject screened, i.e., who signs the informed consent form)
CCI	[redacted]
GCP	Good Clinical Practice
GL	Glabellar Lines
HSA	Human Serum Albumin
ICF	Informed Consent Form
ICH	International Council for Harmonization
i.e.	That is (Latin: id est)
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
Investigator	The Principal Investigator (PI) or other qualified person, i.e., sub-Investigator, designated and supervised by the PI at a study site to

Abbreviation/Term	*Definition*
	perform critical study-related procedures or to make important study-related decisions as specified on the signature and delegation log.
Investigator's site file	Essential documents relating to a clinical study as defined in applicable GCP guidance document(s) and maintained by the Investigator.
Investigational product	A pharmaceutical form of an active ingredient being tested in a clinical study, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use.
IUD	Intrauterine Device
kg	Kilogram
LSFV	Last Subject First Visit (last subject screened, i.e., who signs the informed consent form)
LSLV	Last Subject Last Visit (last subject who completed his/her last clinical study visit)
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
mL	Milliliter
N or n	Number
N/A	Not Applicable
NaCl	Sodium chloride
onabotulinumtoxinA	USAN name for BOTOX®/Vistabel®
PI	Principal Investigator; qualified person responsible for conducting the study at a study site.
PP	Per-Protocol
PQC	Product Quality Complaint
RA	Regulatory Authority
Reference product	An investigational or marketed product (i.e., active control), or placebo, used as a comparator in a clinical study.
s.U	Speywood unit
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SmPC	Summary of Product Characteristics

Abbreviation/Term	*Definition*
SOP	Standard Operating Procedure
Speywood unit	Toxin potency measurement unit
Sponsor file	Essential documents relating to a clinical study as defined in applicable GCP guidance document(s) and maintained by the Sponsor.
Study files	The Investigator site file and Sponsor file
Study products	The investigational product and the reference product under study.
Study sites	The location(s) where the study-related activities are actually conducted.
SUSAR	Suspected Unexpected Serious Adverse Reactions
TEAE	Treatment Emergent Adverse Event
U	Units
BOTOX®/Vistabel®	onabotulinumtoxinA, Botulinum Toxin Type A for injection (reference product)
WHO	World Health Organization

1. BACKGROUND AND RATIONALE

1.1 Medical Background and Short Rationale for the Clinical Study

Over the last few decades, as the aging population continues to grow, there has been an increasing demand for cosmetic procedures to reverse the appearance of advancing age, particularly in the facial area.

This increasing preoccupation with physical appearance has led to the development of many different products and procedures, such as surgery, resurfacing of various types, and the use of filling agents.

While none of these methods are entirely risk free, continuous research is necessary to provide the safest and most effective methods for treatment of the aging face. Although there are five factors that interplay in the production of what is known as the aging face[2], there are primarily two factors interacting to produce the more significant lines and folds, as opposed to wrinkles: the skin and the underlying muscles.

Many therapies have evolved to treat wrinkles and the skin factors of the lines and folds, among them are various types of resurfacing, dermatologic products and injections for soft tissue augmentation.

The use of Clostridium botulinum toxin type A (BoNT-A) has been shown to ameliorate lines and folds by temporarily paralysing specific muscle groups. Many studies regarding the aesthetic use of BoNT-A have now been published in the peer reviewed medical literature[3, 4, 5, 6, 7, 8, 9, 10, 11, 12].

More recently, Clostridium botulinum toxin (BoNT) products have been approved for the improvement in the appearance of glabellar lines in a number of countries in the European Union (EU) and in the United States of America. Based on both clinical observation and objective measurement of glabellar folds, BoNT-A, in low doses, has been shown to suppress the muscular activity of the glabellar area by temporary relaxation of the procerus and corrugator muscle complex. BoNT-A is a potent neurotoxin isolated from the bacterium Clostridium botulinum, a Gram positive, spore forming anaerobe. BoNT-A, a single chain protein (molecular weight ~150,000 Daltons [Da]), is one of seven different serotypes (classed type A through G) of BoNT produced by this organism. Proteins endogenous to the bacterium cleave the single chain protein, resulting in a dichain neurotoxin containing a light chain (molecular weight ~50,000 Da) and a heavy chain (molecular weight ~100,000 Da) that remain linked by an inter chain disulfide and noncovalent bonds. BoNT-A acts selectively on peripheral cholinergic nerve endings, inhibiting acetylcholine release, effectively blocking signal transmission from nerve to muscle and inducing a temporary, partial chemodenervation of the injected muscle.

Most approved BoNT-A preparations in Europe and North America require reconstitution and this is associated with several challenges. Healthcare professionals must spend time on preparation, errors may occur in the dilution which could result in under or over-dosing, more waste than needed is produced which may have economic impacts and the variability of dosing is increased. Therefore, a ready-to-use liquid formulation of BoNT-A will facilitate and standardize injection practice,

ensuring that appropriate doses and concentrations are administered and thus preventing reconstitution errors[13].

Alluzience is a novel BoNT type-A1 produced as a liquid formulation, with recently granted market authorization in the study participating countries. This study seeks to evaluate subject treatment session perception and Investigator treatment experience when using Alluzience and powder BoNT-A.

1.2 Investigational Product Profile

1.2.1 Drug Profile

Alluzience is an injectable liquid form of BoNT-A haemagglutinin complex (BoNT-A-HAC) supplied in a glass vial. The active BoNT-A-HAC is the same as present in the previously marketed product Dysport® 500 units (U), 300 U and 125 U (the latter strength approved as Azzalure® in Europe).

The currently marketed freeze-dried preparations of BoNT-A-HAC products are formulated with lactose (bulking agent) and human serum albumin (HSA) in a glass vial. The potential risk of infectio us diseases due to the transmission of infective agents cannot be totally excluded when HSA and other plasma-derived products are used in the manufacture and formulation of medicinal products[14]. The development of substitutes for plasma-derived HSA as an excipient for medicinal products is encouraged by the European Medicines Agency as described in the Note for Guidance on Plasma-Derived Medicinal Products CPMP/BWP/328/99[15]. CCI

[redacted]

1.2.2 Findings from Pre-Clinical Studies

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Studies on acute toxicity, chronic toxicity and local tolerance at the injection site showed no unusual adverse local or systemic effects at clinically relevant dose levels[16].

1.2.3 Clinical Documentation

A pooled total of 372 patients with moderate to severe glabellar lines were treated in 2 pivotal trials, 250 at the recommended dose of 50 s.U, and 122 with placebo[16].

The majority of patients subjectively reported an effect within 2 to 3 days, including 23% of patients within 1 day. The proportion of responders by investigator assessment was statistically significantly higher for patients treated with Alluzience 1 month after injection compared to placebo (the primary endpoint) as well as at all other timepoints from 8 days up to 6 months (Table 3).

Table 3: Investigator Live Assessment at Maximum Frown – Responder Rate (%) at different time points

Visit after injection	Alluzience (N=250)	Placebo (N=122)
8 days	80.0%	2.5 %
1 month	87.6%	2.5%
2 months	76.8%	1.7%
3 months	57.6 %	1.7%
4 months	36.3 %	1.8%
5 months	17.5 %	0.9%
6 months	10.0 %	0.9%

Note: A responder is defined as having a severity grade of moderate or severe at baseline and a severity grade of none or mild at a given visit. Responder rates, the primary efficacy endpoint at Day 29, was statistically significantly different to placebo ($p<0.0001$). Responder rates at other time points were nominally different to placebo (p-values ranging from ≤ 0.0001 to 0.0008) at all time points).

The proportion of responders according to the patient self-assessment was higher for patients treated with Alluzience compared to placebo at all timepoints from 8 days up to 6 months (Table 4).

Table 4: Patient Self-Assessment – Responder Rate (%) at different time points

Visit after injection	Alluzience (N=250)	Placebo (N=122)
8 days	66.0%	4.9%
1 month	76.8%	5.7%
2 months	72.4%	2.5%
3 months	48.8%	3.4%
4 months	32.7%	4.3%
5 months	23.1%	4.3%
6 months	15.1%	2.6%

Note: A responder is defined as having a severity grade of moderate or severe at baseline and a severity grade of none or mild at a given visit. Responder rates were statistically significantly different to placebo with $p \leq 0.0001$ at all time points.

Patients' level of satisfaction 1 month following injection showed that 85.2% of the patients receiving Alluzience were either satisfied or very satisfied compared to 9% for placebo patients.

Aesthetic and psychological improvement was observed using Face-Q scales. For the facial appearance overall scale (which incorporates subject ratings for facial balance, end-of-day appearance, facial freshness, rested look, appearance when waking up and appearance under bright lights) and the psychological wellbeing scale (which incorporates subject ratings on feeling okay, self-acceptance, comfort with self, feeling good, self-liking, feeling happy, feeling attractive, and feeling confident), one month after injection, subjects treated with Alluzience showed improvement in the score for each of these scales compared to subjects who were treated with placebo (nominal $p<0.0001$).

A total of 595 patients received up to 5 treatment cycles of Alluzience in a 12 months long-term open-label phase III study. Efficacy was maintained over the 12 months period, by the investigator assessment, the patient assessment, patient satisfaction and FACE-Q questionnaires.

The proportion of responders at maximum frown, determined by the investigator 1 month after the injection, was maintained over repeated injection cycles (between 82.2% and 87.8%). The corresponding proportions 3 months after injection ranged between 45.3% and 56.8% across the 5 treatment cycles.

Patients (595 in total) receiving Alluzience over a 12 months period were tested for antibody formation. No patients tested positive for toxin-neutralising antibodies.

1.3 Rationale for Study Design, Doses and Control Group

The purpose of this study is to assess subject treatment session perception and Investigator treatment experience when using Alluzience and powder BoNT-A. Both the investigational drug, Alluzience and the comparator, BOTOX®/Vistabel® (powder BoNT-A) are approved in the EU/EEA to treat glabellar lines. It is believed that a ready to use solution, such as Alluzience, might be advantageous compared to a vacuum dried powder, that needs to be reconstituted before use, when used in a clinical setting. This study and its assessments are therefore aimed at evaluating how the subjects and Investigator experiences the treatment session and the handling of the study product. CCI

[redacted]

The chosen dose of 20 U for powder BoNT-A was based on the dose recommended by the manufacturer[17]. Note that the units for powder BoNT-A are specific to the preparation and are not interchangeable with other preparations of BoNT-A products.

The dose chosen for Alluzience is based on the evaluation of results for the different dose levels studied to date in the clinical program, where the Sponsor has concluded that a 50 s.U dose offers an appropriate balance between efficacy, duration of effect, and safety. 50 s.U is the approved dose for Alluzience for the treatment of GL as per the Summary of Products Characteristics [16].

1.4 Risk/Benefit Assessment

Both study products investigated in this trial are on the market in the participating countries and are considered safe for use in humans.

A majority of adverse reactions reported with Alluzience in clinical trials were of mild to moderate intensity and reversible. The most frequently reported adverse reactions were headache and injection site reactions. The incidence of adverse reactions tended to decrease with repeated treatments.

Adverse effects possibly related to the spread of toxin effect distant from the site of administration have been very rarely reported with botulinum toxin (excessive muscle weakness, dysphagia, aspiration pneumonia with fatal outcomes in some cases). Detailed adverse reaction information can be found in the Alluzience Summary of Products Characteristics[16].

Adverse reactions caused by BOTOX®/Vistabel® are similar to the expected adverse reactions listed above for Alluzience as both drugs are BoNT-A derivatives. Detailed adverse reaction information can be found in the BOTOX®/Vistabel® Summary of Products Characteristics[17].

The dose administered are according to the prescribing information for the study products in the EU/EEA. Therefore, the risks associated with participation in this study are considered acceptable compared to the anticipated high degree of subject satisfaction with treatment and the treatment regimen.

2. CLINICAL STUDY OBJECTIVES, ENDPOINTS, AND CLINICAL HYPOTHESIS

2.1 Clinical Study Objectives

The objective of the study is to assess, subject treatment session perception and Investigator treatment experience when using Alluzience and powder BoNT-A. Additionally, efficacy and safety of a single dose of Alluzience, for the treatment of moderate to severe GL, will be evaluated during a 6-month follow-up period.

2.1.1 Primary Objectives and Endpoints

The primary objective of this study is to evaluate the time needed to prepare Alluzience and powder BoNT-A according to protocol (Appendix 1).

2.1.2 Secondary Efficacy Objective and Endpoints

1. **Objective:** To evaluate preparation/reconstitution experience of Alluzience and powder BoNT-A.

   Endpoints:

   - Proportion of study products prepared by the investigators in front of the patients.
   - Proportion of answers within each answer option (strongly agree, agree, neither agree nor disagree, disagree and strongly disagree) to question comparing Alluzience preparation vs. powder BoNT-A reconstitution with regards to technical issues/problems.
   - Proportion of treatment sessions where the Investigator answers that he/she have experienced issues with powder BoNT-A reconstitution.

   See Appendix 1 (Reconstitution/Preparation of Alluzience and powder BoNT-A) for details.

2. **Objective**: To describe Investigator treatment experience when using Alluzience for the treatment of GL.

   Endpoints:

   - Proportion of answers within each answer option (strongly agree, agree, neither agree nor disagree, disagree and strongly disagree) for each question specified in the Investigator Treatment Session Questionnaire (Appendix 2)

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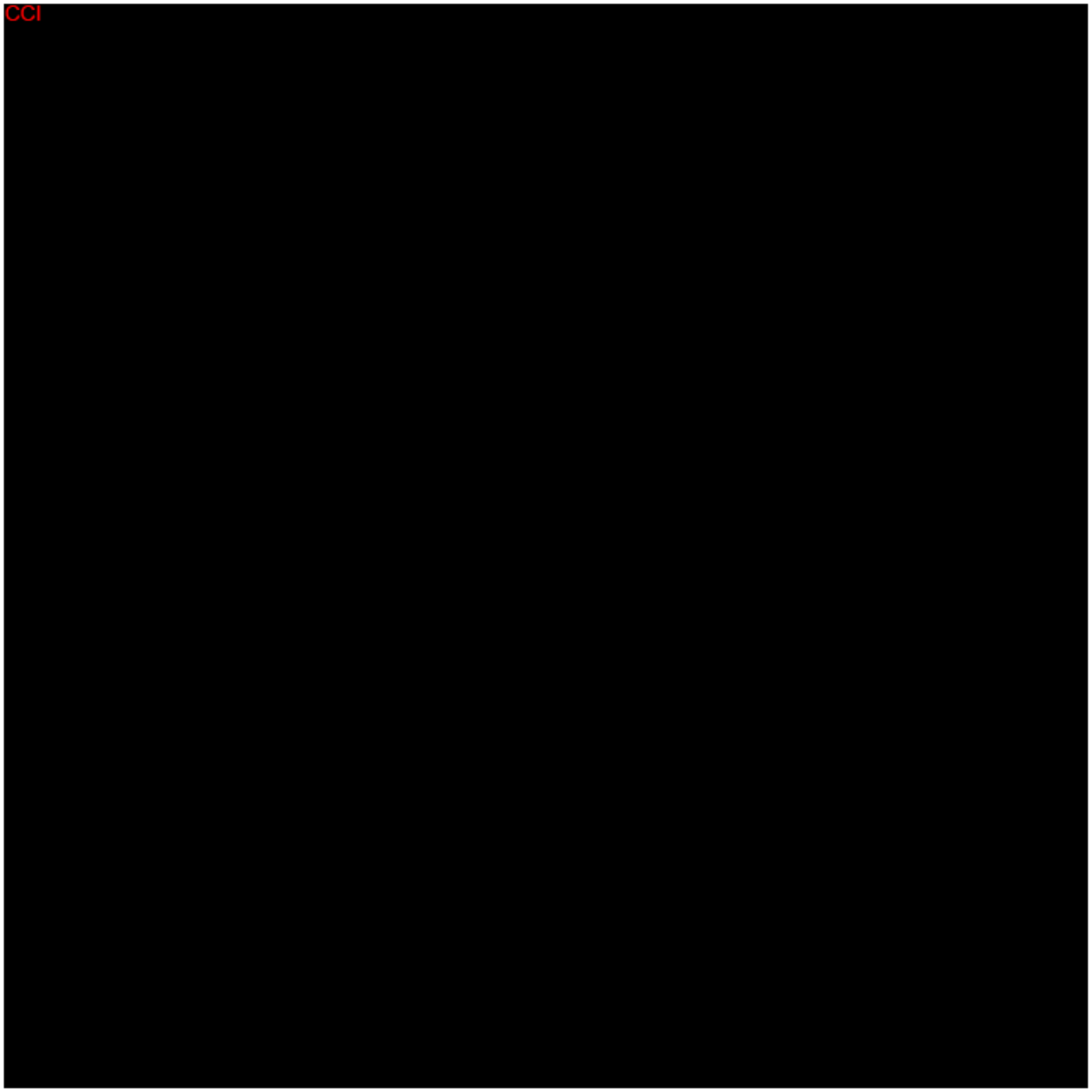

2.1.4 Safety Objectives and Endpoints

The safety objective is to evaluate the safety of a single dose of Alluzience for the treatment of moderate to severe GL.

Endpoints:

- Incidence, causality, severity, and duration of AEs collected during the study.

3. OVERALL CLINICAL STUDY DESCRIPTION

This is an, open-label, randomized, interventional, two-armed, multi-centre study to investigate subject treatment perception and Investigator treatment experience when using Alluzience or vacuum-dried botulinum neurotoxin type A (powder BoNT-A) for treatment of GL.

Approximately 150 subjects will be randomized to either Alluzience or powder BoNT-A treatment in a CCI ratio. Randomization will be stratified by study site. It is estimated that around 170 subjects will be screened to obtain the number of randomized subjects needed for the study.

The study consists of six visits; screening, treatment and four follow-up visits 1, 3, 5 and 6 months after treatment, subjects randomized to be treated with powder BoNT-A will only be followed for 1-month (see Table 1 and Figure 1). The screening visit and the treatment visit might be conducted at the same day. The Investigator and CCI will after the treatment answer questionnaires about how they perceived the treatment session and the Investigator will also answer questionnaires regarding treatment details, reconstitution and CCI of the used study product. CCI .

Adverse events (AEs) will be collected from treatment until the follow-up visit. Any related, unresolved AE will be followed until resolution for up to 3 months after the study or until considered stable.

Efficacy assessments will include (Section 7.1):

- Investigator Assessments:
  - Reconstitution/Preparation Questionnaire
  - Investigator Treatment Session Questionnaire

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Safety assessments will include (Section 7.2):

- AEs
- Pregnancy test

The selection criteria for the study population are described in Section 5. Detailed information about the study tasks for each study visit is outlined in Section 8 and in Table 2. The treatment procedure is provided in Section 6.1.7.1.

4. CLINICAL STUDY DURATION AND TERMINATION

The planned duration of recruitment (from first subject first visit [FSFV] to last subject first visit [LSFV]) is approximately 3 months.

The planned clinical study duration from FSFV to last subject last visit (LSLV) is approximately 9 months.

Clinical study participation is approximately 6.5 months for subjects in the Alluzience treatment group and 1.5 months for subjects in the powder BoNT-A treatment group, including the screening, treatment, and follow-up periods.

The Sponsor may decide to prematurely terminate or suspend the participation of a particular clinical study site (e.g., due to lack of subject enrollment or non-compliance with clinical study protocol (CSP), regulation, or GCP) or prematurely suspend the clinical study (e.g., for safety, study product 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

As a screen failure rate of approximately 10% is anticipated, approximately 170 subjects will be screened in order to enroll approximately 150 subjects in a CCI ratio to 50 s.U of Alluzience (N=100) or 20 U powder BoNT-A (N=50). It is expected that each site will recruit a similar number of subjects (approximately 10 to 20 subjects).

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 (note that 1 month = 4 weeks/28 days).

5.2.1 Inclusion Criteria

Subjects must meet all the following criteria to be eligible for the study:

1. Female 18 to < 65 years of age.

2. Moderate to severe GL at maximum frown as assessed by the Investigator.

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

   OR

   Female of childbearing potential with a negative urine pregnancy test at screening and baseline and agrees to use a highly effective and approved contraceptive method for the duration of the study. A highly effective method of contraception is defined as:

- Bilateral tubal ligation;
- 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;
- Hormonal or copper IUD inserted at least 28 days prior to Day 1;
- Partner vasectomized for at least three months prior to screening visit;
- Progestogen-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 the subject's participation in the study).

4. Time and ability to complete the study and comply with instructions.

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

6. Subjects who have planned to undergo aesthetic facial treatment with powder toxin at the study site.

7. Previous use of any approved botulinum toxin in facial areas.

5.2.2 Exclusion Criteria

The presence of any of the following exclusion criteria excludes a subject from enrollment in the study:

1. Previous use of any botulinum toxin in facial area within 6 months prior to study treatment.

2. Female who is pregnant, breast feeding, or intends to conceive a child during the study.

3. Known allergy or hypersensitivity to any component of the investigational product or any botulinum toxin serotype.

4. Any known contraindication such as subject with bleeding disorder or subject currently using anticoagulants.

5. Previous use of any hyaluronic acid soft tissue augmentation therapy in the treated area within 3 months before baseline.

6. Previous soft tissue augmentation with any permanent (non-biodegradable such as silicone, polyacrylamide, etc) or semi-permanent (i.e., calcium hydroxylapatite, poly-L-Lactic acid or polymethyl-methacrylate) product; lifting threads, or autologous fat in the treatment area.

7. Subject has any prior or current psychiatric illness (e.g. Psychosis, depression, anxiety), alcohol or drug abuse, or is taking antidepressant, anxiolytic, or antipsychotic medication that, in the Investigator's opinion, could affect the subject's safety and/or participation in the study.

8. Other concurrent medical conditions, therapy, or other condition that, in the Investigator's opinion, would interfere with the evaluation of the study medication, safety or efficacy, and/or put the subject at risk if he/she participates in the study.

9. Participation in an investigational device or drug study within 30 days prior to study treatment or plans to enroll in any other investigational study during participation in this study.

10. Study site personnel, close relatives of the study site personnel (e.g. parents, children, siblings, or spouse), employees or close relatives of employees at the Sponsor company.

5.3 Medical History

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

5.4 Previous and Concomitant Therapies

5.4.1 Definition

Previous therapies are defined as therapies that have been stopped within 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, 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, other facial procedures, and 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 below under prohibited concomitant therapies (Section 5.4.5), all concomitant therapies are authorized.

5.4.5 Prohibited Concomitant Therapies

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

- BoNT of any serotype.
- Any other investigational new drug or device.
- Any absorbable (temporary) or non-absorbable (permanent) material in the treatment area.
- Facial aesthetic procedures (e.g., ablative skin resurfacing, laser treatment, micro needling, photodynamic therapy, tattooing or chemical peel) or any other procedures in the treatment area.
- 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 is necessary for the best clinical interest of the subject or due to safety reasons, the Medical Monitor should be notified, if time permits, to discuss possible alternatives prior to administration of a prohibited therapy (contact information for the Medical Monitor provided in the Investigator's site file).

If a subject receives a prohibited therapy during the clinical study, the Medical Monitor should be notified to discuss the subject's continuation in the clinical study (contact information for the Medical Monitor provided in the Investigator's site file). If possible, the subject should continue in the study for the scheduled follow-up visits.

5.5 Procedures/Reasons for Subject Discontinuation

An Investigator may decide to discontinue a subject from the clinical study for medical or 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, s/he will be fully assessed if such assessment is possible. The procedures designated for the Month 1 (powder BoNT-A treatment group) or the Month 6 (Alluzience treatment group)/Early Termination (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 eCRF 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 are listed below:

- Adverse Event: Complete an AE form.
- 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 by e.g., calling three times at different hours and leaving messages, if applicable, before declaring the subject lost to follow-up. 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 may be enrolled (randomized/assigned to treatment) in order to attain the number of evaluable subjects. Under no circumstances shall subjects be enrolled more than once.

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.

For a pregnancy occurring after the screening period, follow the procedures described in Section 7.2.1.2.3. The subject may remain in the study, but no invasive procedure should be

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

6. CLINICAL SUPPLIES

6.1 Clinical Supply Identification and Use

At the baseline visit, each subject will receive a single treatment divided equally among 5 injection points (0.1 mL per injection point) in the glabellar region with either Alluzience or powder BoNT-A according to his or her randomization assignment. For details regarding the treatment procedure, refer to Section 6.1.7.1.

6.1.1 Alluzience

The investigational product Alluzience will be supplied as a liquid in a vial containing 125 s.U of Alluzience at a concentration of 200 U/mL. The drug product should be stored at the recommended temperature (between +2°C and +8°C) should not be frozen. Keep vials in the outer carton in order to protect from light. Each vial contains 0.625 mL of deliverable volume of solution. A volume of 0.25 mL, containing 50 s.U of Alluzience, will be withdrawn from the vial into a syringe for subject administration.
Details of the drug composition and excipients are provided in the current SmPC for Alluzience[16,59].

6.1.2 Powder BoNT-A

The reference product onabotulinumtoxinA/powder BoNT-A will be supplied in a sterile vial containing 50 U of vacuum-dried BoNT Type A. The drug composition, and how to reconstitute the reference product before injection, is provided in the SmPC[17].

The unopened vial and reconstituted solution should be stored at the recommended temperature (between +2°C and +8°C). The reference product should not be frozen.

6.1.3 Study Products Description

Table 5 Description and Usage of the Study Products

	Investigational product	Reference product
Name of drug substance	AbobotulinumtoxinA	OnabotulinumtoxinA
Name of investigational product/ reference product	Alluzience	BOTOX®/Vistabel®
Pharmaceutical form	Solution for injection	Vacuum-dried powder
Concentration	200 s.U/mL, each vial contains 125 s.U in 0.625 mL of solution ready for use, 10U/0,05 mL per injection point	50 U/vial Diluted in 0.9% sodium chloride before use to 4 U/0.1 mL per injection point
Buffer composition	CCI	N/A
Packaging	Glass vial	Glass vial
Reconstitution	N/A	1.25 mL (0.9% NaCl solution)
Storage conditions	2-8°C	2-8°C
Dosage	50 s.U 0.25 mL total 0.05 mL per injection point	20 U 0.5 mL total 0.1 mL per injection point
Route	Intramuscular injection	Intramuscular injection
Dose regimen	Single treatment at baseline visit	Single treatment at baseline visit
Location of treated area	Glabellar region	Glabellar region

6.1.4 Subject Identification Number

Each study participant who has signed the ICF will be assigned a screening number during the screening visit. Upon randomization, a subject is considered enrolled and will be assigned a subject number which will be used for the duration of the study for all documentation and discussion. The subject numbers shall be allocated in ascending sequential order for each study site. If a subject is deemed ineligible for 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 site will be generated by a statistician independent from the study. When the Investigator has confirmed subject eligibility, the subject will be allocated a study product within the electronic web response system.

6.1.6 Randomization Number

Eligible subjects will be allocated a randomization number and which treatment to give the subject within the electronic web response system (e.g. the eCRF). The randomization number will not be pre-printed on the study product, however, the vial used for the treatment will have to be marked with the subject's randomization number for accountability of study product.

Randomization number will be allocated in ascending sequential order, within each site, to each eligible subject.

6.1.7 Instructions for Use and Administration

In this study, Alluzience (50 s.U) will be compared to reference product powder BoNT-A (20 U) administered according to each products SmPC[16, 17].

Alluzience is supplied as a liquid in a buffered solution. Powder BoNT-A is supplied as a white and dry substance that is reconstituted in sterile NaCl solution (saline) before use. For a description of the study products, see Section 6.1.3.

Both Alluzience and the saline used for reconstituting powder BoNT-A should be allowed to equilibrate to room temperature for 15 - 30 min before injection. The preparation of the syringe with Alluzience and the reconstitution of powder BoNT-A must be performed in the same room and in front of the subject by the Treating Investigator.

The injection procedure is identical for both treatment groups. In addition to being trained in the administration technique prior to study initiation, all Treating Investigators will need to have previous experience with BoNT-A products for the studied indication.

The handling of accidently damaged or spilled study products are described in the Material Safety Data Sheets.

6.1.7.1 Treatment Procedure

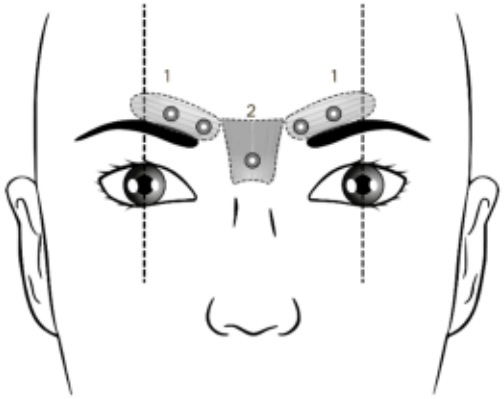
Prior to injection, the treatment area should be cleaned with a suitable antiseptic solution. An appropriately sized syringe and needle should be used to administer the treatment. The needle size (gauge) used by the Investigator in the study should be collected.

Treatment of the glabellar region with Alluzience or powder BoNT-A is administered as an intramuscular injection, given as 0.05 mL per injection point for Alluzience (0.25 mL in total), and

given as 0.1 mL per injection point for powder BoNT-A (0.5 mL in total), using an appropriately sized syringe and needle.

The 5 injection sites include 2 injections into each corrugator supercilii muscle, and 1 injection into the procerus muscle. Before injection, place the thumb or index finger firmly below the orbital rim in order to prevent extravasation below the orbital rim. The needle bevel should be pointed upward and medially during the injection. In order to reduce the risk of ptosis, avoid injections near the levator palpebrae superioris muscle, particularly in patients with larger brow-depressor complexes (depressor supercilii). Injections should be made into the central part of the corrugator muscle, at least 1 cm above the orbital rim. The recommended injection points for GLs are shown below in Figure 2.

Figure 2 Injection Sites for Treating Glabellar Lines



1. Corrugator muscles
2. Procerus muscle

6.1.7.2 Treatment Regimen

Each subject will receive a single treatment with 50 s.U Alluzience, 20 U of powder BoNT-A at the baseline visit. The total injection volume for Alluzience is 0.25 mL in 5 injection points, i.e. 0.05 mL (10 s.U) per injection point. The total injection volume for powder BoNT-A is 0.5 mL in 5 injection points, i.e. 0.1 mL (4 U) per injection point.

6.2 Study Products Packaging and Labeling

Alluzience and onabotulinumtoxinA are manufactured under aseptic conditions and supplied in a glass vial, closed with a rubber stopper and sealed with an aluminum over seal. The study products should be transported and stored at 2-8ºC (see Table 5).

The labels will be printed in English and/or local language containing the information requested by Good Manufacturing Practice and local regulations, and at a minimum, will include the protocol

number, storage conditions, and an investigational test article disclaimer (e.g., for clinical trial use only).

6.3 Supplies Management

6.3.1 Accountability

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

All study products sent to the Investigator/Institution will be accounted for and no unauthorized use is permitted. A Clinical Research Associate (CRA)/monitor will assess and verify accountability of the study products.

6.3.2 Storage of the Study Products

The study products must be stored in a safe and secure area with restricted access, under the storage conditions specified by the Sponsor (see Table 5). The storage temperature will be recorded and kept at the study site.

6.3.3 Dispensing and Return

All study products 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 and properly documented.

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

All used study products and/or supplies will be destroyed at the study site. Destruction will occur according to applicable regulations and the site's drug destruction Standard Operating Procedure (SOP). Unused or expired study product will be returned for destruction to the Sponsor representative at time points approved by the Sponsor.

6.3.4 Treatment Compliance Management and Record

The treatment is an injection administered by the Investigator. Details of the injection procedure will be recorded in the eCRF and subject source documents. 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 using the e-mail listed in the study administrative structure on page 3. A PQC is an external judgement presuming a quality defect or quality issue for a product relating to its presentation or use and is identified by a subject, practitioner, Investigator site personnel, 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 site personnel and forwarded to the Sponsor or designee within 24 hours of awareness. Any 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

Not applicable – open-label study.

7. CLINICAL STUDY ASSESSMENT

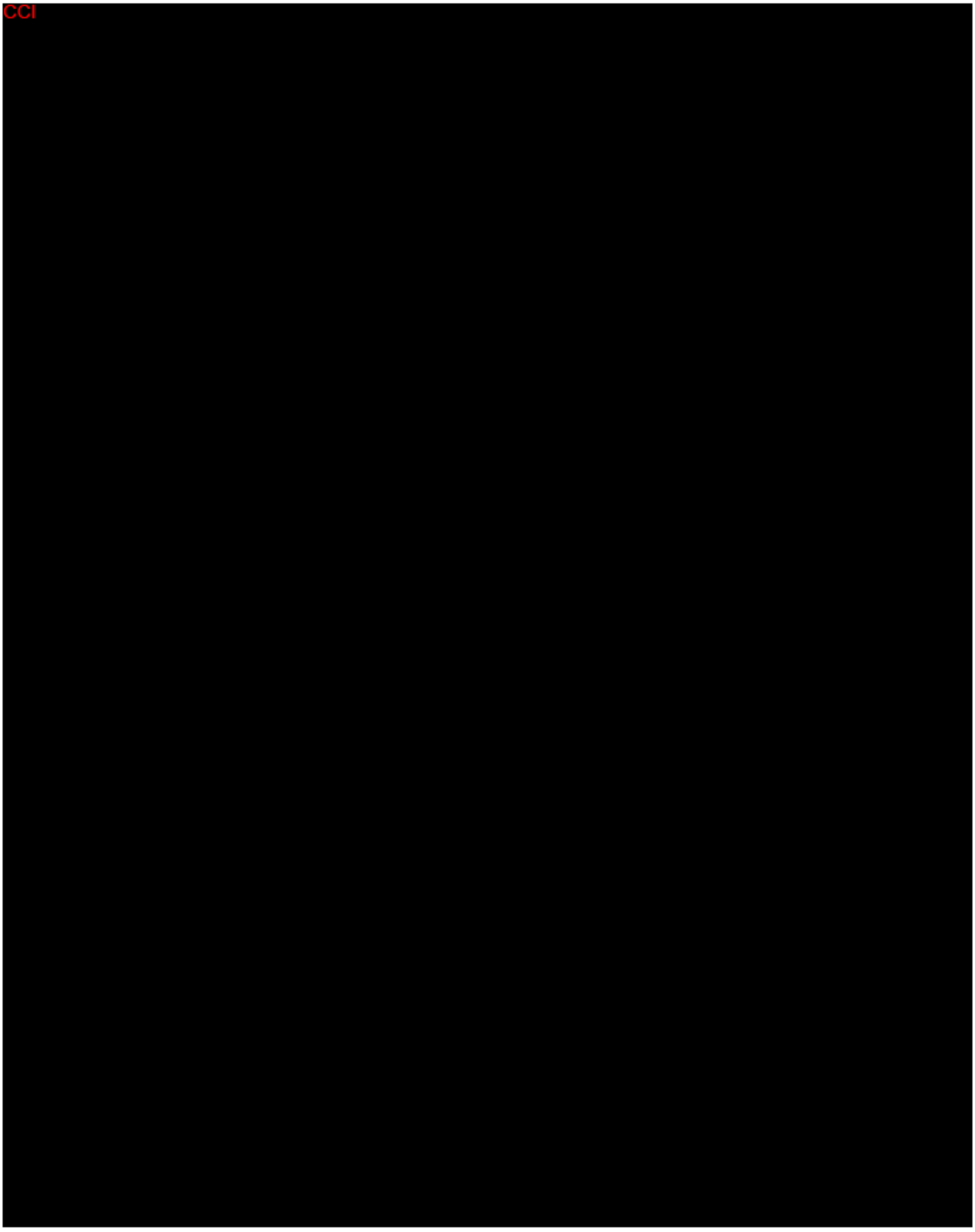
7.1 Efficacy Assessments

7.1.1 Reconstitution/Preparation Questionnaire

The Reconstitution and Preparation Questionnaire (Appendix 1) should be completed by the Treating Investigator after the subject has been treated at Visit 2 (Baseline). The questionnaire is divided into two treatment specific parts, one for Alluzience and one for powder BoNT-A.

7.1.2 Investigator Treatment Session Questionnaire

The Investigator Treatment Session Questionnaire (Appendix 2) should be completed by the Treating Investigator after the subject has been treated at Visit 2 (baseline). The questionnaire should only be completed for Alluzience treated subjects.



CCI [redacted]

7.2 Safety Assessments

7.2.1 Adverse Events (AE)

AEs are to be monitored throughout the course of the clinical study from treatment (see schedule of assessments in Table 2). All AEs are to be reported on the AE form in 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 site personnel for reporting AEs and medical emergencies.

At each follow-up 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?" Additional questioning and examination will then be performed as appropriate.

7.2.1.1 Definitions

7.2.1.1.1 Adverse Events (AE)

According to ICH E2A[19], 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 an AE. Lack of efficacy is not considered 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 an AE; however, it is an important medical event that must be monitored as described in Section 7.2.1.2.3.

- The effects of 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. BoNT is contraindicated in individuals with known hypersensitivity to any BoNT preparation or to any of the components in the formulation.

7.2.1.1.2 Treatment Emergent Adverse Event (TEAE)

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

7.2.1.1.3 Serious Adverse Events (SAE)

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

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

If the subject has had to stay for a night in the hospital, in-patient hospitalization is considered to have occurred. 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 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).

7.2.1.1.4 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., SmPC).

7.2.1.1.5 Adverse Event (AE) Reporting Period

The clinical study period during which AEs must be reported is the period from when the subject is treated with study product 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.

7.2.1.1.6 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 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.

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

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

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

If the answer is "Yes" to either of these questions, 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.

7.2.1.2 Reporting Procedures

7.2.1.2.1 Procedures for Reporting Adverse Events (AE)

The collection of AEs is from the time that a subject is treated to the end of the subject's participation.

At each follow-up 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 in the eCRF along with the date of onset, severity, relationship to the study product, action taken, and outcome, without omitting any requested and known information. Additional information will be requested under certain circumstances.

At study end, AEs assessed as related to the treatment or study procedure will be monitored until they are resolved or have reached a stable condition. Other AEs will be monitored until the last visit if they are not resolved or stable.

The Investigator will maintain all pertinent medical records in the subject's study file. If necessary and approved by the subject or their legal healthcare representative, the Investigator may contact the subject's personal physician or other healthcare provider(s) to obtain further details.

For SAEs (see Section 7.2.1.2.2) and pregnancies (see Section 7.2.1.2.3), the Sponsor is to be informed immediately by e-mail. The event must be reported to the Safety e-mail within 24 hours of receipt of the information (contact details in Section 7.2.1.2.2).

7.2.1.2.2 Procedure for Reporting a Serious Adverse Event (SAE)

For an SAE occurring during the clinical study, regardless of whether it is related to the treatment or not, and 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 7.2.1.1.3).

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

   Print and complete the SAE form. The completed form, accompanied by any other relevant information or anonymized medical records (e.g., laboratory test results), is sent within 24 hours of receipt of the information to the Safety e-mail 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 electronic data capture (EDC) system at the time of the report.

4. Immediately send the completed SAE report form to the Safety e-mail and discuss further actions to be taken.

   E-mail: drugsafetypv@advancedclinical.com

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

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

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

7. Inform the Sponsor of the final outcome of the event. Send a follow-up SAE form, when appropriate, to the Safety e-mail.

8. Prompt notification of SAEs by the Investigator to the Sponsor is essential to ensure that legal obligations and ethical responsibilities are met regarding the safety of the subjects. The Sponsor has a legal responsibility to notify both the local regulatory authority (RA) 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 Ras, Independent Ethics Committees (IECs), and Investigators. Investigator safety reports are prepared for Suspected Unexpected Serious Adverse Reactions (SUSARs) according to local regulatory requirements and the Sponsor's policy, and are forwarded to Investigators as necessary. An Investigator who receives an Investigator safety report describing SAE(s) or other specific safety information (e.g., summary or listing of SAEs) from the Sponsor will file it with the Investigators Brochure and will notify the IEC, if appropriate, according to local requirements.

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

7.2.1.2.3 Procedures for Reporting Pregnancies

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

Subjects who have a positive pregnancy test during the screening period are considered screen failures and are recorded as such in the eCRF, and no pregnancy form is to be completed.

If a subject becomes pregnant after receiving study medication, the Investigator is to do the following:

1. The subject does not need to be withdrawn from the clinical study, i.e., she may continue to attend the planned study visits, but no invasive procedure should be conducted (e.g., no sample should be taken for lab testing).

2. Complete the Pregnancy Report Part A as fully as possible. Send the form within 24 hours of receipt of the information to the Safety e-mail (listed in Section 7.2.1.2.2).

3. Monitor and record the progress of the pregnancy until its outcome. If necessary and approved by the subject or their legal healthcare representative, contact the subject's regular physician (general practitioner or gynecologist) or hospital staff to obtain further details and ask for regular follow-up information.

4. At the outcome of the pregnancy, complete the Pregnancy Report Part B. For all additional evaluations, send the follow-up information to the Safety e-mail within 24 hours of receipt of the information. If the subject can no longer be reached (lost to follow-up), documentation of

the non-response/attempted contact consisting of, e.g. calling three times at different hours and leaving messages, is required.

5. If the pregnancy leads to an abortion (elective abortion, spontaneous abortion or therapeutic abortion), *in utero* death or congenital anomaly, follow the procedure for declaration of an SAE (see Section 7.2.1.2.2).

7.3 Other Assessments

7.3.1 Photography

Standardized digital photographs will be taken of the subject's glabellar region and the full face at Visit 2 (baseline, prior to treatment), Visit 3, 4 and 6.

Each Investigator (or designee) will take photographs using the site's camera equipment, conditions, and settings. Detailed instructions for photography will be provided in a separate photography manual.

7.3.2 Pregnancy Test

For females of childbearing potential, a urine pregnancy test will be performed prior to treatment at screening and baseline (prior to treatment). A negative pregnancy test is required for study inclusion. The result will be documented. Pregnancies during the study should be reported as described in Section 7.2.1.2.3.

7.4 Appropriateness of Measurements

The type of efficacy and safety measurements chosen for this study have been used in previous clinical studies and are considered to be adequate measurements that are widely recognized as reliable, accurate, and relevant for the target indication and study objective.

8. CLINICAL STUDY VISITS DESCRIPTIONS AND PROCEDURES

8.1 Description of Clinical Study Visits

For an overview of the schedule of assessments for each study visit, please refer to Table 2.

A written, signed ICF 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 of the ICF.

8.1.1 Screening, Visit 1 (Day -21 to Day 0)

The screening and baseline visits may be performed on the same day; however, a maximum of 21 days is allowed between the screening and baseline visits.

At the screening visit, the Investigator or designee will:

1. Review and explain the nature of the study to the subject, particularly the prohibited activities and constraints (e.g., restrictions for other aesthetic treatments and the use of topical and systemic medications, see Section 5.4.5).
2. Obtain the signed and dated ICF, and provide the subject with a fully completed, dated and signed copy of the ICF.
3. Collect information regarding demographics (i.e., date of birth, gender, race, ethnicity, height, and weight), relevant medical history and concurrent diseases, previous facial treatments/procedures (including toxin naïve/non-toxin naïve), previous medications and procedures, and concomitant medications and procedures (see Table 2).
4. If the subject is a female of childbearing potential, collect urine for pregnancy test and document the test result (see Section 7.3.2). A negative result is required for study inclusion.
5. Investigator assigns a screening number to all subjects, reviews the inclusion/exclusion criteria (Sections 5.2.1 and 5.2.2), and confirms whether or not the subject meets study eligibility requirements.
    - If yes, schedule the baseline visit.
    - If no, document the subject as a screen failure.

8.1.2 Baseline/Treatment, Visit 2 (Day 0)

If the screening and baseline visits are performed on the same day, the study assessments that are common to both study visits will only be performed once (i.e., AE, concomitant therapies/procedures, UPT, inclusion/exclusion review). A maximum of 21 days is allowed between the screening and baseline visits.

At the baseline visit, the Investigator or designee (*Note: the treating investigator must perform both the reconstitution/preparation and the treatment*) will:

1. Ask the subject about any changes in his/her concomitant therapies/procedures (added, removed or changed) since the previous visit. Record changes in concomitant therapies/procedures as appropriate (Section 5.4).
2. If the subject is a female of childbearing potential, collect urine for pregnancy test and document the test result (see Section 7.3.2). A negative result is required for study inclusion.
3. Investigator reviews the inclusion/exclusion criteria (Section 5.2.1 and 5.2.2), and confirm whether or not the subject meets study eligibility requirements.
    - If yes, enroll/randomize the subject in the clinical study. Proceed to the next steps.

- If no, document the subject as a screen failure.

4. For subjects who meet all eligibility requirements, the Investigator will receive notification of the subject's randomization assignment.
5. Take subject photographs (see Section 7.3.1) for future GAIS assessments according to separate photography manual. If the subject is wearing make-up, instruct the subject to remove it prior to taking the photographs.
6. Make sure to equilibrate Alluzience, or the saline used for reconstitution of powder BoNT-A, for 30 min to room temperature before injection.
7. Ask the subject to complete the Subject Satisfaction Questionnaire (Appendix 6). **Note:** must be performed before treatment.
8. The Investigator should prepare Study Product according to the assigned treatment in the same room and in front of the subject (Section 6.1.7).
9. Prior to injection, clean the subject's treatment area with a suitable antiseptic solution.
10. The Investigator will administer treatment. See Section 6.1.7.1 for injection technique and treatment procedure requirements.
11. Ask the subject about any Aes experienced, in connection to, and after the treatment. Record Aes, as appropriate, on the corresponding eCRF form(s).
12. Record post-treatment concomitant therapies/procedures.
13. Ask the subject to complete the Subject Treatment Session Questionnaire (Appendix 4).
14. Complete the Reconstitution/Preparation Questionnaire (Appendix 1) and the Investigator Treatment Session Questionnaire (Appendix 2).
15. Schedule the next visit (Month 1 ±7 days).

8.1.3 Month 1 (±7 days), Follow-up visit and End of Study Visit for powder BoNT-A treatment group, Visit 3

The Investigator or designee will:

1. Ask the subject about Aes using an open-ended question, such as "*Have you noticed any change in your health since the last visit?*" Record all Aes as appropriate (Section 7.2.1).
2. Ask the subject about any changes in his/her concomitant therapies/procedures (added, removed or changed) since the previous visit. Record changes in concomitant therapies/procedures as appropriate (Section 5.4).
3. Take subject photographs (see Section 7.3.1).
4. <u>For powder BoNT-A treated subjects:</u>
   - Exit the subject from the study.
5. <u>For Alluzience treatment group subjects:</u>

CCI [redacted]

- Schedule the next visit (Month 2 ±7 days).

CCI [redacted]

8.1.4 Month 3, 5 and 6 (±7 days), Follow-up visits and End of Study Visit/Early Termination Visit for Alluzience treatment group, Visit 4, 5 and 6

The Investigator or designee will:

1. Ask the subject about Aes using an open-ended question, such as "Have you noticed any change in your health since the last visit?" Record all Aes as appropriate (Section 7.2.1).
2. Ask the subject about any changes in his/her concomitant therapies/procedures (added, removed or changed) since the previous visit. Record changes in concomitant therapies/procedures as appropriate (Section 5.4).
3. Take subject photographs (see Section 7.3.1) (only visit 4 and 6).
4. CCI [redacted]
5.
6. Schedule the next visit Month 5 (±7 days), OR Month 6 (±7 days), OR complete the end of study form at visit month 6 (Visit 6), depending on current visit.
7. Exit the subject from the study.

8.2 Unscheduled Visits

When necessary, unscheduled visits may be conducted, in particular if an AE occurs and needs to be assessed and/or treated.

8.3 Subject Instructions

Subjects will be advised that any facial make-up will need to be removed before taking the study photographs.

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 detailed and technical description regarding specific data conventions, calculations and the statistical procedures that will be used to perform the analyses that are specified in the sections below. The SAP will be finalized prior to database lock.

Any changes made to the finalized SAP will be documented in the Clinical Study Report.

9.1.1 Populations Analyzed and Evaluability

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

9.1.1.1 Full Analysis Set (FAS) Efficacy Population

The FAS includes all randomized and treated subjects. FAS will be used for all efficacy evaluations.

9.1.1.2 Per-protocol (PP) Efficacy Population

The Per Protocol (PP) population is a subset of the subjects in the FAS population who complete the Month 1 visit and have no protocol deviations considered to have a substantial impact on the primary efficacy outcome. The primary efficacy endpoint will be evaluated using the PP population if the PP population consists of less than 95% of the FAS population.

9.1.1.3 Safety Population

The safety population includes all subjects who were administered study product (i.e., Alluzience or powder BoNT-A). Safety analysis will be performed based on the Safety population.

9.1.1.4 Imputation of Missing Data

No imputation of missing data will be performed, i.e. analyzes will be performed on observed cases (OC). The number of missing values will be summarized and reported as appropriate.

9.1.2 Data Presentation and Graphics

All statistical analyses, including summary tables and data listings, will be performed using the SAS® system (Version 9.4 or higher).

All efficacy, safety and baseline characteristics variables will be presented using descriptive statistics within each treatment group, and graphs as appropriate. Continuous data will be summarized using n (number of observations), mean, standard deviation, median, minimum and

maximum value, while categorical data will be presented by n and percentages. All data will also be listed in subject data listings.

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

9.1.2.1 Subgroup Analysis

No subgroup analyzes will be performed.

9.1.2.2 Safety Analysis

Adverse Events (AE) will be summarized by number of subjects and number of events per treatment group. Aes will be summarized by causality, system organ class , preferred term and maximum intensity. All related Aes will also be summarized by time to onset, duration and action taken.

Aes occurring before treatment will only be provided in subject data listings.

9.1.2.3 Efficacy Analysis

All efficacy analysis will be performed descriptively by treatment group (if applicable).

The Investigator Treatment Session Questionnaire, CCI [redacted] will be presented by category and also by using three categories (Strongly agree/Agree, Neither agree nor disagree, and Disagree/Strongly disagree).

CCI [redacted]

CCI [redacted]

9.1.3 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. They will also be summarized in total (by treatment group and overall) as well as by study site. Depending on the seriousness of the deviation, the subject might be excluded from the PP population, which shall be documented prior to database lock.

9.1.4 Inferential Statistical Analyses

No inferential statistics will be performed.

9.2 Sample Size Determination

The sample size of approximately 150 subjects, 100 subjects in the Alluzience treatment group and 50 in the powder BoNT-A treatment group, 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.

9.2.1 Interim Analysis

No interim analysis will be performed.

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 signature and delegation log. Study staff shall provide a curriculum vitae or equivalent, as appropriate.

It is the responsibility of the Principal Investigator (PI) to ensure that all personnel involved in the study are fully informed regarding 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 that the rights and well-being of the subjects are protected; the reported data are accurate, complete, and verifiable from source documents; and to verify adherence to the CSP, ICH GCP guidelines, national regulations, and applicable SOPs.

The Investigator will allow the CRO/Sponsor representatives to have direct access to all clinical study records, case report forms (CRFs), corresponding subject medical records, study products, dispensing records, and any other documents considered as 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 CRO/Sponsor representative when required.

CSP deviations shall be reported, verified by the monitor, and appropriate corrective and preventive actions shall be taken. The PI is responsible for promptly reporting any deviations from the CSP that affects the rights, safety or well-being of the subject or the scientific integrity of the study, including

those which occur under emergency circumstances, to the Sponsor as well as the IEC if required by national regulations. Deviations shall be reviewed to determine the need to amend the CSP or to terminate the study. Handling of CSP deviations shall be performed as described in the monitoring manual.

10.3 Data Management

Data management based on GCP refers to the activities that ensure secure and robust routines for efficiently entering clinical data into a database. The data management routines include procedures for database set-up and management, data entry and verification, data validation, and documentation of the performed activities and any discrepancies in the process. The data management process will be described in detail in the Data Management Plan (DMP).

The database and data entry screens will be designed in accordance with CSP and eCRF specifications. The EDC system is compliant with regulatory requirements for software validation. Data validation will be performed by computerized logical checks and manual review. Drugs and events will be coded in accordance with the World Health Organization (WHO) Drug database and the Medical Dictionary for Regulatory Activities (MedDRA) as specified in the DMP. Safety data (SAE, and if applicable, Aes of special interest) in the clinical database will be reconciled against the data in the safety database.

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

10.4 Quality Assurance/Audit/Inspection

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

Audits of clinical study sites may be conducted by the CRO/Sponsor representatives, and inspection may be performed by RA inspectorates or an IEC before, during or after the clinical study. For audits performed by or on behalf of the Sponsor, audit certificate(s) will be provided by Quality Assurance.

The Investigator will allow and assist the CRO/Sponsor representatives, IEC and regulatory agencies to have direct access to all requested clinical study-related records.

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 CSP 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 CSP are authorized. The Investigator should document and explain any deviation from the CSP.

10.5.2 Amendments

The Sponsor may modify the CSP 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 IECs. 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) and Regulatory Authorities (RA)

This CSP and all applicable amendments will be reviewed and approved by the appropriate IEC. It is the responsibility of the PI 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 PI 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.

This study requires application for approval from the RA. The study will not be started until the Sponsor has received written approval or until the statutory waiting period from the appropriate authority has elapsed. The Sponsor will provide the PI with a copy of the relevant RA approval documentation.

The collection, access to, processing, and transfer of protected health information or sensitive personal data shall be carried out in accordance with applicable rules and regulations.

11.2 Ethical Conduct of the Clinical Study

This clinical study will be conducted in accordance with the protocol, the HELSINKI declaration (1964) and its subsequent amendments, ICH GCP, national regulations, and in compliance with other 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 GCP guidelines, national regulations and guidelines, and in accordance with local requirements.

The ICF, approved by an 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

For the purposes of the study, the Sponsor is considered the data controller, and the Institution and PI are both considered to be 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 PI are responsible for complying with all requirements pursuant to national legislation in the country in which the Institution and PI are located. The Sponsor will ensure that all requirements are complied with for data processing, which is carried out in Sweden by the Sponsor. Institution and PI are aware of, and will obtain the required approvals prior to the transfer of sensitive personal data which is subject to pre-approval, prior to the transfer of such data outside Europe.

The ICF shall contain information about which personal data will be collected in the study and that the data will be kept confidential. The provided information shall be sufficient to enable all subjects to give their 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 data collection processing, data transfer to countries outside of Europe, and the length of time during which the personal data will be stored. The subject shall have the right to access the stored personal data, and the right to correct any incorrect or obsolete information. If a subject decides to terminate the study prematurely, data collected before withdrawn consent will be used in the evaluation of the study, however no new data may be collected. Authorized representatives from the Sponsor or a RA may visit the study site 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.

11.5 Contractual Requirements

The clinical trial agreement (CTA) outlines the compensation and payment terms of the study. The CTA must be signed before the first subject is screened in the study. If there are differences between the CTA and the CSP regarding certain rights and obligations, the CTA is the prevailing document.

11.6 Data Collection and Archiving

11.6.1 Data Collection

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

11.6.2 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.

The source data location log specifies what data that shall be available in the medical record. The source data location log shall also specify the data for which the eCRF serves as the source. Such data only need to be recorded in the eCRF and are typically associated with study-specific procedures and not with normal clinical care practice. For this type of study data the Investigator would not be expected to duplicate the information into the medical record.

The PI is responsible for maintaining adequate source documentation. Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, i.e., without obscuring the original data entry and with an explanation if necessary.

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

11.6.3 Archives

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

The Investigator/Institution should maintain the essential clinical study documents according to the applicable regulatory requirements.

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

If the PI retires, relocates, or withdraws from the responsibility of keeping the clinical study records for any reason, 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

Q-Med AB's obligations in this clinical study are covered by Galderma's global general liability program. An insurance certificate will be provided upon request. The institution/PI is obligated to maintain insurance coverage for their obligations in the clinical study according to the CTA.

11.8 Publication Policy

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

The aim is to submit the results of this study for publication in the public database (http://www.clinicaltrials.gov) and to a peer-reviewed medical journal for publication. Each person listed as an author of the results of this multicenter study shall have made a substantial, direct, and 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; (2) drafting the work or revising it critically for important intellectual content; (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 designated as an author. Those who do not meet all four criteria will be acknowledged. Among the authors that fulfill the above-mentioned criteria, one author will be appointed by the Sponsor to take primary responsibility for the overall work as primary author.

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

12. LITERATURE REFERENCE LIST

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    Vistabel®, 4 Allergan Units/0.1 ml, Powder for solution for injection, revision 24/09/2018.
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13. SUMMARY OF CHANGES

Section in the clinical study protocol	Rational for changes	Description of changes
Synopsis	As per request from EC no interim analysis will be performed.	Removed possibility to perform an interim analysis before study completion.
7.2.1.2.2 Procedure for Reporting a Serious Adverse Event (SAE)	Updated to match the SAE reporting process.	Added "Print and complete the SAE form" under bullet 3.
9.2.1 Interim Analysis	As per request from EC no interim analysis will be performed.	Removed possibility to perform an interim analysis before study completion.
Appendix 4, 5 and 6	Request from EC to remove signature row for subject questionnaires to protect pseudo-anonymisation.	Removed signature row.

Note: Minor corrections and editorial changes are not listed above.

14. APPENDICES

Appendix 1 Preparation of Alluzience and Reconstitution of powder BoNT-A

Alluzience Preparation Questionnaire

Time for study product to equilibrate to room temperature
(*Note: should be 15 – 30 min according to CSP*)

☐☐☐☐
MM:SS

How long did it take to prepare the product to have it ready for injection?
Time from opening the outer box to having a syringe ready for use.

☐☐☐☐
MM:SS

Did you prepare the product in front of the subject? Yes ☐ No ☐

I did not experience any technical issues/problems when using a ready to use product as compared to a product to be reconstituted

Strongly agree	Agree	Neither agree nor disagree	Disagree	Strongly disagree
☐	☐	☐	☐	☐

BOTOX/Vistabel Reconstitution Questionnaire

NOTE: Reconstitution information can be found on the next page.

Time for solvent to equilibrate to room temperature
(*Note: should be 15 – 30 min according to CSP*)

☐☐☐☐
MM:SS

How long did it take to prepare the product to have it ready for injection?
Time from opening the outer box to having a syringe ready for use.

☐☐☐☐
MM:SS

Did you reconstitute in front of the subject? Yes ☐ No ☐

Any product problems associated with the reconstitution? Yes ☐ No ☐
If "Yes" above:

☐ Wrong final concentration (U/mL)
☐ Wrong concentration of NaCl used/wrong diluent used
☐ Vacuum not pulling the solvent into the vial
☐ Difficulties to insert the needle into the vial
☐ Particles in solution
☐ Bubble/Foam formation
☐ Waste of product
Other, please describe:_____

Have you ever had any issues to reconstitute the powder BoNT-A in the past? Yes ☐ No ☐

If "Yes" above:

☐ Wrong final concentration (U/mL)
☐ Wrong concentration of NaCl used/wrong dilutient used
☐ Vacuum not pulling the solvent into the vial
☐ Difficulties to insert the needle into the vial
☐ Particles in solution
☐ Bubble/Foam formation
☐ Waste of product

Other, please describe:_____

Remember to follow the reconstitution description in the summary of product characteristics (see list below), any deviation (e.g. removing the rubber cap should be recorded as a protocol deviation).

- Reconstitution should be performed in accordance with good practices rules, particularly for the respect of asepsis.
- BOTOX®/VISTABEL® has to be reconstituted with sterile unpreserved normal saline solution (0.9% sodium chloride solution for injection). As per the dilution table below, the requested amount of sterile unpreserved normal saline solution (0.9% sodium chloride solution for injection) has to be drawn up into a syringe in order to obtain a reconstituted solution at a concentration of 4 Units/0.1 mL

Vial size	Amount of solvent added (sterile unpreserved normal saline solution (0.9% sodium chloride solution for injection))	Resulting dose (Units per 0.1 mL)
50 Units	1.25 mL	4.0 Units

- To avoid BOTOX®/VISTABEL® denaturation, the solution is prepared by injecting the solvent slowly into the vial and by gently rotating the vial avoiding bubble formation.
- The vial has to be discarded if the vacuum does not pull the solvent into the vial.

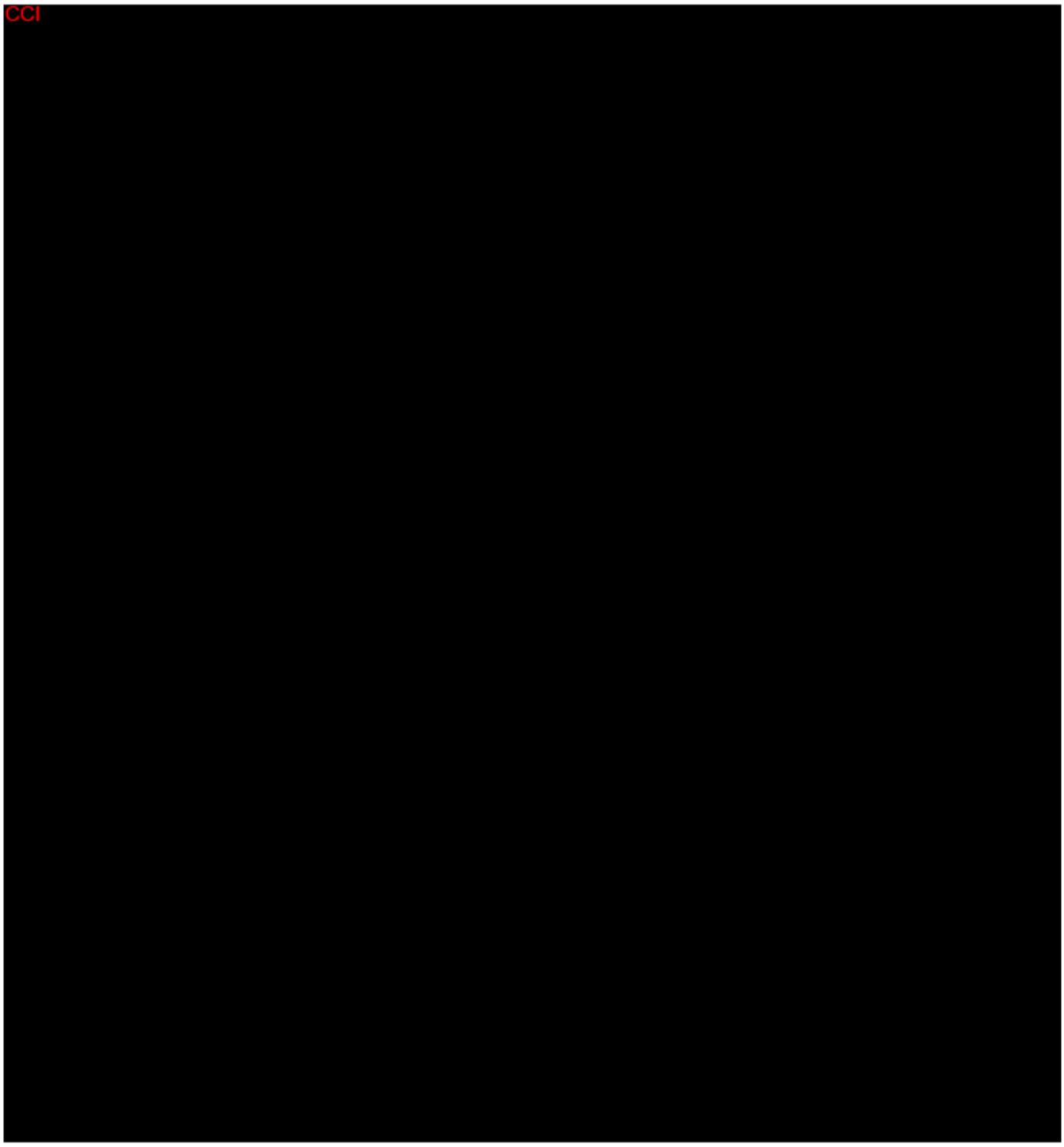
Once reconstituted, the solution should be visually inspected prior to use. Only clear, colourless to slightly yellow solution without particles should be used.

Appendix 2 Investigator Treatment Session Questionnaire (for Alluzience only)

NOTE: **To be answered for Alluzience only**	Strongly agree	Agree	Neither agree nor disagree	Disagree	Strongly disagree
1. I prefer to utilize a ready to use product as compared to a product to be reconstituted	❑	❑	❑	❑	❑
2. I could dedicate more time to explain the treatment procedure in using a ready to use product as compared to a product to be reconstituted	❑	❑	❑	❑	❑
3. I could save time on the reconstitution and injection procedure to do something else	❑	❑	❑	❑	❑
4. I felt more relaxed/less stressed in not having to reconstitute the product to be injected	❑	❑	❑	❑	❑
5. I feel more secure when I have a pre-diluted solution and don't have to reconstitute the product myself	❑	❑	❑	❑	❑
6. I have a good feeling about injecting a modern and innovative product as compared to the reconstituted product	❑	❑	❑	❑	❑
7. I feel I am more precise in my injection with a ready to use product compared to a product to be reconstituted	❑	❑	❑	❑	❑
8. I like to propose new innovative treatment with liquid ready to use product to my patient	❑	❑	❑	❑	❑
9. I produced substantially less waste of non-toxin material (syringes, needles, saline etc.) using ready-to-use product as compared to the reconstituted product	❑	❑	❑	❑	❑
10. When I use a ready to use toxin I spend less materials for injection	❑	❑	❑	❑	❑
11. I believe that the use of ready to use toxin is better for the environment as I produce less waste	❑	❑	❑	❑	❑
12. I feel more confident when injecting a product free from animal and human excipients	❑	❑	❑	❑	❑

CCI

[redacted]



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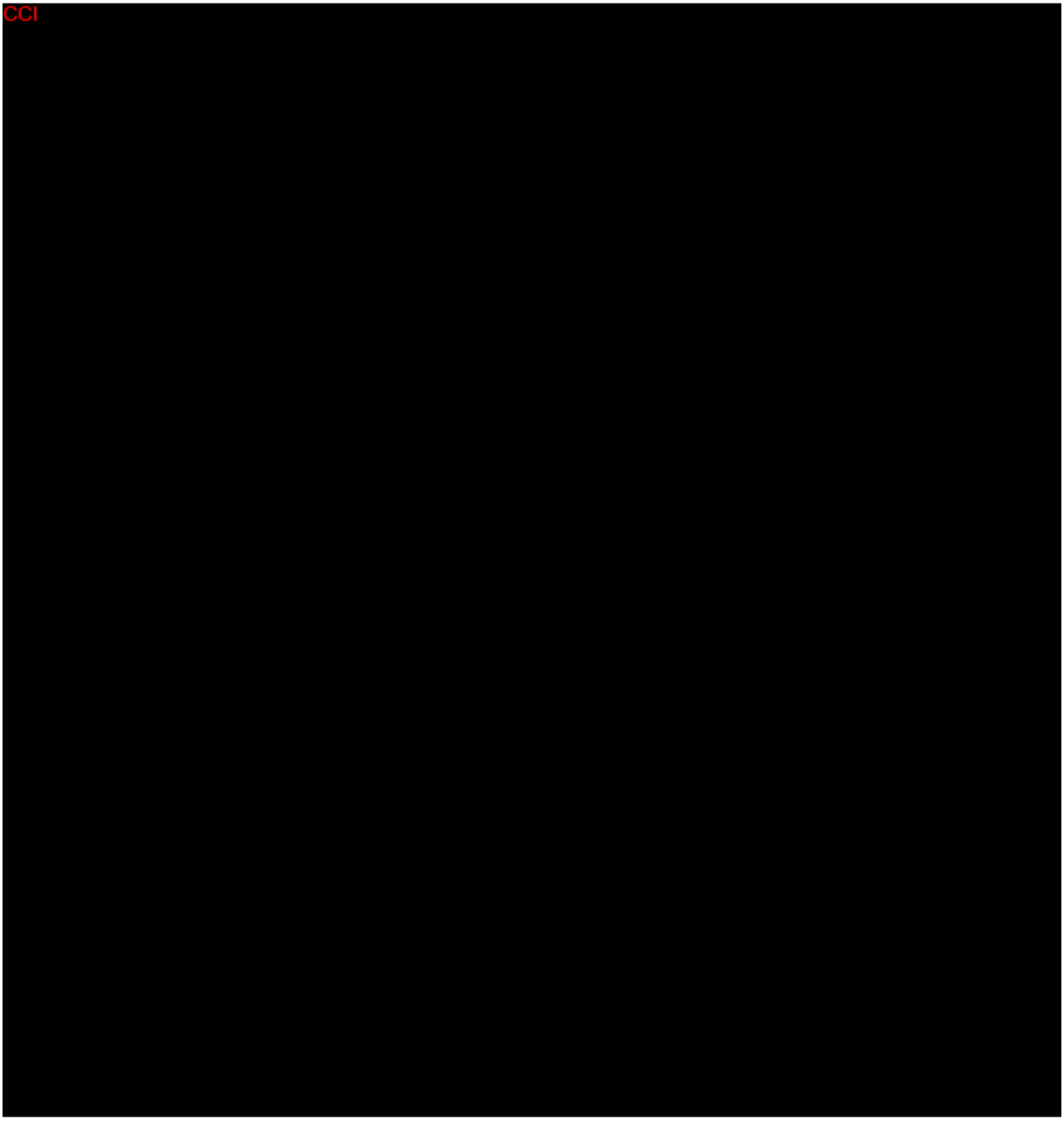

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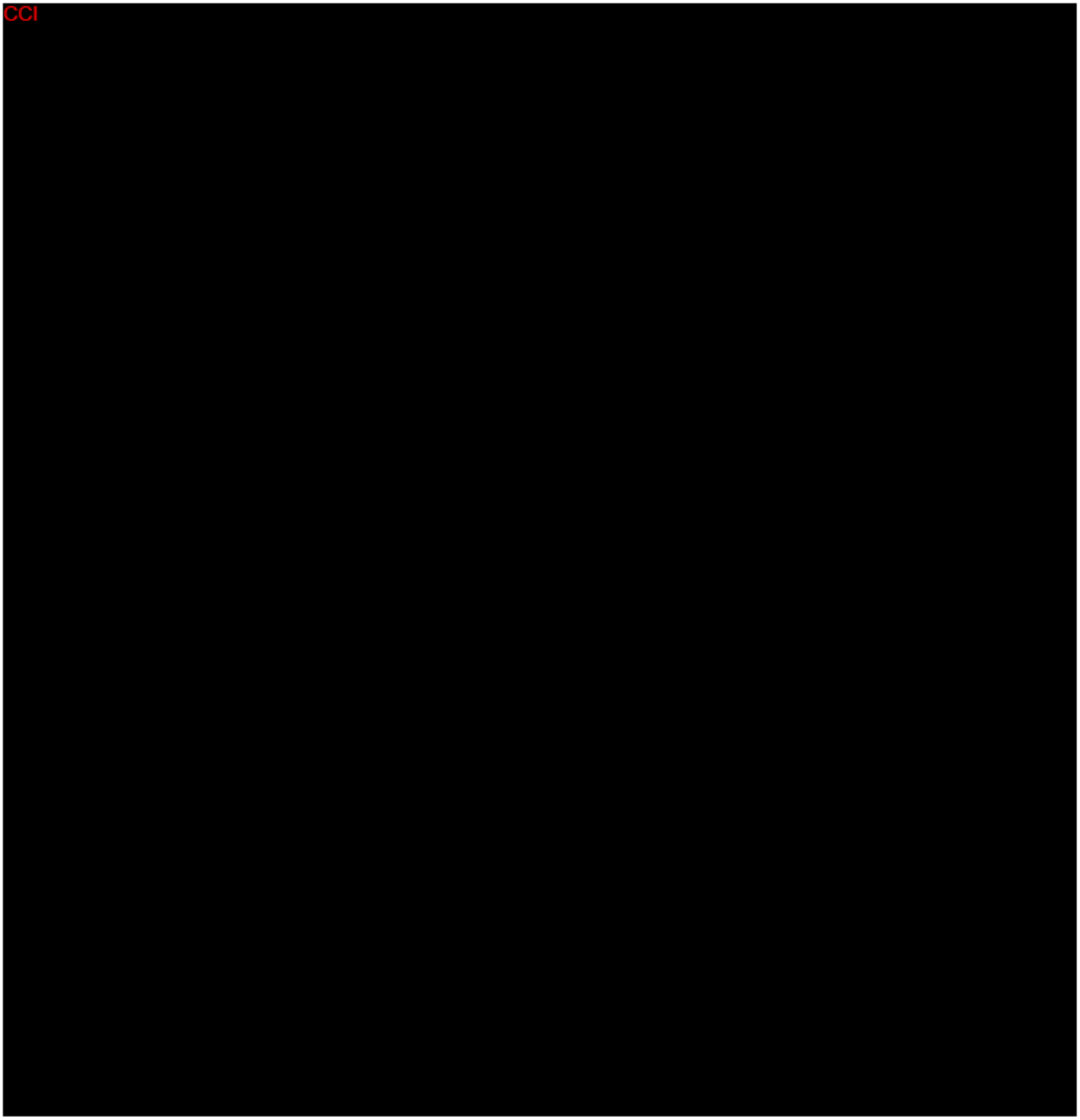

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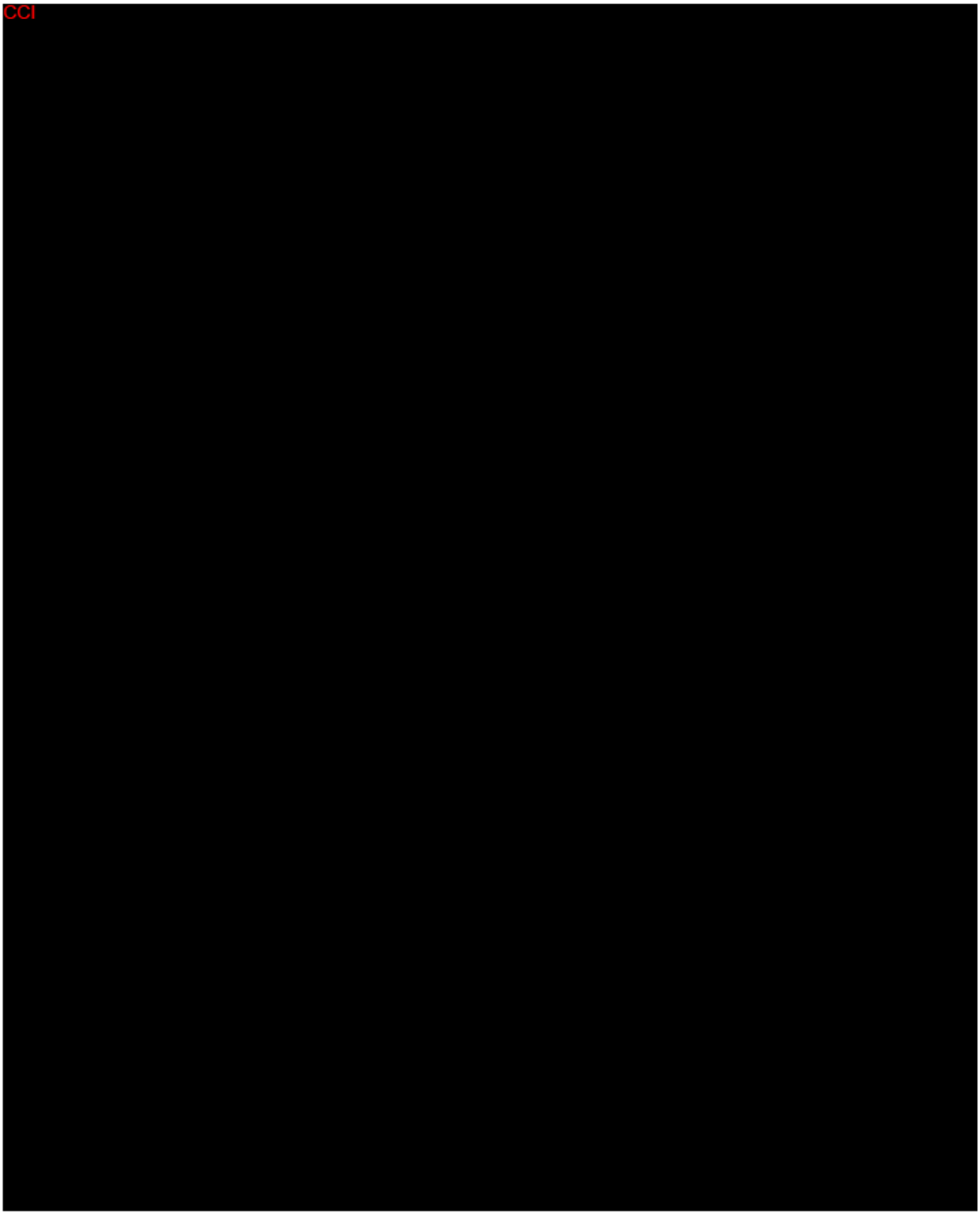

GALDERMA	Title 05PF2005 Clinical Study Protocol - STAR	Doc id MA-48441

CCI

SIGNED AGREEMENT OF THE CLINICAL STUDY PROTOCOL (CSP)

CTN:	05PF2005
CSP title:	A Phase IV, Randomized, Interventional, Study to Assess Subject Treatment Session Perception and Investigator Treatment Experience of Alluzience and Vacuum-Dried Botulinum Neurotoxin Type A for Aesthetic Use

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 SmPC will serve as a basis for co-operation in this study.

Principal Investigator

Printed name	Signature	Date

Study site

GALDERMA	Title 05PF2005 Clinical Study Protocol - STAR	Doc id MA-48441

SIGNATURES PAGE

Date	Signed by
2021-11-30 20:57	PPD
Justification	Approved by Technical Expert
2021-12-01 07:02	PPD
Justification	Approved by Technical Expert
2021-12-01 09:49	PPD
Justification	Approved by Technical Expert
2021-12-01 14:31	PPD
Justification	Compiled by
2021-12-01 17:39	PPD
Justification	Approved by PPD