NCT05320393

STUDY PROTOCOL

EVOLUS-CLIN201

A Phase II Multi-Center, Prospective, Randomized, Double Blind, Active-Controlled, Single Treatment, Increasing Dose Trial to Study the Safety and Duration of Effect of 40U of PrabotulinumtoxinA-xvfs in Adult Subjects for Treatment of Moderate-to-Severe Glabellar Lines

Phase II
Version 2.0
23-NOV-2022

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Phase II

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23-Nov-2022

Study Sponsor
Evolus, Inc.
520 Newport Center Drive, Suite 1200
Newport Beach, California 92660

Clinical Research Organization
ethica CRO Inc.
3551 St. Charles Blvd, Suite 501
Kirkland, Quebec H9H 3C4

PROTOCOL VERSION HISTORY

Version and Date	Description
v.1.0; 22-Jan-2022	*Final protocol*
v.1.1; 21-Feb-2022	*The following administrative amendments were incorporated into the study protocol in address to conditions placed on the study during the 08-Feb-2022 review by the central IRB:* • *Additional pregnancy testing: Additional requirement of a negative UPT at Visit 2 (Inclusion Criterion 2)* • *Additional information regarding Confidentiality: Section 3.4 Confidentiality was added to provide additional details regarding confidentiality safeguards.* • *Information regarding participant recruitment: Specifics on participant recruitment were added to Section 5. Study Subject Selection and Identification.* • *Informed consent process: Clarification was added to Section 13.1 Informed Consent to specific that the study coordinator will lead the participant consenting process.*
v.2.0; 23-Nov-2022	*The following amendments were incorporated into the study protocol:* • *Interim analysis will be conducted (Section 12.8)* • *The Protocol Clarification Letters dated on March 7th,2022 and April 27th,2022*

PROTOCOL APPROVAL SIGNATURE PAGE

The following individuals approve this version of Protocol EVOLUS-CLIN201. These signatures, in conjunction with the signature of the investigator, confirms the agreement of all parties that the clinical study will be conducted in accordance with the protocol and all applicable laws and regulations including, but not limited to, the International Conference on Harmonization (ICH) Guideline for Good Clinical Practice (GCP), the Code of Federal Regulations (CFR), the ethical principles that have their origins in the Declaration of Helsinki, and applicable privacy laws.

Accepted for the Sponsor – Evolus, Inc.:

DocuSigned by:
Rui Avelar
Signer Name: Rui Avelar
Signing Reason: I approve this document
Signing Time: 06-Dec-2022 | 16:12:49 EST
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06-Dec-2022 | 16:12:56 EST

Rui Avelar, Chief Medical Officer DATE

Accepted for the CRO – ethica CRO, Inc.:

DocuSigned by:
Murray Jensen
Signer Name: Murray Jensen
Signing Reason: I approve this document
Signing Time: 06-Dec-2022 | 14:13:32 EST
F05F770148D14CD49ED698357A8F5C0F

06-Dec-2022 | 14:13:35 EST

Murray Jensen, Managing Director DATE

INVESTIGATOR SIGNATURE PAGE

My signature, in conjunction with the signature of the sponsor, confirms the agreement of all parties that the clinical study will be conducted in accordance with the protocol and all applicable laws and regulations including, but not limited to, the International Conference on Harmonization (ICH) Guideline for Good Clinical Practice (GCP), the Code of Federal Regulations (CFR), the ethical principles that have their origins in the Declaration of Helsinki, and applicable privacy laws.

Nothing in this document is intended to limit the authority of a physician to provide emergency medical care under applicable regulations.

By my signature below, I hereby attest that I have read, understood, and agree to abide by all conditions, instructions and restrictions contained in Evolus, Inc., Newport Beach, CA, Protocol Number: EVOLUS-CLIN201.

Principal Investigator *(Print Name)*	Signature	Date

SYNOPSIS

Version	Version 2.0 (23-Nov-2022)	**Investigational Therapy**	PrabotulinumtoxinA 40 Units
Study Number	EVOLUS-CLIN201		
Phase	Phase II	**Control Therapies**	PrabotulinumtoxinA 20 Units OnabotulinumtoxinA 20 Units
Indication	Moderate-to-severe glabellar lines	**Study Sites**	5 sites (US)
Title	A Phase II Multi-Center, Prospective, Randomized, Double Blind, Active-Controlled, Single Treatment, Increasing Dose Trial to Study the Safety and Duration of Effect of 40U of PrabotulinumtoxinA-xvfs in Adult Subjects for Treatment of Moderate-to-Severe Glabellar Lines		
Sponsor	Evolus, Inc.		
Study Duration per Subject	Up to 379 days	**Sample Size**	150 subjects
Study Design	This is a multicenter, prospective, randomized, double-blind, active-controlled, single-treatment, increasing dose design. Up to one hundred and fifty subjects will be randomized 1:1:1, to either 20U onabotulinumtoxinA, 20U prabotulinumtoxinA-xvfs, or 40U prabotulinumtoxinA-xvfs. Subjects with moderate or severe glabellar lines at maximum frown on the 4-point validated Glabellar Line Scale, as judged by the investigator and the subject, will be eligible. Safety and effectiveness will be assessed on days 3, 7, and 30, then every 30 days up to 365 days or until the subject has returned to Baseline as assessed by the Investigator, at which point the subject will exit the study. Duration of effect will be estimated by Kaplan-Meier analysis and will be based on the number of days from Treatment Day (Baseline) to the day that GLS severity (Investigator assessment) at maximum frown returns to the Baseline value (i.e., the treatment will be considered to remain effective for the amount of time during which GLS severity at maximum frown has not returned to Baseline severity). The Evaluating Investigator (i.e., Blinded Investigator) will be responsible for managing the subject, monitor for related and unrelated adverse effects, and carrying out the evaluations. Injections of study drug will be performed by an "Unblinded Injector" (i.e., physician or nurse practitioner appropriately skilled in injecting botulinum toxin into the glabellar area and not responsible for subject follow-up).		
Hypothesis	The general form of duration of effect hypotheses will be: H_o: $\beta = 0$ H_A: $\beta < 0$ where exp(β) is the hazard ratio (experimental treatment / comparator treatment) for loss of effect. The study is not powered for formal hypothesis testing and any analyses presented will be for interpretation purposes only.		
Primary Objectives	The primary objectives of this study are to demonstrate the safety and duration of effect of 40U of prabotulinumtoxinA-xvfs in providing temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugators and/or procerus muscle activity in adult subjects.		
Inclusion Criteria	1. Outpatient, male or female of any race, 18 years of age or older. 2. Female subjects of childbearing potential must have a negative UPT during Visit 1 (Screening), Visit 2 (if applicable) and practice a reliable method of contraception for the duration of the study. 3. Moderate to severe glabellar lines (i.e., score of 2 or 3) on maximum frown as assessed by		

	the investigator using the GLS. 4. Subject has moderate to severe glabellar lines (i.e., score of 2 or 3) at maximum frown as assessed by the subject using the GLS. 5. Able to follow study instructions and likely to complete all required visits. 6. Sign the IRB-approved ICF prior to any study-related procedures being performed.
Exclusion Criteria	1. Female subjects who are pregnant, breast-feeding, or of childbearing potential and not practicing reliable birth control. 2. Known hypersensitivity or previous allergic reaction to any constituent of the IP or control. 3. Any active infection in the area of the injection sites. 4. Inability to substantially lessen glabellar frown lines even by physically spreading them apart. 5. Marked facial asymmetry (Investigator discretion). 6. Ptosis of eyelid and/or eyebrow, or history of eyelid and/or eyebrow ptosis. 7. History of facial nerve palsy. 8. Excessive dermatochalasis, deep dermal scarring, thick sebaceous skin (Investigator discretion). 9. Medical condition that may affect neuromuscular function (e.g., myasthemia gravis, Eaton-Lambert syndrome, amyotrophic lateral sclerosis). 10. Previous treatment with botulinum toxin of any serotype above the level of the lateral canthus within the last 6 months. 11. Planned treatment with botulinum toxin of any serotype below the level of the lateral canthus during the study period. 12. Previous treatment with any facial aesthetic procedure (e.g., injection with biodegradable fillers, chemical peeling, photo rejuvenation) in the glabellar area within the last 12 months. 13. Previous insertion of permanent material in the glabellar area. 14. Any previous energy based or cryotherapy-based treatment of facial muscles superior to the lateral canthus. 15. Any other planned facial aesthetic procedure during the trial period, superior to the level of the lateral canthus (can continue with their usual skin care routine). 16. Any surgery in the glabellar area including surgical removal of the corrugator, procerus, or depressor supercilii muscles, or a combination of these, or scars in the glabellar area and the surrounding areas (including eyebrow). 17. Medical or psychiatric conditions that may increase the risk associated with study participation or may interfere with the interpretation of study results and, in the judgment of the Investigator, would make the subject inappropriate for entry into this study. 18. Evidence of recent alcohol or drug abuse (Investigator discretion). 19. History of poor cooperation or unreliability. 20. Planning to move out of the area prior to study completion. 21. Subjects who are investigational site staff members or family members of such employees. 22. Exposure to any other investigational drug/device within 30 days prior to Visit 1.
Drug Administration	**20U of onabotulinumtoxinA (control):** prepared by reconstituting with 1.25 ml of 0.9% sterile, non-preserved saline solution in a 50U vial for a final dilution of 4 U/0.1 ml. After reconstitution, a total of 0.5ml will be drawn up into a 0.5ml syringe. **20U of prabotulinumtoxinA (control):** prepared by reconstituting with 2.5 ml of 0.9% sterile, non-preserved saline solution for a final dilution of 4 U/0.1 ml. After reconstitution, a total of 0.5ml will be drawn up into a 0.5ml syringe.

	40U of prabotulinumtoxinA (study drug): prepared by reconstituting with 0.625 ml of 0.9% sterile, non-preserved saline solution for a final dilution of 8U/0.05 ml. After reconstitution, a total of 0.25ml will be drawn up into a 0.3ml. Using the preloaded syringe with a 30G needle, the subject will be injected intra-muscularly into a total of five sites, the mid-line of the procerus, the inferomedial aspect of each corrugator muscle and the superior middle aspect of each corrugator, at least 1 cm above the bony orbital rim. Both controls (i.e., 20U of prabotlinumtoxinA, 20U of onabotulinumtoxinA) will be injected with 0.1 ml (4U) per site, for a total of 20 U and 0.5 ml. The study drug (i.e., 40U prabotulinumtoxinA) will be injected with 0.05 ml (8U) per site, for a total of 40 U and 0.25 ml.
Blinding	An "Unblinded Injector" (i.e., physician or nurse practitioner appropriately skilled in injecting botulinum toxin into the glabellar area and not responsible for subject follow-up) will have access to the Randomization Schedule, be aware of treatment assignment, will prepare syringes of reconstituted IP, and will administer injections of study drug to study subjects. The Unblinded Injector will be a different individual than the Blinded Evaluator. The Blinded Evaluator and the study coordinators responsible for subject assessment and follow-up, as well as study subjects, will remain blinded to which study treatment was injected.
Primary Effectiveness Endpoint	The primary effectiveness endpoint will be duration of effect, defined as the number of days from Treatment Day (Baseline) to the day that GLS severity (Investigator assessment) at maximum frown returns to the Baseline value. The treatment will be considered to remain effective for the amount of time during which GLS severity at maximal frown has not returned to Baseline severity. Duration of effect will be estimated by Kaplan–Meier analysis. Although the trial is not powered for inferential analysis, this will be the most influential outcome in the overall assessment of the effectiveness of prabotulinumtoxinA 40 Units, compared to prabotulinumtoxinA 20 Units, in treating moderate to severe glabellar lines.
Secondary Effectiveness Endpoints	Secondary effectiveness endpoints will be used to provide additional evidence of prabotulinumtoxinA 40 Units superiority to prabotulinumtoxinA 20 Units. Secondary endpoints, in order of importance, will be: 1. Duration of effect, defined as the number of days from Treatment Day (Baseline) to the day that GLS severity (subject assessment) at maximum frown returns to the Baseline value. 2. Duration of effect in GAIS responders (score of 2 or 1) as assessed by Investigator. 3. Duration of effect in GAIS responders (score of 2 or 1) as assessed by subject. 4. Duration of effect in SSS responders (score of 2 or 1) as assessed by subjects.
Tertiary Effectiveness Endpoints	Tertiary effectiveness endpoints will be used to compare prabotulinumtoxinA 40 Units to onabotulinumtoxinA 20 Units, as well prabotulinumtoxinA 20 Units to onabotulinumtoxinA 20 Units. Tertiary endpoints, in order of importance, will be: 1. Duration of effect, defined as the number of days from Treatment Day (Baseline) to the day that GLS severity (Investigator assessment) at maximum frown returns to the Baseline value. 2. Duration of effect, defined as the number of days from Treatment Day (Baseline) to the day that GLS severity (subject assessment) at maximum frown returns to the Baseline value. 3. Duration of effect in GAIS responders (score of 2 or 1) as assessed by Investigator. 4. Duration of effect in GAIS responders (score of 2 or 1) as assessed by subject. 5. Duration of effect in SSS responders (score of 2 or 1) as assessed by subjects.
Exploratory Effectiveness Endpoints	Exploratory effectiveness endpoints will be evaluated for signals of effectiveness to explore whether any should be elevated in importance for subsequent trials. Comparisons will be made between all treatment groups. Exploratory endpoints will be:

	1. GLS score of 0 or 1 (maximum frown) as assessed by Investigator and subject at each visit. 2. GAIS response (score of 2 or 1) as assessed by Investigator and subject at each visit. 3. SSS response (score of 2 or 1) as assessed by subjects at each visit. 4. 1-point or greater, 2-point or greater, and 3-point or greater improvement on the GLS (maximum frown) as assessed by Investigator at each visit. 5. 1-point or greater, 2-point or greater, and 3-point or greater improvement on the GLS (maximum frown) as assessed by subject at each visit. 6. Duration of effect in responders with a 1-point or greater, 2-point or greater, and 3-point or greater improvement on the GLS (maximum frown) as assessed by Investigator at each visit. 7. Duration of effect in responders with a 1-point or greater, 2-point or greater, and 3-point or greater improvement on the GLS (maximum frown) as assessed subject at each visit. 8. Duration of effect in GLS responders (responder = ≥1-point improvement on GLS at Day 30) as assessed by Investigator. 9. Duration of effect in GLS responders (responder = ≥1-point improvement on GLS at Day 30) as assessed by subject. 10. Onset of effect as assessed by subjects through the 7-Day Subject Diary.
Safety Endpoints	1. Adverse Events 2. Concomitant Medications 3. Physical Exam 4. Vital Signs: blood pressure, respiratory rate, heart rate 5. Clinical Safety Laboratory Tests: hematology, chemistry, urinalysis, botulinum antibodies 6. 12-Lead ECG 7. Urine Pregnancy Test 8. Directed Questionnaire: review of problems regarding speaking, swallowing, breathing, headaches, eyelid or eyebrow drooping. 9. Directed Review of Systems: review of the following systems: Head and Neck, Respiratory, Cardiovascular, Neurological, Musculoskeletal, Dermatological.
Sample Size	A total of 150 subjects will be randomized to the study, 50 subjects in each of the three treatment arms; 20U onabotulinumtoxinA, 20U prabotulinumtoxinA and 40U prabotulinumtoxinA. Assuming 50 subjects per treatment group, exponential distributions for failure and censoring times, a median duration of effect of 4 months in the reference group, and an annual censoring rate of 10%, the study will have 80% power to detect a hazard ratio of 0.47 based on a one-sided hypothesis test of the primary effectiveness endpoint with alpha = 0.025. As such, it is the opinion of the study Sponsor that 50 subjects per group (total sample size n=150) will be sufficient to address the objectives of this study.
Statistical Methods	**Analysis Populations:** The Modified Intent-to-Treat (mITT) Population is defined as all subjects who were randomized, received their injection of IP, and have at least one post-dosing assessment for the primary effectiveness endpoint. Subjects will be summarized and analyzed according to randomized treatment. Per Protocol (PP) Population is defined as treated subjects who complete the entire study up to the final visit with no protocol deviations that could affect effectiveness assessments. Safety (SAFT) Population will consist of all randomized subjects who received treatment with the IP and will be analyzed as per treatment received. **Primary Effectiveness Endpoint:** Duration of effect will be described by Kaplan-Meier curves and the respective median times with associated 2-sided 95% confidence interval (CI) for each treatment group. Statistical analyses of treatment group differences will be done using Cox proportional hazards regression with time to return to Baseline as the dependent variable, treatment group as the independent variable, and age, gender, and Baseline GLS score

	(Investigator assessment) at maximum frown as covariates. Statistical significance will be established at the 0.025 level with one-sided hypothesis testing. Analysis will be performed using the modified Intent-To-Treat (mITT) population. **Secondary Effectiveness Endpoints:** As duration of effect outcomes, secondary endpoints will be assessed as described above for the primary endpoint. The mITT population will be used for summaries and comparisons. **Tertiary Effectiveness Endpoints:** As duration of effect outcomes, tertiary endpoints will be assessed as described above for the primary endpoint. The mITT population will be used for summaries and comparisons. **Exploratory Effectiveness Endpoints:** Exploratory endpoints will be assessed using either logistic regression (for binary endpoints) or survival analysis-type methods as described above. Comparisons will be made between all treatment groups. Chi-square tests of association or Fisher's exact tests will be used to compare treatment group differences in proportion of subjects returning to Baseline at each time point in the study. The mITT population will be used for summaries and comparisons. **Safety Assessments** will be summarized for the SAFT population using descriptive statistics: frequencies and percentages for categorical assessments, and means, variability, and ranges for continuous assessments.

TABLE 1. SCHEDULE OF EVENTS AND PROCEDURES

Visit Number	V1 [1] Screening	V2 [1]	V3	V4 (phone f/u)	V5 to V15 [2]	V16 [3] (or Final Visit, or ET)	Unscheduled Visit [11]
Day/Week/Month	**≤ 14D**	**Tx Day**	**48Hr**	**D7**	**D30 to D330** **Monthly Visits**	**D365**	
Visit Windows	--	--	--	±1 Day	D30 ±3D, ≥D60 ±7D	±14D	
Assessment and Procedures							
Informed Consent	X						
Inc/Excl Criteria	X						
Demographics, Med Hx	X						
Randomization to Study Tx [4]		X					
Effectiveness - Investigator							
Glabellar Line Scale [5]	X	X	X		X	X	X
Global Aesthetic Improvement			X		X	X	X
Effectiveness - Subject							
Glabellar Line Scale [5]	X	X	X		X	X	X
7-Day Subject Diary		X →					
Global Aesthetic Improvement			X		X	X	X
Subject Satisfaction Score			X		X	X	X
Clinical Interview [6]					D30 only	X	X
Safety Evaluations							
Directed Questionnaire [7]	X		X		X	X	X
Directed Review of Systems	X		X		X	X	X
Vital Signs [8]	X		X		X	X	X
Physical Exam [9]	X		X		X	X	X
UPT (as applicable)	X	X				X	
Clinical Laboratory Tests [10]	X					X	X
ECG	X					X	X
Safety Assessment Phone Call				X			
Brow Area Photography	X	X	X		X	X	X
Concomitant Medications	X	X	X	X	X	X	X
AE Assessment		X	X	X	X	X	X

1. Screening and treatment visit can take place the same day, at the discretion of the investigator
2. Subjects will be followed monthly until their Glabellar Line Scale score is back to Baseline (Investigator assessment)
3. Subject exits study once their Glabellar Line Scale Score has returned to Baseline (Investigator assessment)
4. IP may be administered same day as Screening
5. Glabellar Line Scale at Maximum Frown, 0=none, 1=mild, 2=moderate, 3=severe
6. Clinical Interview Questions
   - What did you like about the treatment (clinically or other feedback)?
   - What did you dislike about the treatment (clinically or other feedback)?
   - If treated with botulinum toxin before this study, which treatment did you prefer, the study treatment or the previous treatment?
7. Directed Questionnaire: Have you noticed any problems with speaking, swallowing, or breathing? Have you had any headaches, eyelid or eyebrow drooping?
8. Blood pressure, heart rate, respiration rate
9. Physical exam to be based on the Investigator judgment as a response to the Medical History, Questionnaire, Review of Systems, and any other relevant information. Neurological exam includes extraocular movement, cranial nerve and muscle weakness assessment
10. Clinical Laboratory Tests:
    - Hematology: Hemoglobin, Hematocrit, RBC, WBC, WBC differential, Platelets
    - Serum: ALP, BUN, Creatinine, ALT, AST, Alb, total protein, UA, Glucose, Na, K, Cl, Ca, anti-botulinum toxin antibodies
    - Urinalysis: Specific Gravity, pH, Protein, Glucose, WBC, Blood
11. Unscheduled Visit: May occur at any time during the study to complete missed study procedures, assess AEs, or assess ongoing unresolved drug-related AEs after study exit. During a visit, some or all of the safety and effectiveness evaluations may be performed.

TABLE OF CONTENTS

ABBREVIATIONS

AE	Adverse Event
BLA	Biologic License Application
BP	Blood Pressure
CFR	U. S. Code of Federal Regulations
CI	Confidence Interval
CRA	Clinical Research Associate
CRO	Clinical Research Organization
ECG	Electrocardiogram
ET	Early Termination
eCRF	electronic Case Report Form
FDA	Food and Drug Administration
GCP	Good Clinical Practices
GAIS	Global Aesthetic Improvement Scale
GLS	Glabellar Line Scale (0=none, 1=mild, 2=moderate, 3=severe)
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IND	Investigational New Drug
IP	Investigational Product
IRB	Institutional Review Board
ITT	Intent-to-Treat
PI	Principal Investigator
PP	Per protocol
SAE	Serious Adverse Event
SAFT	Safety
SAP	Statistical Analysis Plan
SMMP	Safety and Medical Monitoring Plan
SOC	System Organ Class
SSS	Subject Satisfaction Scale
TRAE	Treatment Related Adverse Event
UADR	Unanticipated Adverse Drug Reaction
ULN	Upper Limit of Normal
UPT	Urine Pregnancy Test
US	United States

1 BACKGROUND AND RATIONALE

Botulinum toxin type A, now manufactured by several pharmaceutical/biotechnology companies, has been approved for the temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity in adult subjects.

The clinical study designs that have supported the New Drug Applications for these products have generally followed the same pattern in that they were all multicenter, randomized, double-blind, placebo-controlled studies that assessed the efficacy of the product to reduce the severity of glabellar lines at 30 days following injection of the targeted glabellar muscles.

More recently, approved botulinum toxins approved in the US have investigated the effect of increasing dose on duration of effect (REF 1). In this clinical investigation, the dose of prabotulinumtoxinA will be increased and the safety and duration of effect will be studied.

1.1 Clinical Review

PrabotulinumtoxinA was approved by the FDA in the US in 2019, it is also approved for use in Canada and Europe. In 2014, a comprehensive five-study prabotulinumtoxinA clinical development program was initiated in the United States, EU, and Canada to meet the regulatory requirements for a BLA in the United States, a MAA in the EU, and a NDS in Canada, for the treatment of moderate to severe glabellar lines. The program, included three multicenter, randomized, double-blinded, controlled, single dose Phase III studies titled EV-001, EV-002 and EVB-003. Each Phase III study lasted 150 days. It also included two open-label, multiple dose, long-term Phase II studies titled EV-004 and EV-006, each lasting one year. Between September 2014 and August 2016, over 2,100 adult male and female subjects with moderate to severe glabellar lines at maximum frown participated in this program.

Subjects received intramuscular injections in five target sites; the midline of the procerus, the inferomedial aspect of each corrugator, and the superior middle aspect of each corrugator. Each of the five target sites was injected with 0.1mL for a total of 0.5mL. Subjects assigned (in the open label studies) or randomized (in the controlled studies) to prabotulinumtoxinA received a total of 20 units per treatment, administered as 4 units per 0.1 mL and those subjects who were randomized to the placebo group received 0.5 mL saline. In our EVB-003 Phase III trial, the only study of the five with both a placebo and active control arm, subjects randomized to the active control received a total of 20 units of onabotulinumtoxinA administered as 4 units per 0.1 mL. In the multiple dose studies, eligible subjects could receive up to four treatments of 20 units of prabotulinumtoxinA each.

Phase III U.S. Based Clinical Trials

The two identical U.S. Phase III studies, EV-001 and EV-002, enrolled subjects who were selected from a population of healthy adults, at least 18 years of age, who had moderate to severe glabellar lines at maximum frown (REF 2). Eligible subjects were randomly assigned in a 3:1 ratio to receive a single treatment of either prabotulinumtoxinA or placebo. Subjects were followed for 150 days.

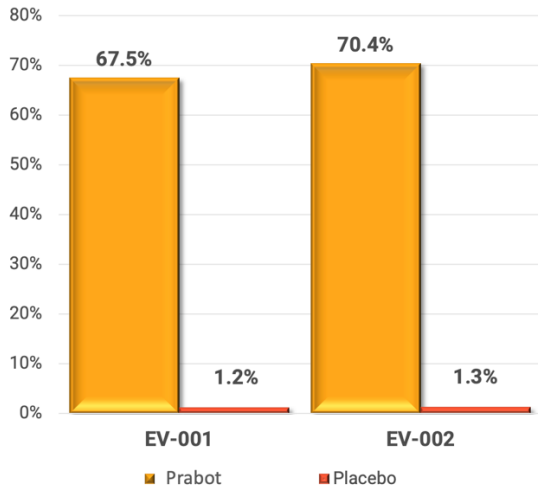
The primary efficacy endpoint was defined as the proportion of subjects classified as responders on Day 30. This was a composite endpoint in which a responder was a subject with a 2-point improvement or greater on the GLS from Day 0 to Day 30 at maximum frown, only if independently agreed by both investigator and subject assessment.

Both studies met the primary endpoint of superiority over placebo. The percentages of responders in the intent to treat population for the composite primary endpoint, a two point or greater score

composite improvement, in each of the two controlled single dose studies were:

- EV-001: 1.2% placebo, 67.5% prabotulinumtoxinA, with an absolute difference between the groups of 66.3%, 95% CI (59.0, 72.4).
- EV-002: 1.3% placebo, 70.4% prabotulinumtoxinA, with an absolute difference between the groups of 69.1%, 95% CI (61.5, 75.1).

U.S. Phase III Primary Endpoint - Composite Score ≥ 2 Point GLS Improvement at Maximum Frown on Day 30



In the **EV-001 study**, analysis of the secondary endpoints investigated the response at maximum frown beyond Day 30 using a two-point composite score. A subject was considered a responder only if a ≥2 point improvement had occurred on the GLS at maximum frown from Day 0, by both investigator and subject assessment:

- At Day 90 (post hoc), the percentage of responders was 1.3% in the placebo group and 26.5% in the prabotulinumtoxinA group with an absolute difference of 25.2%, p<0.001.
- At Day 120, the percentage of responders was 1.3% in the placebo group and 8.3% in the prabotulinumtoxinA group with an absolute difference of 7.0%, p=0.023.
- At Day 150 or early termination, the percentage of responders was 0.0% in the placebo group and 4.6% in the prabotulinumtoxinA group. The absolute difference of 4.6% between the groups remained statistically significant for the composite endpoint, p=0.041.

The 2-point composite score results were similar in the EV-002 study to the EV-001 study for the secondary endpoints:

- At Day 90 (post hoc), the percentage of responders was 0.0% in the placebo group and 25.8% in the prabotulinumtoxinA group with an absolute difference of 25.8%, p<0.001.
- At Day 120, the percentage of responders was 0.0% in the placebo group and 12.4% in the prabotulinumtoxinA group, with an absolute difference of 12.4%, p<0.001.
- At Day 150 or early termination, the percentage of responders was 0.0% in the placebo group and 4.6% in the prabotulinumtoxinA group. The absolute difference of 4.6% between the groups remained statistically significant for the composite endpoint, p=0.047.

EV-002 Subject - Glabellar Lines at Maximum Frown

In the **EV-001 study**, the AE rate was 32.1% in the placebo group and 38.2% in the prabotulinumtoxinA group. Placebo and prabotulinumtoxinA groups were similar in the overall incidence of subjects who experienced one or more AEs. Three prabotulinumtoxinA subjects (3/246, 1.2%) experienced SAEs, but none were assessed as study drug related. Placebo and prabotulinumtoxinA groups were also similar in the percentages of subjects who experienced AEs assessed by the investigator as study drug related: 13.1% of placebo subjects and 15.4% of prabotulinumtoxinA subjects. The eyelid and eyebrow ptosis rates, the drooping of an upper eyelid or eyebrow, respectively, in the prabotulinumtoxinA group was 0.8% and 0.4%, respectively.

In the **EV-002 study**, the AE rate was 26.9% in the placebo group and 28.5% in the prabotulinumtoxinA group. Placebo and prabotulinumtoxinA groups were similar in the overall incidence of subjects who experienced one or more AEs. Four prabotulinumtoxinA subjects (4/246, 1.6%) experienced a SAE, but none were assessed as study drug related. Placebo and prabotulinumtoxinA groups were also similar in the percentages of subjects who experienced an AE assessed by the investigator as study drug related: 7.7% of placebo subjects and 9.8% of prabotulinumtoxinA subjects. The eyelid and eyebrow ptosis rates in the prabotulinumtoxinA arm were 1.2% and 0.4% respectively. Overall, AEs with an incidence of 1% or greater were headache at 9.3% in the prabotulinumtoxinA groups and 7.6% in the placebo groups and eyelid ptosis at 1% in the prabotulinumtoxinA groups and 0% in the placebo groups.

U.S. Phase III Trials - Adverse Event Rate Summary

	US PIII EV-001		US PIII EV-002	
	Placebo	**Prabot**	**Placebo**	**Prabot**
All	32.1%	38.2%	26.9%	28.5%
Related	13.1%	15.4%	7.7%	9.8%

Phase III European Clinical Trial for Glabellar Lines

The **EVB-003 study** was the third Phase III safety and efficacy study in the prabotulinumtoxinA clinical development program and was conducted in Europe and Canada (REF 3). 540 subjects

with moderate to severe glabellar lines, or a GLS score of 2 or 3, as assessed by the investigator at maximum frown, were eligible to be enrolled provided that subjects also felt their glabellar lines had an important psychological impact, such as on their mood, anxiety, or depressive symptoms. On Day 0, eligible subjects were randomly assigned in a 5:5:1 ratio to receive a single treatment of 20 units of prabotulinumtoxinA, 20 units of onabotulinumtoxinA or placebo.

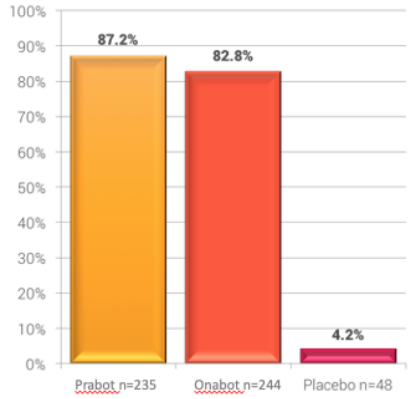
The primary efficacy endpoint was defined as the proportion of subjects classified as responders on Day 30. A responder was a subject with a GLS score of 0 or 1, as assessed by the investigator at maximum frown. The primary analysis of the primary efficacy endpoint in the EVB-003 study showed prabotulinumtoxinA's superiority over placebo, and established prabotulinumtoxinA's non-inferiority to BOTOX. The percentages of responders for the primary efficacy endpoint were:

- 4.2% in the placebo group, 95% CI (0.0, 9.8);
- 82.8% in the onabotulinumtoxinA group, 95% CI (78.1, 87.5); and
- 87.2% in the prabotulinumtoxinA group, 95% CI (83.0, 91.5).

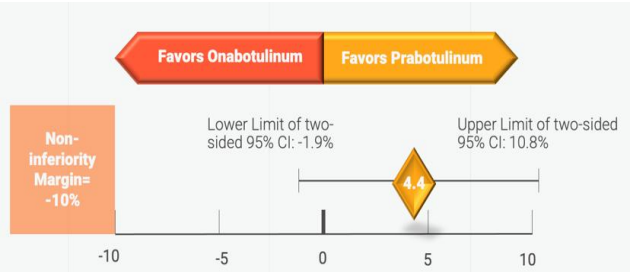
The absolute differences between the treatment groups were:

- 83.1% between prabotulinumtoxinA and placebo groups, 95% CI (70.3, 89.4), ($p<0.001$), indicating prabotulinumtoxinA was superior to placebo; and
- 4.4% between prabotulinumtoxinA and onabotulinumtoxinA groups, 95% CI (-1.9, 10.8), with non-inferiority of prabotulinumtoxinA versus onabotulinumtoxinA concluded based on the lower bound of the 95% CI for the absolute difference exceeding -10.0%.

EU Phase III Primary Endpoint - Responder Rates at Maximum Frown on Day 30 (GLS = 0 or 1) by Investigator Assessment



EU Phase III Primary Endpoint - Non-Inferiority, at Maximum Frown on Day 30 by Investigator Assessment



As presented in the table below, within each group, 32.7% of placebo subjects, 41.9% of onabotulinumtoxinA subjects and 37.6% of prabotulinumtoxinA subjects experienced AEs. One placebo subject (1/49, 2.0%), one onabotulinumtoxinA subject (1/246, 0.4%) and three prabotulinumtoxinA subjects (3/245, 1.2%) experienced a total of 11 SAEs and none were assessed as study drug related. The eyelid ptosis rates were 1.6% in the prabotulinumtoxinA arm and 0% in the onabotulinumtoxinA arm and the eyebrow ptosis rates were 0% in the prabotulinumtoxinA arm and 0.4% in the onabotulinumtoxinA arm.

EU Phase III Trial - Adverse Event Rate Summary

	EU PIII EVB-003		
	Placebo	Onabot	Prabot
All	32.7%	41.9%	37.6%
Related	4.1%	14.6%	15.5%

Phase II Repeat Dose Clinical Trial for Glabellar Lines

The primary objective of the Phase II **EV-004 study** was to demonstrate the safety of prabotulinumtoxinA in adult subjects receiving repeat doses of prabotulinumtoxinA of the course of a year for the treatment of moderate to severe glabellar lines (REF 4).

The test product in this study was different from all the other studies because each vial contained lyophilized prabotulinumtoxinA, while all the other studies used vials containing vacuum dried prabotulinumtoxinA.

Over the course of the one year study, the 352 subjects in the study received a median total dose of 60 units, or 3 treatments.

Total AEs

- 148 subjects (148/352, 42.0%) experienced a total of 265 AEs.
- 7 subjects (7/352, 2.0%) experienced a total of 9 SAEs, none assessed as study drug related.

Study Drug Related AEs

- 51 subjects (51/352, 14.5%) experienced a total of 59 AEs (59/265 events, 22.3%) assessed by the investigator as study drug related.
- 39 subjects (39/352, 11.1%) experienced a study drug related AE following the initial treatment visit, representing 76.5% of all subjects who experienced study drug related AEs (39/51). Progressively lower percentages of subjects experienced study drug related AEs following each repeat treatment: 3.4% (11/319) after the first repeat treatment, 1.5% (4/262) after the second repeat treatment, and none after the third repeat treatment.

The primary objective of the phase II **EV-006 study** objective was also to demonstrate the safety of prabotulinumtoxinA in adult subjects receiving repeat doses of prabotulinumtoxinA over the course of a year for the treatment of moderate to severe glabellar lines (REF 5).

Over the course of the one-year study, the 570 subjects in the study received a median total dose of 60 units, or 3 treatments.

Total AEs

- 235 subjects (235/570, 41.2%) experienced a total of 475 AEs.
- Seven subjects (7/570, 1.2%) experienced eight SAEs, none of the SAEs were assessed as study drug related. One death (1/570, 0.2%) was reported during the study, a SAE, this event was not related to the study drug.

Study Drug Related AEs

- 61 subjects (61/570, 10.7%) experienced a total of 91 AEs (91/473 events, 19.2%) assessed by the investigator as study drug related.
- 37 subjects (37/570, 6.5%) experienced 46 study drug related AEs following the initial treatment visit, representing 60.7% of all subjects who experienced study drug related AEs (37/61). Progressively lower percentages of subjects experienced study drug related AEs following each repeat treatment: 3.6% (19/524) after the first repeat treatment, 3.2% (14/431) after the second repeat treatment, and 1.9% (4/214) after the third repeat treatment.

The combined eyelid ptosis rate for the EV-004 and EV-006 studies was 0.9%.

1.2 Rationale for Study

PrabotulinumtoxinA, using a total dose of 20 Units (i.e., 4 Units injected into five sites of the glabellar complex muscles), has been approved by the FDA for the treatment of moderate to severe glabellar lines. The current study will explore the safety and effectiveness of injecting 40 Units of prabotulinumtoxinA into the glabella and determine if the duration of effect of prabotulinumtoxinA 40 Units is superior to that of prabotulinumtoxinA 20 Units.

Exploratory analyses will determine if the duration of effect of prabotulinumtoxinA 40 Units is superior to that of onabotulinumtoxinA 20 Units, as well as if the duration of effect of prabotulinumtoxinA 20 Units is superior to that of onabotulinumtoxinA 20 Units.

1.3 Hypothesis

The general form of duration of effect hypotheses will be:

H_o: $\beta = 0$
H_A: $\beta < 0$

where exp(β) is the hazard ratio (experimental treatment / comparator treatment) for loss of effect. The study is not powered for formal hypothesis testing and any analyses presented will be for interpretation purposes only.

2 STUDY OBJECTIVE

The primary objectives of this study are to demonstrate the safety and duration of effect of 40U of prabotulinumtoxinA-xvfs in providing temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugators and/or procerus muscle activity in adult subjects.

3 COMPLIANCE STATEMENT

This clinical study will be conducted in accordance with the U.S. Code of Federal Regulations governing Protection of Human Subjects (21 CFR 50), Financial Disclosure by Clinical Investigators (21 CFR 54), Institutional Review Boards (21 CFR 56), Investigational New Drug (21 CFR 312), and Electronic Records; Electronic Signatures (21 CFR Part 11), as appropriate. As such, these sections of U.S. Title 21 CFR are commonly known as Good Clinical Practices (GCPs), which are consistent with the Declaration of Helsinki.

The sites' Principal Investigator (PI) is responsible for ensuring the privacy, safety, and welfare of the subjects during and after the study and must ensure that site personnel are appropriately trained. The PI must be familiar with the background and requirements of the study and with the properties of the IP as described in the Investigator Brochure. The PI at each site has the overall responsibility for the conduct and administration of the study at their site, contact with study site management, as well as the Institutional Review Board (IRB) and local authorities.

3.1 Variations to the Protocol

No changes from the final approved (signed) protocol will be initiated without the prior approval of the FDA and the IRB except 1) when necessary to eliminate immediate hazards to the subjects or when the change involves only logistics or administration, or 2) minor administrative or typographical corrections. The sites' PIs and the Sponsor must sign any protocol amendments.

While a protocol or ICF change intended to eliminate an apparent immediate risk to subjects may be implemented immediately, the change must be documented in an amendment and reported to the IRB within 5 working days and be submitted to the appropriate regulatory agency in the required time frame.

All protocol amendments must be reviewed and approved following the same process as the original protocol. The version number and date of amendments shall be documented, and a justification statement shall be included with each amended section of the document.

3.2 Investigational Sites

Approximately five (5) investigational sites in the U.S. will participate in this study. Each site will obtain written approval from an appropriate IRB prior to recruitment and enrollment of any subject into the study. Any changes to the study procedures must be made with the mutual agreement of the PI and the Sponsor, documented in an amendment to the protocol, and approved by the reviewing IRB.

3.3 Medical Monitor

A Medical Monitor will provide safety oversight for this clinical study. The Medical Monitor, in consultation with the Sponsor's team, will review and evaluate AEs and SAEs on a regular basis, review safety reports, and will provide consultation and recommendations with regard to inclusion/exclusion criteria, concomitant medications/treatments, and subject discontinuations. The Medical Monitor will follow the Safety Management Plan and report the trends of AEs and SAEs with the Sponsor.

3.4 Confidentiality

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location

for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored by ethica CRO Inc. using a 21 CFR Part 11 compliant eCRF housed on a secure server. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by ethica CRO Inc. research staff will be secured and password protected. At the end of the study, all study databases will be archived at ethica CRO Inc. and the study Sponsor.

The electronic diary will housed on the same 21 CFR Part 11 compliant eCRF and will ensure the research participants' privacy and confidentiality, does not share data with third parties or link data with data from other sources, or use research participants' data in any other way or for any other purpose than mentioned in this study protocol and the informed consent documentation.

4 STUDY DESIGN AND TREATMENT

4.1 Study Design

The study is a multicenter, prospective, randomized, double-blind, active-controlled, single-treatment, increasing dose design.

Up to one hundred and fifty subjects will be randomized 1:1:1, to either 20U onabotulinumtoxinA, 20U prabotulinumtoxinA-xvfs, or 40U prabotulinumtoxinA-xvfs. Subjects with moderate or severe glabellar lines at maximum frown on the 4-point validated Glabellar Line Scale (*GLS, 0=none, 1= mild, 2=moderate, 3=severe*), as judged by the investigator and the subject, will be eligible. See Section 5 for a full description of the inclusion and exclusion criteria.

Safety and effectiveness will be assessed on days 3, 7, and 30, then every 30 days up to 365 days or until the subject has returned to Baseline as assessed by the Investigator, at which point the subject will exit the study.

Duration of effect will be estimated by Kaplan-Meier analysis and will be based on the number of days from Treatment Day (Baseline) to the day that GLS severity (Investigator assessment) at maximum frown returns to the Baseline value (i.e., the treatment will be considered to remain effective for the amount of time during which GLS severity at maximum frown has not returned to Baseline severity).

The Evaluating Investigator (i.e., Blinded Investigator) will be responsible for managing the subject, monitor for related and unrelated adverse effects, and carrying out the evaluations. Ideally, the same Evaluating Investigator will perform assessments for a given subject during the entire trial. Injections of study drug will be performed by an "Unblinded Injector" (i.e., physician or nurse practitioner appropriately skilled in injecting botulinum toxin into the glabellar area and not responsible for subject follow-up).

After exiting the study, subjects are eligible for a treatment of their glabellar lines at no cost provided that the investigator deems it appropriate.

4.2 Primary Endpoint

The primary effectiveness endpoint will be duration of effect, defined as the number of days from Treatment Day (Baseline) to the day that GLS severity (Investigator assessment) at maximum frown returns to the Baseline value. The treatment will be considered to remain effective for the amount of time during which GLS severity at maximum frown has not returned to Baseline severity. Duration of effect will be estimated by Kaplan–Meier analysis.

Although the trial is not powered for inferential analysis, this will be the most influential outcome in the overall assessment of the effectiveness of prabotulinumtoxinA 40 Units, compared to prabotulinumtoxinA 20 Units, in treating moderate to severe glabellar lines.

5 STUDY SUBJECT SELECTION AND IDENTIFICATION

The Institutional Review Board (IRB) must review and approve the protocol and informed consent form before any subjects provide consent. Each subject must participate in the informed consent process, sign and date an informed consent form for this protocol before any protocol-required procedures are performed.

If informed consent has not been obtained, no protocol required procedures are to be performed on the subject and no subject data are to be recorded and transferred to the sponsor. Documentation of informed consent must be recorded in the source documents for each subject. Subjects who are unable to provide informed consent will not be able to participate in the study.

Study participants will be identified and recruited from advertising (e.g., social media, newspapers, posters, flyers) and from established site lists of potential study participants who have expressed interest in participating in future clinical trials. The study coordinator will present study specifics to potential participants and will lead the consenting process. The study Investigator and study coordinator will assess and confirm inclusion/exclusion criteria.

In order to be eligible for enrollment in the study, the subject must meet all of the following inclusion criteria and none of the exclusion criteria.

5.1 Inclusion Criteria

A subject must meet the following key criteria in order to be eligible for enrollment in the study:

1. Outpatient, male or female of any race, 18 years of age or older.
2. Female subjects of childbearing potential must have a negative UPT during Visit 1 (Screening), Visit 2 (if applicable) and practice a reliable method of contraception for the duration of the study.

   A female is considered of childbearing potential unless she is:
   - *postmenopausal for ≥12 months prior to study treatment administration;*
   - *without a uterus and/or both ovaries; or*
   - *has been surgically sterile for ≥6 months prior to study treatment administration.*

   Reliable methods of contraception are:
   - *hormonal methods (contraceptive pill or implant) or IUD in use ≥90 days prior to enrolment;*
   - *barrier methods (e.g., diaphragm w/ spermicide or condom w/ spermicide in use ≥14 days prior to study treatment administration; or*
   - *partner vasectomized ≥3 months (or confirmed '0' sperm count) prior to enrolment.*

   [Exception: Females of childbearing potential who are not sexually active are not required to practice a reliable method of contraception. These subjects may be enrolled at Investigator's discretion if they are counseled to remain sexually inactive during the study or agree to use an approved method of contraception should they become sexually active and understand the possible risks in getting pregnant during the study.]
3. Moderate to severe glabellar lines (i.e., score of 2 or 3) on maximum frown as assessed by the investigator using the GLS.
4. Subject has moderate to severe glabellar lines (i.e., score of 2 or 3) at maximum frown as assessed by the subject using the GLS.
5. Able to follow study instructions and likely to complete all required visits.
6. Sign the IRB-approved ICF prior to any study-related procedures being performed.

5.2 Exclusion Criteria

A subject is ineligible to enroll in the study if he/she meets any of the following key criteria:

1. Female subjects who are pregnant, breast-feeding, or of childbearing potential and not practicing reliable birth control.
2. Known hypersensitivity or previous allergic reaction to any constituent of the IP or control.
3. Any active infection in the area of the injection sites.
4. Inability to substantially lessen glabellar frown lines even by physically spreading them apart.
5. Marked facial asymmetry (Investigator discretion).
6. Ptosis of eyelid and/or eyebrow, or history of eyelid and/or eyebrow ptosis.
7. History of facial nerve palsy.
8. Excessive dermatochalasis, deep dermal scarring, thick sebaceous skin (Investigator discretion).
9. Medical condition that may affect neuromuscular function (e.g., myasthemia gravis, Eaton-Lambert syndrome, amyotrophic lateral sclerosis).
10. Previous treatment with botulinum toxin of any serotype above the level of the lateral canthus within the last 6 months.
11. Planned treatment with botulinum toxin of any serotype below the level of the lateral canthus during the study period.
12. Previous treatment with any facial aesthetic procedure (e.g., injection with biodegradable fillers, chemical peeling, photo rejuvenation) in the glabellar area within the last 12 months.
13. Previous insertion of permanent material in the glabellar area.
14. Any previous energy based or cryotherapy-based treatment of facial muscles superior to the lateral canthus.
15. Any other planned facial aesthetic procedure during the trial period, superior to the level of the lateral canthus (can continue with their usual skin care routine).
16. Any surgery in the glabellar area including surgical removal of the corrugator, procerus, or depressor supercilii muscles, or a combination of these, or scars in the glabellar area and the surrounding areas (including eyebrow).
17. Medical or psychiatric conditions that may increase the risk associated with study participation or may interfere with the interpretation of study results and, in the judgment of the Investigator, would make the subject inappropriate for entry into this study.
18. Evidence of recent alcohol or drug abuse (Investigator discretion).
19. History of poor cooperation or unreliability.
20. Planning to move out of the area prior to study completion.
21. Subjects who are investigational site staff members or family members of such employees.
22. Exposure to any other investigational drug/device within 30 days prior to Visit 1.

6 SUBJECT NUMBERING, RANDOMIZATION AND BLINDING

6.1 Subject Numbering

In order to maintain confidentiality, the subject will be identified by his/her Subject Number and initials, and every effort will be made to ensure the confidentiality of this subject information.

All subjects will receive a 3-digit subject number, starting at 001. Subject numbers will be assigned at site level and in ascending order and will be coupled with the site identification number for unique identification of each subject. The subject number will be used to identify the subject throughout the study. Subject Numbers will not be reassigned or reused for any reason. Subjects withdrawn from the study will retain their subject number; new subjects will be allocated a new subject number.

Subjects who do not meet eligibility criteria will be deemed screen failures. Screen Failures will not be entered in the eCRF. However, these subjects may be re-screened at a later date.

6.2 Subject Randomization

At Visit 2/Treatment Day, subjects will be randomized to a study group utilizing hardcopy computer generated "Randomization Schedules" that will link treatment assignment to each Subject Number. The Randomization Schedule will be maintained by the "Unblinded Injector" (Section 6.3).

The Randomization Schedules will provide for equal randomization (1:1:1 ratio) to treatment with either 20U onabotulinumtoxinA, 20U prabotulinumtoxinA-xvfs, or 40U prabotulinumtoxinA-xvfs.

Subjects will be randomized using a blocked randomization scheme that will be stratified by the following factors:

- Baseline GLS: moderate vs. severe
- Age group: ≤65 vs. >65 within each stratum
- Gender: female vs male

6.3 Blinding

To maintain study blind, the "Unblinded Injector" (i.e., physician or nurse practitioner appropriately skilled in injecting botulinum toxin into the glabellar area and not responsible for subject follow-up) will have access to the Randomization Schedule, be aware of treatment assignment, will prepare syringes of reconstituted IP, and will administer injections of study drug to study subjects.

The Unblinded Injector will be a different individual than the Blinded Evaluator. The Blinded Evaluator and the study coordinators responsible for subject assessment and follow-up, as well as study subjects, will remain blinded to which study treatment was injected.

6.4 Unblinding

The treatment assignments for all enrolled subjects will be unblinded only after the conclusion of the study. Specifically, the blind will be broken only after all data are verified, entered into the database and validated, and the database is locked.

If it is medically imperative to know what study treatment was injected, the Investigator or authorized person will contact the Unblinded Injector to obtain the treatment assignment for that

subject. Prior to unblinding, the investigator should attempt to contact the Medical Monitor and ethica CRO Inc. to discuss the rationale for unblinding. The rationale for breaking the code must be recorded in the subjects' medical record and eCRF.

The Sponsor's pharmacovigilance staff or designee may unblind the treatment assignment for any subject with a treatment-related SAE. If the SAE requires that an expedited regulatory report be sent to one or more regulatory agencies, a copy of the report, identifying the subject's treatment assignment, may be sent to clinical investigators in accordance with local regulations and/or Sponsor policy.

Any subject who is unblinded should be withdrawn from the study. An exception may be granted in cases where there are ethical reasons to have the subject remain in the study. In these rare cases, the investigator must obtain documented approval from the Sponsor to allow the subject to continue in the study.

7 INVESTIGATIONAL PRODUCT MANAGEMENT

7.1 Study Drug

PrabotulinumtoxinA-xvfs (Jeuveau®): Each vial of JEUVEAU (prabotulinumtoxinA-xvfs) for injection contains 100 Units of botulinum toxin type A neurotoxin complex, human serum albumin (0.5 mg), and sodium chloride (0.9 mg) in a sterile, vacuum-dried form without a preservative.

OnabotulinumtoxinA (Botox® Cosmetic): Each vial of BOTOX contains 50 Units of Clostridium botulinum type A neurotoxin complex, 0.25 mg of Albumin Human, and 0.45 mg of sodium chloride in a sterile, vacuum-dried form without a preservative.

7.2 Labeling, Packaging and Storage

Vials of IP will be provided to the sites in bulk (i.e., individual kits per subject will not be provided). It is forbidden to use IP for purposes other than defined in this protocol.

IP is to be stored refrigerated (2°C to 8°C) in a secure restricted area; avoid freezing. IP will be shipped to sites in controlled temperature shipments with a temperature monitor. Appropriate temperature records will be filed at the site and in the eTMF. It is the responsibility of the PI to verify that IP is within its expiry date before being used.

The external packaging of IP will be labeled with study information (i.e., study number, study Sponsor, name and address of Evolus, Inc., quantity, "CAUTION: Investigational Drug. Limited by Federal law to investigational use", etc.).

The Investigator Brochure will provide all relevant contraindications, hazards, AEs, warnings, and precautions.

7.3 Investigational Product Supply and Accountability

In accordance with 21 CFR Part 312.140 (a) (2), the investigator must maintain accurate records of receipt, use or disposition of a drug that relate to:

- The type and quantity of the drug, the dates of its receipt, and the drug identification (lot number, batch number or code mark);
- The names of all persons who received, used, or disposed of each drug;
- Why and how many units of the drug have been returned to the sponsor or otherwise disposed of.

The sponsor must notify the FDA and IRB of any request that an Investigator return or dispose of any IP. The notice must be made within 30 working days after the request is made and must state why the request was made.

In addition, accurate records will be kept regarding when and how much test article is dispensed and used by each subject in the study. Reasons for departure from the expected dispensing regimen must also be recorded. At the completion of the study, to satisfy regulatory requirements regarding drug accountability, all study drug will be reconciled and retained or destroyed according to applicable regulations.

Unless otherwise confirmed in writing, all used and unused study drug will be returned to Sponsor/designee for destruction at the conclusion of the study. The site monitor will be provided access to the study IP and records for periodic review.

8 STUDY TREATMENT

Subjects will be treated either with the study drug 40U of prabotulinumtoxinA or one of the two controls; 20U of prabotulinumtoxinA or 20U of onabotulinumtoxinA.

The study drug and active controls will be prepared, reconstituted, and loaded into the syringes by an appropriate and protocol trained person at the site (i.e., study nurse or other designee). The reconstitution and syringe preparations will be done in a double-blinded fashion.

Using a 25G needle each vial will be constituted, gently, without shaking:

- 20U of onabotulinumtoxinA (control) will be prepared by reconstituting with 1.25 ml of 0.9% sterile, non-preserved saline solution in a 50U vial for a final dilution of 4 U/0.1 ml. After reconstitution, a total of 0.5ml will be drawn up into a 0.5ml syringe.
- 20U of prabotulinumtoxinA (control) will be prepared by reconstituting with 2.5 ml of 0.9% sterile, non-preserved saline solution for a final dilution of 4 U/0.1 ml. After reconstitution, a total of 0.5ml will be drawn up into a 0.5ml syringe.
- The study drug, 40U of prabotulinumtoxinA will be prepared by reconstituting with 0.625 ml of 0.9% sterile, non-preserved saline solution for a final dilution of 8U/0.05 ml. After reconstitution, a total of 0.25ml will be drawn up into a 0.3ml.

Using the preloaded syringe with a 30G needle, the subject is to be injected intra-muscularly into a total of five sites, the mid-line of the procerus, the inferomedial aspect of each corrugator muscle and the superior middle aspect of each corrugator, at least 1 cm above the bony orbital rim (Diagram 1). Both controls (i.e., 20U of prabotlinumtoxinA, 20U of onabotulinumtoxinA) will be injected with 0.1 ml (4U) per site, for a total of 20 U and 0.5 ml. The study drug (i.e., 40U prabotulinumtoxinA) will be injected with 0.05 ml (8U) per site, for a total of 40 U and 0.25 ml.

Topical anesthesia is allowed if required; the type(s) used is to be recorded as a concomitant medication.

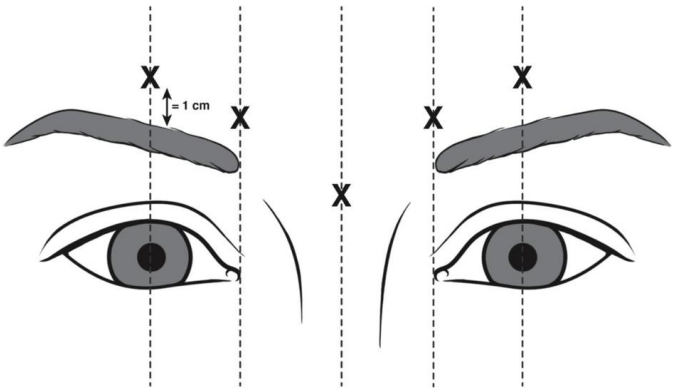


Diagram 1: Injection Sites

8.1 Concomitant Medications

All treatment/procedures received by the subject within 14 days prior to Visit 2 (Treatment Day) and throughout the treatment period, including the name of the treatment/procedure, must be recorded in the eCRF with start date, stop date, dosage, frequency and indication, if applicable.

Medications that may interfere with neuromuscular transmission (e.g., aminoglycosides, curare-like agents) or muscle relaxants need to be observed closely since botulinum toxin may potentiate the effects. Botulinum toxin may also potentiate the systemic anticholinergic effects of anticholinergic drugs. If any of these medications are taken, the Investigator will ensure that all appropriate therapy and follow-up for the subject is provided.

If prohibited therapies and/or procedures are administered during the study, the Medical Monitor will be contacted to discuss details of the event. At a minimum, the event will be documented by the site staff as a protocol deviation, as instructed by the Medical Monitor. Depending upon the nature of the prohibited therapy and the timing relative to the determination of the primary endpoint, the Medical Monitor may decide to discontinue the subject.

The decision to administer a prohibited medication/treatment is done with the study subjects' safety as the primary consideration. If permissibility of a medication/treatment is in question, the Medical Monitor should be contacted before the prohibited medication/treatment is administered.

8.1.1 Prohibited and Restricted Medications

As per Exclusion Criteria (Section 5.2), subjects are prohibited from using various medications or undergo various procedures while enrolled in the study from Visit 1 until study exit.

The following medications/procedures have either restriction for usage and/or are prohibited during the course of the study, and appropriate washout periods noted below must be respected:

Treatment/Procedure	Washout	During Study
Botulinum toxin injections (any serotype) above the level of the lateral canthus	*≥6 months*	*Prohibited*
Botulinum toxin injections (any serotype) in any other body region below the level of the lateral canthus	*n/a*	*Prohibited*
Any facial aesthetic procedure (e.g., injection with biodegradable fillers, chemical peeling, photo rejuvenation, etc.) in the glabellar area	*≥12 months*	*Prohibited*
Insertion of permanent material in the glabellar area	*Any previous use prohibited*	*Prohibited*
Energy based or cryotherapy-based treatment of facial muscles superior to the lateral canthus	*Any previous use prohibited*	*Prohibited*
Surgery in the glabellar area including surgical removal of the corrugator, procerus, or depressor supercilii muscles, or a combination of these, or scars in the glabellar area and the surrounding areas (including eyebrow)	*Any previous surgery prohibited*	*Prohibited*
Any planned facial aesthetic procedure superior to the level of the lateral canthus (can continue with their usual skin care routine)	*n/a*	*Prohibited*
Exposure to any other investigational drug/device	*≥30 days*	*Prohibited*

9 DATA COLLECTION

9.1 Electronic Case Report Form

Treatment and follow-up of subjects will be recorded in a 21 CFR part 11 compliant eCRF. Data will be first recorded into the medical record and study specific source document worksheets prior to entry into the eCRF. The study coordinator will refer to these worksheets in conjunction with the medical record in order to complete data entry into the eCRF.

In order to review and electronically sign the eCRF, the PI will have an individual login password that will allow him/her to view data that has been generated. The PI must ensure that he/she electronically signs for completed eCRFs on a timely basis.

9.2 Coding

Adverse Events will be coded using the current MedDRA dictionary. Concomitant medications will be coded using the current WHODrug dictionary.

10 STUDY EVALUATIONS

10.1 Informed Consent

The PI (or designate) will explain the benefits and risks of study participation to each subject. Written informed consent must be obtained prior to any study related procedure.

10.2 Visit Procedures

10.2.1 Visit 1 (Screening Visit; ≤14 Days)

Subjects can be treated any day after initial screening (within 14 days), including the day of screening at the discretion of the Investigator. The following screening assessments will be conducted at Visit 1:

- Written informed consent
- Inclusion / exclusion criteria
- Demographics and medical history (including previous use of botulinum toxins)
- Brow Area Photography (Section 10.3.4)
- Effectiveness Evaluations - Investigator (Blinded Evaluator)
  - *GLS (max frown) (Section 10.3.1)*
- Effectiveness Evaluations - Subject
  - *GLS (max frown)*
- Safety Assessments
  - *Directed Questionnaire (Section 10.4.1)*
  - *Directed Review of Systems (Section 10.4.2)*
  - *Vital Signs (Section 10.4.3)*
  - *Physical Exam (Section 10.4.4)*
  - *UPT (if female subject of childbearing potential) (Section 10.4.5)*
  - *Clinical Laboratory Tests (Section 10.4.6)*
  - *ECG (Section 10.4.7)*
  - *Concomitant Medications (Section 10.4.9)*

10.2.2 Visit 2 (Treatment Day)

Subjects who successfully complete screening and sign the informed consent will be treated with 20U onabotulinumtoxinA, 20U prabotulinumtoxinA, or a 40U prabotulinumtoxinA. At the discretion of the Investigator, the screening visit and first treatment visit may take place on the same day. The following assessments and procedures will be conducted at Visit 2:

- UPT (if female subject of childbearing potential)
- Brow Area Photography
- Effectiveness Evaluations - Investigator (Blinded Evaluator)
  - *GLS (max frown) prior to injection*
- Effectiveness Evaluations - Subject
  - *GLS (max frown) prior to injection*
- Randomization to study treatment and IP injections (Unblinded Injector)
- Effectiveness Evaluations - Subject
  - *7-Day Subject Diary (Section 10.3.5)*
- Safety Assessments - Investigator (Blinded Evaluator)
  - *Concomitant Medications*
  - *Adverse Events (Section 10.5)*

10.2.3 Visit 3 (Safety and Effectiveness Follow-up; 48hrs ±0 day)

- Brow Area Photography
- Effectiveness Evaluations - Investigator (Blinded Evaluator)
  - *GLS (max frown)*
  - *GAIS (Section 10.3.2)*
- Effectiveness Evaluations - Subject
  - *GLS (max frown)*
  - *GAIS*
  - *Subject Satisfaction (Section 10.3.3)*
  - *7-Day Subject Diary*
- Safety Assessments - Investigator (Blinded Evaluator)
  - *Directed Questionnaire*
  - *Directed Review of Systems*
  - *Vital Signs*
  - *Physical Exam*
  - *Concomitant Medications*
  - *Adverse Events*

10.2.4 Visit 4 (Phone Follow-up; Day 7 ±1 day)

- Safety Assessments
  - *Safety Assessment Phone Call (Section 10.4.8)*
  - *Concomitant Medications*
  - *Adverse Events*

10.2.5 Visits 5 to 15 (Visits each 30 Days; V5 ±3 days, V6 to V15 ±7 days)

Subjects will continue to be monitored for safety and effectiveness at one-month intervals. On and after **Day 90**, subjects are eligible to exit the study once their GLS score at maximum frown has returned to Baseline (Investigator assessment). Subjects will return for monthly assessments until they reach their Baseline GLS score (Investigator assessment). Assessment procedures include:

- Brow Area Photography
- Effectiveness Evaluations - Investigator (Blinded Evaluator)
  - *GLS (max frown)*
  - *GAIS*
- Effectiveness Evaluations - Subject
  - *GLS (max frown)*
  - *GAIS*
  - *Subject Satisfaction*
  - *Clinical Interview (Visit 5; Day 30 only) (Section 10.3.4)*
- Safety Assessments - Investigator (Blinded Evaluator)
  - *Directed Questionnaire*
  - *Directed Review of Systems*
  - *Vital Signs*
  - *Physical Exam*
  - *Concomitant Medications*
  - *Adverse Events*

10.2.6 Visit 16 (Final Visit or ET Visit; Day 365 ±14 days)

The Final visit (or ET visit) will take place when subjects GLS score (Investigator assessment) has returned to Baseline. Subjects may withdraw from participation in the study at any time for any

reason. If withdrawal occurs, the subject should be asked to complete a follow-up or early termination visit, if possible. During the final or early termination visit, both safety and effectiveness evaluations will be performed as follows:

- Brow Area Photography
- UPT (if female subject of childbearing potential)
- Effectiveness Evaluations - Investigator (Blinded Evaluator)
  - *GLS (max frown)*
  - *GAIS*
- Effectiveness Evaluations - Subject
  - *GLS (max frown)*
  - *GAIS*
  - *Subject Satisfaction*
  - *Clinical Interview*
- Safety Assessments - Investigator (Blinded Evaluator)
  - *Directed Questionnaire*
  - *Directed Review of Systems*
  - *Vital Signs*
  - *Physical Exam*
  - *Clinical Laboratory Tests*
  - *ECG*
  - *Concomitant Medications*
  - *Adverse Events*

10.2.7 Unscheduled Visit

An unscheduled in-office visit may occur at any time during the study to complete missed study procedures, assess adverse events, or assess ongoing unresolved drug-related adverse events after study exit. During the visit, some or all of the safety and effectiveness evaluations may be performed as follows:

- Brow Area Photography
- Effectiveness Evaluations - Investigator (Blinded Evaluator)
  - *GLS (max frown)*
  - *GAIS*
- Effectiveness Evaluations - Subject
  - *GLS (max frown)*
  - *GAIS*
  - *Subject Satisfaction*
  - *Clinical Interview*
- Safety Assessments - Investigator (Blinded Evaluator)
  - *Directed Questionnaire*
  - *Directed Review of Systems*
  - *Vital Signs*
  - *Physical Exam*
  - *Clinical Laboratory Tests*
  - *ECG*
  - *Concomitant Medications*
  - *Adverse Events*

10.3 Effectiveness Assessments

10.3.1 Glabellar Lines Scale (GLS)

The severity of glabellar lines at "maximum frown" will be assessed by both the Investigator (Blinded Evaluator) and subjects using the validated 4-point GLS as per Table 2 and in Appendix C. The accompanying photonumeric guidance will be provided separate from this protocol.

Table 2. GLS at Maximum Frown

Grade	Score	Description
None	**0**	No lines
Mild	**1**	Line seen, not sharp
Moderate	**2**	Line sharper, deep, may see heaping of skin
Severe	**3**	Deeper line, heaping of skin, skin may be opposed

10.3.2 Global Aesthetic Improvement Scale (GAIS)

GAIS will be assessed by both the Investigator (Blinded Evaluator) and subjects using the 5-grade scale as per Table 3 below. Instruction for assessment: "Compare your pre-injection photograph to the photograph provided and rate the degree of aesthetic improvement by using the following scale". Investigator and subject will assess using the same pre-injection photograph.

Table 3. GAIS

Grade	Score	Description
Much Improved	**2**	Marked improvement in appearance
Improved	**1**	Improved in appearance, but would like more
No Change	**0**	The appearance is essentially the same as the original condition
Worse	**-1**	The appearance is worse than the original condition
Much Worse	**-2**	The appearance is much worse that the original condition

10.3.3 Subject Satisfaction Scale (SSS)

SSS will be assessed by the subject using the following 5-grade scale as detailed in Table 4 below. Subject will be instructed: "Rate your level of satisfaction with the effect of study treatment on your frown lines by using the following scale":

Table 4. Subject Satisfaction Scale

Grade	Score	Description
Very Satisfied	**2**	I am very satisfied with the treatment
Satisfied	**1**	I am satisfied with the treatment
Indifferent	**0**	I am indifferent with the treatment
Unsatisfied	**-1**	I am unsatisfied with the treatment
Very Unsatisfied	**-2**	I am very unsatisfied with the treatment

10.3.4 Brow Area Photography

Photos of the brow area will be collected at all visits except at Visit 4. A photography instruction manual will be provided separate from this protocol.

10.3.5 Clinical Interview (Day 30, Final Visit/Early Termination, and Unscheduled Visit)

Subject opinion regarding study treatment will be assessed through a clinical interview employing the following questions:

- What did you like about the treatment (clinically or other feedback)?

- What did you dislike about the treatment (clinically or other feedback)?
- If treated with botulinum toxin before this study, which treatment did you prefer, the study treatment or the previous treatment?

10.3.6 7-Day Subject Diary

In the morning of the day after study treatment, subjects will be issued a 7-day electronic subject diary that will assess subjects' opinion regarding onset of study treatment effect. Subjects will respond "Yes" or "No" to the following question: "*Since being injected, have you noticed any effect on the appearance of your glabellar lines?*"

10.4 Safety Assessments

10.4.1 Directed Questionnaire

The following questions will be asked looking for signs of local or distant botulinum toxin spread and to set a baseline:

- Have you noticed any problems with speaking, swallowing, or breathing?
- Have you had any headaches, eyelid or eyebrow drooping?

10.4.2 Directed Review of Systems

Directed Review of Systems will include review of the following systems: Head and Neck, Respiratory, Cardiovascular, Neurological, Musculoskeletal, Dermatological.

10.4.3 Vital Signs

Blood pressure (systolic, diastolic), respiratory rate, and heart rate will be recorded.

10.4.4 Physical Exam

Based on the response to the medical history, directed questions, directed reviews of systems, inclusion and exclusion criteria, an appropriate physical examination will be conducted by the Investigator. The neurological examination should include extraocular movement, cranial nerve and muscular weakness assessments. This exam will also establish a baseline for the subject.

10.4.5 Urine Pregnancy Test

Standard commercially available UPTs will be used to confirm pregnancy status at Screening (Visit 1), Visit 2 (if applicable) and end of study. The urine pregnancy test employed should have a sensitivity of at least 50 mIU/mL for human chorionic gonadotropin (hCG).

10.4.6 Clinical Safety Laboratory Tests

The clinical laboratory data consist of blood analysis (including hematology, clinical chemistry, and urinalysis) will be conducted as per the visit schedule. A designated central laboratory will analyze clinical laboratory samples. All tests and laboratory reports will be reviewed and signed by the Investigator. Any abnormal findings will be dealt with in a clinically appropriate manner, per the clinical judgment of the Investigator. Clinically significant results (Investigator opinion) will be reported as AEs.

Approximately 12ml of blood will be drawn for each testing at Screening and end of the study (or early termination), for a total of 24ml for each subject. The following tests will be performed:

- Hematology: hemoglobin, hematocrit, red blood cell count, white blood cell count, neutrophils, lymphocytes, monocytes, eosinophils, basophils, platelet count
- Chemistry: alkaline phosphate, urea nitrogen, creatinine, ALT, AST, albumin, total protein,

uric acid, glucose, sodium, potassium, chloride, calcium

- Urinalysis: specific gravity, pH, protein, glucose, leukocytes, occult blood
- Botulinum antibodies

10.4.7 12-Lead ECG

12-lead ECGs will be at Screening and at the final study visit and will include heart rate, PR, QRS, QT, and QTc. ECG results will be interpreted by as Normal, Abnormal; not clinically significant (NCS), or Abnormal; clinically significant (CS). If Abnormal, details will be provided, and "Abnormal Clinically Significant" results (Investigator opinion) will be reported as AEs."

10.4.8 Safety Assessment Phone Call

General safety assessments above that can be conducted over the phone will be verbally administered.

10.4.9 Concomitant Medications

All treatment/procedures received by the subject within 14 days prior to study treatment and throughout the treatment period, including the name of the treatment/procedure, must be recorded in the eCRF with end dates, if applicable.

10.4.10 Pregnancy and Contraception

All women of childbearing potential who participate in the study should be counseled on the need to practice adequate birth control and on the importance of avoiding pregnancy during study participation by using effective birth control methods (e.g., oral contraceptive, condom, IUD, injectable contraceptive, diaphragm, or vasectomized partner). Male subjects have no contraceptive restrictions. Women should be instructed to contact the PI or study staff immediately if pregnancy occurs or is suspected.

Urine pregnancy testing (sensitivity of at least 50 mIU/mL for hCG) will be conducted at Screening (Visit 1), Visit 2 (if applicable), and at the end of the study on every woman of childbearing potential. A woman who is found to be pregnant at screening will be excluded from the study and considered to be a screen failure.

Pregnancies will be recorded using the Unanticipated Problems Reporting Form and are not be considered AEs.

10.5 Adverse Events

All observed or volunteered AEs regardless of treatment group or suspected causal relationship to the study treatment will be recorded in the eCRF. Subjects will be questioned for the occurrence of any new or worsening signs or symptoms at each visit by the following methods:

- Information volunteered by the subject
- Open ended and non-leading questions such as: Have you had any health problems since your last visit?
- Observation by the investigational team, other care providers or relatives

10.5.1 Definition of an Adverse Event

An AE is any untoward medical occurrence in a subject administered the study treatment and which may, but does not necessarily, have a causal relationship with study treatment. An AE can therefore be any unfavorable or unintended sign (for example an abnormal laboratory finding),

symptom or disease temporally associated with the study treatment, whether or not considered related to the study treatment.

AEs may include, but are not limited to, subjective or objective symptoms spontaneously offered by the subject, solicited via subject interviews, uncovered by review of concomitant medications or therapies, and/or observed by the site staff. A blinded Investigator will determine the description (sign, symptom, diagnosis), onset, resolution, seriousness, severity, cause, and action taken for any event.

Disease signs and symptoms that existed prior to study enrolment are not considered AEs. Recurring symptoms associated with pre-existing conditions are not considered AEs unless they have a clinically significant increase in severity and/or frequency, as determined by the blinded Investigator.

Clinically significant abnormal laboratory tests (if applicable) must be recorded as an AE.

Changes resulting from normal growth and/or development occurring at a physiologically appropriate time that do not vary significantly from the frequency or severity expected, for example, the onset of menses or menopause, are not to be considered AEs.

10.5.2 Serious Adverse Events (SAEs)

A **SAE** is defined as any unfavorable medical occurrence that meets any of the following:

1. Results in death.
2. Is life-threatening: “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.
3. Requires inpatient hospitalization or prolongation of existing hospitalization: Planned and routine hospital admissions for pre-existing conditions are not considered SAEs and do not require reporting as an AE unless the condition has worsened beyond what would reasonably be expected for that subject. If a subject experiences an additional AE that prolongs a pre-planned hospitalization this is considered to be an SAE and should be reported as an SAE. Pre-planned admissions must be recorded in the subject’s source documentation.
4. Results in persistent or significant disability/incapacity.
5. Is a congenital anomaly or birth defect resulting from a pregnancy occurring during the study.
6. Is an important medical even that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed above should usually be considered serious.

10.5.3 Unexpected Adverse Drug Reaction (UADR)

A UADR is an adverse reaction where the nature or severity of which is not consistent with the applicable product information in the source documents (e.g., Investigator's Brochure.).

10.5.4 Causality Assessment

A blinded Investigator’s assessment of an AE’s relationship to the study treatment is part of the documentation process, but it is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event will be reported. A blinded Investigator will assign the causality assessment according to his/her clinical experience and the subject’s description of the event. The Sponsor will be responsible for the final causality

judgment. The causal relationship should be classified according to the following criteria (not all variables need to be present to be indicative of relationship to the treatment):

Definitely related:

- The temporal sequence of AE onset relative to study treatment is reasonable.
- The AE is more likely explained by study treatment than by another cause.
- The AE shows a pattern consistent with previous knowledge of study treatment.

Probably related:

- The temporal sequence of AE onset relative to study treatment is reasonable.
- The AE is more likely explained by the study treatment than by another cause.

Possibly related:

- The temporal sequence of AE onset relative to study treatment is reasonable.
- The AE could have been due to another equally likely cause.

Probably not related:

- There is another more likely cause of the AE.

Definitely not related:

- The temporal sequence of AE onset relative to study treatment is not reasonable.
- There is another obvious cause of the AE.

10.5.5 Severity Assessment

For events reported on the AE eCRF, a blinded Investigator will determine the severity classification based on his/her clinical experience and by using the following definitions of severity (note: a "severe" AE is not the same as a SAE):

- Mild: Symptoms are barely noticeable or do not make the subject uncomfortable. The AE does not influence performance or functioning. Prescription drugs are not ordinarily needed for relief of symptom(s).
- Moderate: Symptoms are of sufficient severity to make the subject uncomfortable. Performance of daily activities is influenced. Treatment of symptom(s) with prescription drugs or therapies may be needed.
- Severe: Symptoms are of sufficient severity to cause the subject severe discomfort. Performance of daily activities is compromised. Treatment for symptom(s) with prescription drugs or therapies may be needed.

The maximal severity for the AE will be recorded, even if the AE presented as being less severe at some point during the event.

10.5.6 Safety Reporting

It is the PI's responsibility to oversee the safety of the investigation at his/her site, including careful assessment and appropriate reporting of all safety events. The site should follow all applicable governance, including FDA regulations, FDA guidance, and IRB requirements for notification of all types of AEs. The PI or designee must report to ethica CRO any of the following events:

- SAEs (see section 10.5.2) - using the SAE Report Form
- Pregnancies - using the Unanticipated Problem Reporting Form
- New findings/updates in relation to already reported events

These events must be reported immediately but no later than within 24 hours of first becoming aware of them by completing, signing, and dating the applicable form, verifying the accuracy of the information recorded in the form with the source documents and the eCRF, and sending the applicable form to the CRO by e-mail.

10.5.6.1 All Adverse Events

All AEs, whether serious or not, will be recorded from the time of IP injection until the last study visit. A blinded Investigator will assess all AEs and record details of seriousness, severity, date of onset, date of resolution or stop date, and action taken with study treatment, and relationship to the IP.

If an AE occurs, the first concern will be the safety of the study subjects. All Treatment-Related AEs will be followed until the event has resolved or stabilized or until follow-up is no longer possible or the blinded Investigator deems it unnecessary.

If the Sponsor determines that an AE presents an unreasonable risk to subjects, the Sponsor will terminate participation in the study as soon as possible (i.e., within 5 working days after the Study Sponsor makes this determination and not later than 15 days after the Study Sponsor first receives notice of the event).

The Sponsor is responsible for ensuring that reporting of AEs to the relevant governing authorities is within the time frame applicable according to international and local law.

In the event that adjudication of a safety issue is required, an independent committee will be convened. The committee will be comprised of three medical doctors, one dermatologist, and two plastic surgeons.

10.5.6.2 Serious Adverse Events (SAEs)

All SAEs that occur after the time of IP injection through 7 days after subject completion of the study must be reported to ethica CRO within 24 hours of awareness. Initial report must be made by completing the paper SAE Report Form with all available information and providing it to ethica CRO by email. It is the site's responsibility to perform the following:

- Obtain and maintain all pertinent medical records, information, and medical judgments from colleagues who assisted in the treatment and follow-up of the subject.
- Provide ethica CRO with a complete, written case history, including copies of pseudonymized supporting reports (e.g., progress notes, laboratory reports) and a statement as to whether the event was or was not related to study treatment.
- With the assistance of the CRO, notify the governing IRB of the SAE in accordance with the requirements of SAE reporting stipulated by the governing IRB.

Serious Adverse Event Reporting: The PI will report SAEs by email using the paper SAE report form within 24 hours of awareness and complete the eCRF within 48 hours of awareness. **SAE reports should be scanned and emailed to the ethica CRO Clinical Project Manager.** ethica CRO will handle the SAE report according to the process described in the SMMP. Any missing or additional relevant follow-up information concerning the SAE should be sent to ethica CRO as soon as possible, together with the following information, at a minimum: initial report, AE, date of occurrence, subject identification, study ID, and site number; this will allow the follow-up information to be linked to the initial SAE report. Specific information may be requested by opening queries in the eCRF or via e-mail communication.

10.5.6.3 Adverse Events of Special Interest (AESI) Reporting

AESI are important medical events that may be consistent with botulinum toxin effects, such as:

- Swallowing or breathing difficulties
- Asthenia
- Generalized muscle weakness
- Diplopia
- Dysphagia
- Dysphonia
- Dysarthria

All AESIs need to be reported within 24 hours of awareness using the SAE/UADE/AESI report form and recorded in the eCRF within 48 hours of awareness. ethica CRO will handle the AESI report according to the process described in the SMMP.

The report must include date of IP injection, symptoms that were observed, time to onset and resolution, and any intervention(s) that were implemented. All AESIs will be evaluated carefully by the Sponsor and the study medical monitor. Follow-up actions will be decided on case-by-case basis and documented.

The study Sponsor will handle the AESI report according to the process described in the SMMP, including evaluation of the AESI, and reporting of the AESI to the FDA, all reviewing IRBs, and participating Investigators within 10 working days of awareness.

As the AESI are considered as reportable event to the FDA, the Sponsor will provide further information to the PI within 7 working days of receipt of the AESI report form to allow the PI to report the event to the reviewing IRB as applicable.

10.5.6.4 Unexpected Adverse Drug Reaction (UADR) Reporting

A UADR is a treatment-related adverse reaction where the nature or severity is not consistent with the applicable product information in the Investigator's Brochure. An AE will be considered as a UADR if it is a treatment-related event not associated with the following Expected Adverse Drug Reactions:

- Headache
- Facial paresis (eyelid ptosis, brow ptosis)
- Blepharospasm
- Injection site pain
- Injection site hematoma
- Injection site reaction
- Eyelid edema
- Nausea

Unanticipated Adverse Drug Events occurring during a treatment must be documented in the appropriate CRF AE page. If the event meets one of the seriousness criteria, it will be handled like any other SAE and the Sponsor must be informed of this Serious UADR and any follow-up information by scanning and emailing the completed SAE reporting form within 24 hours of becoming aware of the occurrence of the SAE to the ethica CRO Clinical Project Manager.

The Sponsor will conduct an evaluation of the UADR and report results of such evaluation to FDA and to all reviewing IRBs and participating Investigators within 10 working days after the Sponsor first receives notice of the event.

10.5.6.5 Other Reportable Information

Certain information, although not considered an SAE, must be recorded, reported, and followed up. This includes the following:

- Breach of confidentiality.
- Change to the protocol taken without prior IRB review to eliminate apparent immediate hazard to a research participant.
- Complaint of a participant when the complaint indicates unexpected risks, or the complaint cannot be resolved by the research team.
- Protocol violation (meaning an accidental or unintentional deviation from the IRB approved protocol) that in the opinion of the investigator placed one or more participants at increased risk or affects the rights or welfare of subjects.
- Pregnancy after receiving study treatment. If a pregnancy is confirmed, the subject will remain in the study and will be followed to term even if the study has completed.

10.5.7 Pregnancy

The PI must report pregnancy to the CRO within 24 hours of learning of it using the Unanticipated Problems Reporting Form and send it to the same e-mail address as for SAE reporting. Pregnancy complications such as spontaneous abortion/miscarriage, elective abortion due to a congenital abnormality, or a complication of pregnancy or a congenital abnormality diagnosed at any time during the pregnancy or postpartum are considered SAEs and must be reported as such. An elective abortion of a normal pregnancy without complications is not considered an SAE.

Every effort should be made to gather information regarding the pregnancy outcome and condition of the infant. It is the responsibility of the PI to obtain this information within 28 calendar days after the initial notification and approximately 28 calendar days postpartum. The need for safety follow-up until birth will not delay study database lock. If the study is completed and/or the study database is locked before the postpartum follow-up is expected, the PI will notify the CRO of the outcome of the pregnancy only via e-mail and the Unanticipated Problems Reporting Form will be processed accordingly.

In addition to the above, if the PI determines that the pregnancy meets seriousness criteria, it must be reported also as an SAE (in addition to reporting the pregnancy itself).

11 STUDY COMPLETION / SUBJECT COMPLETION / WITHDRAWAL

11.1 Study Completion

The Investigator will provide a summary of the study's outcome to the IRB within 3 months following the Investigator's completion, termination, or discontinuation of participation in the study and will forward a copy of this summary to the Sponsor.

At the completion of the study, the Investigator will return all remaining drugs not used in the study along with all clinical supplies to the Sponsor, unless otherwise directed by the Sponsor, in accordance with Good Clinical Practices.

11.2 Subject Completion

A subject will be considered to have completed the study if he/she has completed all assessments and applicable study visits or experienced an event that precludes further study participation.

11.3 Withdrawal

Approximately 150 subjects will be enrolled to ensure that a minimum of 135 evaluable subjects complete the study. If a subject withdraws from the study, he or she will not be replaced.

A subject **will be** withdrawn (i.e., dropouts) from the study for any of the following reasons:

- Lost to follow-up;
- Deemed ineligible (following screening) at Visit 1;
- Subject request/Withdrawal of Informed Consent: A subject may withdraw consent any time without negative implication to the subject. The withdrawal will be documented in source documents and the Case Report Form (CRF);
- Non-compliant in the judgment of the Investigator;
- Adverse event that requires intervention in region injected;
- Termination of study by the Sponsor;
- The PI believes that for safety reasons (e.g., AE, concurrent illness) it is in the best interests of the subject to be withdrawn from study participation;
- The subject's attending physician requests that the subject be withdrawn from the study;
- The PI or the Sponsor, for any reason, stops the study or stops the subject's participation in the study;

Protocol deviations will not lead to automatic withdrawal unless they indicate a significant risk to the subject's safety. All major protocol deviations must be discussed promptly with the Medical Monitor.

A subject **may be** withdrawn from the study, in consultation with the Medical Monitor, for any of the following reasons:

- Lack of compliance to study procedures;
- A major protocol deviation or violation;
- Poor visit attendance.

If a subject decides to withdraw from the study, or should the PI decide to withdraw the subject, the PI (or designate) will complete and report the observations up to the time of withdrawal.

Unless withdrawn during a study visit, subjects who are withdrawn from the study will be requested to come in to complete an Early Termination Visit as soon as reasonably possible so that a complete evaluation at the time of the subject's withdrawal should be made. Additionally, subjects who withdraw from the study will be requested to allow continued safety monitoring, either via telephone interviews or clinic visits, whichever is more appropriate.

The reason and date of withdrawal must be noted on the eCRF. If the reason for withdrawal is an AE or an abnormal laboratory test result, monitoring will continue until resolution or until an appropriate medical judgment concerning the cause or importance has been made. The specific event or test result(s) must be recorded on the eCRF.

11.4 Termination of Study

11.4.1 Termination by Sponsor

The Sponsor may terminate the study at any time for any of the following reasons:

- Failure to enroll subjects
- Inaccurate or incomplete data
- Unsafe or unethical practices
- Questionable safety of the study drug
- Administrative decision

The Investigator/Institution will be promptly informed by the Sponsor in writing of termination of the study and reason(s) for termination. The Investigator must inform the IRB promptly and provide a detailed written explanation of the termination and must also promptly notify all participating subjects of the termination of the study within 24 hours and assure that all appropriate therapy and follow-up for subjects is provided.

11.4.2 Termination by Investigator

If the Investigator terminates the study prematurely, the Investigator will:

- Provide the IRB and the Sponsor with a written statement describing why the study was terminated prematurely. Prompt compliance with this requirement is essential so that the Sponsor may comply with regulatory obligations.
- Notify all participating subjects of the termination within 24 hours and ensure that all appropriate therapy and follow-up for subjects is provided.
- Return all CRFs, and related study materials to the Sponsor.

12 STATISTICAL METHODS

12.1 Primary Endpoint

The primary effectiveness endpoint will be duration of effect, defined as the number of days from Treatment Day (Baseline) to the day that GLS severity (Investigator assessment) at maximum frown returns to the Baseline value. Although the trial is not powered for inferential analysis, this will be the most influential outcome in the overall assessment of the effectiveness of prabotulinumtoxinA 40 Units, compared to prabotulinumtoxinA 20 Units, in treating moderate to severe glabellar lines. Analysis will be performed using the modified Intent-To-Treat (mITT) population.

Duration of effect will be described by Kaplan-Meier curves and the respective median times with associated 2-sided 95% confidence interval (CI) for each treatment group. Statistical analyses of treatment group differences will be done using Cox proportional hazards regression with time to return to Baseline as the dependent variable, treatment group as the independent variable, and age, gender, and Baseline GLS score (Investigator assessment) at maximum frown as covariates.

Statistical significance will be established at the 0.025 level with one-sided hypothesis testing.

12.2 Secondary Endpoints

Secondary effectiveness endpoints will be used to provide additional evidence of prabotulinumtoxinA 40 Units superiority to prabotulinumtoxinA 20 Units. As duration of effect outcomes, secondary effectiveness endpoints will be assessed as described above for the primary endpoint. The mITT population will be used for summaries and comparisons. Secondary endpoints, in order of importance, will be:

1. Duration of effect, defined as the number of days from Treatment Day (Baseline) to the day that GLS severity (subject assessment) at maximum frown returns to the Baseline value.
2. Duration of effect in GAIS responders (score of 2 or 1) as assessed by Investigator.
3. Duration of effect in GAIS responders (score of 2 or 1) as assessed by subject.
4. Duration of effect in SSS responders (score of 2 or 1) as assessed by subjects.

12.3 Tertiary Endpoints

Tertiary effectiveness endpoints will be used to compare prabotulinumtoxinA 40 Units to onabotulinumtoxinA 20 Units, as well prabotulinumtoxinA 20 Units to onabotulinumtoxinA 20 Units. As duration of effect outcomes, tertiary effectiveness endpoints will be assessed as described above for the primary endpoint. The mITT population will be used for summaries and comparisons. Tertiary endpoints, in order of importance, will be:

1. Duration of effect, defined as the number of days from Treatment Day (Baseline) to the day that GLS severity (Investigator assessment) at maximum frown returns to the Baseline value.
2. Duration of effect, defined as the number of days from Treatment Day (Baseline) to the day that GLS severity (subject assessment) at maximum frown returns to the Baseline value.
3. Duration of effect in GAIS responders (score of 2 or 1) as assessed by Investigator.
4. Duration of effect in GAIS responders (score of 2 or 1) as assessed by subject.
5. Duration of effect in SSS responders (score of 2 or 1) as assessed by subjects.

12.4 Exploratory Effectiveness Endpoints

Exploratory effectiveness endpoints will be evaluated for signals of effectiveness to explore whether any should be elevated in importance for subsequent trials. These endpoints will be assessed using either logistic regression (for binary endpoints) or survival analysis-type methods as described above. Comparisons will be made between all treatment groups. Chi-square tests of association or Fisher's exact tests will be used to compare treatment group differences in proportion of subjects returning to Baseline at each time point in the study. Exploratory endpoints will be:

1. GLS score of 0 or 1 (maximum frown) as assessed by Investigator and subject at each visit.
2. GAIS response (score of 2 or 1) as assessed by Investigator and subject at each visit.
3. SSS response (score of 2 or 1) as assessed by subjects at each visit.
4. 1-point or greater, 2-point or greater, and 3-point or greater improvement on the GLS (maximum frown) as assessed by Investigator at each visit.
5. 1-point or greater, 2-point or greater, and 3-point or greater improvement on the GLS (maximum frown) as assessed by subject at each visit.
6. Duration of effect in responders with a 1-point or greater, 2-point or greater, and 3-point or greater improvement on the GLS (maximum frown) as assessed by Investigator at each visit.
7. Duration of effect in responders with a 1-point or greater, 2-point or greater, and 3-point or greater improvement on the GLS (maximum frown) as assessed subject at each visit.
8. Duration of effect in GLS responders (responder = ≥1-point improvement on GLS at Day 30) as assessed by Investigator.
9. Duration of effect in GLS responders (responder = ≥1-point improvement on GLS at Day 30) as assessed by subject.
10. Onset of effect as assessed by subjects through the 7-Day Subject Diary.

12.5 Safety Endpoints

Safety endpoints will include incidence of treatment-emergent and treatment-related AEs and changes from Baseline in ECG parameters, safety laboratory parameters, physical exams, and vital signs. The SAFT Population will be used for descriptive summaries of the safety endpoints.

12.5.1 Adverse Events (AEs)

AEs will be coded to system organ class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage (incidence) of subjects reporting an AE and the number of AEs will be summarized.

A treatment-emergent AE will be defined as AEs that started at or after the first injection.

The following AE incidence tables will be provided for treatment-emergent AEs:

- All AEs by SOC and PT
- Related AEs by SOC and PT
- All AEs by PT sorted by decreasing frequency among all subjects
- Related AEs by PT sorted by decreasing frequency among all subjects
- All SAEs by seriousness criterion
- Related SAEs by seriousness criterion

- All SAEs by SOC and PT
- Related SAEs by SOC and PT

Treatment-related AEs will be defined as possibly, probably, or definitely related. Two-sided Wilson 95% confidence intervals will be calculated for the overall incidence of AEs and SAEs.

12.5.2 Laboratory Variables

The number and percentage of subjects with a clinically significant laboratory abnormality (Investigator opinion) will be summarized for each laboratory test with available normal ranges.

Descriptive statistics will be used to summarize observed values and changes from Baseline. Shift tables and other tabular and graphical methods may be used to present results for laboratory tests of interest. Listings will be provided with flags indicating clinically significant abnormalities.

12.5.3 Vital Signs

The number and percentage of subjects with a clinically significant vital sign abnormality (Investigator opinion) will be summarized for each parameter; percentages will be based on subjects with non-missing values.

Descriptive statistics will be used to summarize observed values and changes from Baseline. Tabular and graphical methods may be used to present results for parameters of interest. Listings will be provided with flags indicating clinically significant abnormalities.

12.5.4 12-Lead Electrocardiograms

The number and percentage of subjects with a clinically significant ECG abnormality (Investigator opinion) will be summarized for each parameter; percentages will be based on subjects with non-missing values.

Descriptive statistics will be used to summarize results and changes from Baseline. Tabular and graphical methods may be used to present results for parameters of interest. Listings will be provided with flags indicating clinically significant abnormalities.

12.6 Analysis Populations

Three analysis populations are defined: Modified Intent-to-Treat (mITT) Population, Per Protocol (PP) Population, and Safety (SAFT) Population. All analysis populations will be defined and determined prior to database closure and unblinding for the final analysis.

12.6.1 Modified Intent-to-Treat Population

The mITT Population is defined as all subjects who were randomized, received their injection of IP, and have at least one post-dosing assessment for the primary effectiveness endpoint. The ITT principle will be followed in that subjects in the mITT population will be analyzed according to the treatment assigned as per the randomization schedule. The mITT Population will be the primary population used for effectiveness analyses of primary, secondary, tertiary, and exploratory effectiveness endpoints.

12.6.2 Per Protocol Population

The PP Population is defined as treated subjects who complete the entire study up to the final visit with no protocol deviations that could affect effectiveness assessments. The decision whether a protocol violation/deviation is relevant for the exclusion of subjects from the PP Population will be made in a data review meeting prior to breaking the study blind. The PP Population will be used for supportive effectiveness analyses.

12.6.3 Safety Population

The SAFT Population will be used for safety analysis and will consist of all randomized subjects who received treatment with the IP and will be analyzed as per treatment received. The SAFT population will be the primary population for safety analyses.

12.7 Sample Size Considerations

This study is not powered for inferential analyses. A total of 150 subjects will be randomized to the study, 50 subjects in each of the three treatment arms; 20U onabotulinumtoxinA, 20U prabotulinumtoxinA and 40U prabotulinumtoxinA.

Assuming 50 subjects per treatment group, exponential distributions for failure and censoring times, a median duration of effect of 4 months in the reference group, and an annual censoring rate of 10%, the study will have 80% power to detect a hazard ratio of 0.47 based on a one-sided hypothesis test of the primary effectiveness endpoint with alpha = 0.025. As such, it is the opinion of the study Sponsor that 50 subjects per group (total sample size n=150) will be sufficient to address the objectives of this study.

12.8 General Considerations

Data will be listed by subject number. Data will be summarized by treatment and study visit, where applicable. For categorical parameters, the number and percentage of subjects/observations in each category will be presented; percentages will be based on the number of subjects in the relevant analysis population in each treatment group. For continuous parameters, descriptive statistics will include n (number of subjects or observations), mean, standard deviation, median, and range. A full description of the statistical methods planned for this study will be provided in the Statistical Analysis Plan (SAP). All programs for data output and analyses will be written in SAS version 9.4 or higher (SAS Institute, Inc., Cary, NC).

Missing Values: For the mITT analysis of primary, secondary, tertiary, and exploratory duration of effectiveness endpoints, in the case of a missed visit, subjects will be considered to have returned to Baseline if they are confirmed to have returned to Baseline at the next non-missed visit. Subjects will be considered to have to have returned to Baseline if they fail to attend 2 consecutive visits or drop out of the study. For missing observations for exploratory endpoints other than duration of effect data will be analyzed as observed without imputation.

Discontinuation and Drop-Outs: Dropouts will not be replaced. Subject disposition will summarize the number of subjects who were randomized and who discontinued from the study (including reasons for discontinuation).

Interim Analysis: An interim analysis will be conducted when >90% of subjects have completed Visit 8 (Day 120) to evaluate response to exposure (efficacy, duration) and adverse events. For assessment of the primary effectiveness endpoint, 95% CIs will be presented but statistical analyses will not be conducted and a statistical penalty for the final analysis will not be employed. While data by treatment group will be presented, individual subjects will not be unblinded.

Poolability of Investigative Sites: Data from all investigative sites will be pooled based on the assumption of clinical comparability: the same protocol will be used for all sites, all sites will be monitored for protocol compliance, and the same data collection instrument and methodology will be used across all sites.

Impact of COVID-19: Any material disruption to the study due to COVID-19 will be addressed, as appropriate, in post-hoc sensitivity analyses.

13 ETHICAL ASPECTS

13.1 Informed Consent

This study will be conducted in compliance with 21 CFR Part 50. Written informed consent will be obtained from each subject before any study procedures or assessments are done and after the aims, methods, anticipated benefits, potential hazards, compensation and/or honoraria and insurance arrangements are explained. Subjects will also be explained that they are free to refuse entry into the study and free to withdraw from the study at any time without prejudice to future treatment. The study coordinator will present study specifics to potential participants and will lead the consenting process.

The subject's willingness to participate in the study will be documented in writing on the consent form, which will be signed and dated by the subject. The site will keep the original consent forms and copies will be given to the subjects.

See also Section 10.1.

13.2 Health Authorities and IRBs

Before starting this study, the protocol will be submitted to the FDA and IRB for evaluation. As required, the study will not start before approval is obtained from the IRB and the FDA.

In accordance with 21 CFR 56, the protocol (including amendments), any advertisement, and informed consent form will be reviewed and approved by a properly instituted Institutional Review Board (IRB) for each study center. The Sponsor will supply relevant material for the Investigator to submit to the IRB for review and approval. The IRB will comply with applicable requirements, defined in the U.S. Code of Regulations, Title 21, Part 56. The study will not begin at an investigational site until an IRB has approved the protocol and the Informed Consent form.

The Investigator will inform the IRB of any UADE. The Investigator will provide the IRB with progress reports at intervals specified by the IRB (but in no event less often than yearly), and a final report within 3 months following the completion, termination, or discontinuation of the Investigator's participation in the study.

13.3 Confidentiality Regarding Study Subjects

The PI must ensure that the privacy of the subjects, including their personal identity and all personal medical information, will be maintained at all times. In eCRFs and other documents submitted to the Sponsor, subjects will not be identified by their names, but by an identification code (e.g., subject or screen number).

The site monitor, properly authorized persons on behalf of the Sponsor, or competent authorities may scrutinize personal medical information for the purpose of verifying data recorded on the eCRF. Personal medical information will always be treated as confidential, according to local privacy regulations.

14 STUDY MANAGEMENT & ADMINISTRATION

14.1 Protocol Amendments

No amendments to the protocol will be implemented without the prior written consent of the Sponsor. Should an amendment be necessary, the reviewing IRB and FDA may require review and approval prior to its implementation.

14.2 Monitoring and Quality Assurance

14.2.1 Information to Study Personnel

The PI, with the assistance of the CRO, is responsible for ensuring that all study personnel are qualified for their designated roles and for providing information about the study to all staff members involved in the study or in any element of subject management, both before starting the practical performance of the study and during the course of the study (e.g., when new staff become involved).

The CRO site monitor is responsible for initiating the site, conducting interim monitoring visits, ensuring site compliance with the protocol, and closing out the site at the end of the study. Additional information available during the study should be given as agreed upon, either by the PI or the site monitor, and always when new staff members become involved in the study.

14.2.2 Study Monitoring

The CRO clinical monitors will conduct on-site and/or remote interim monitoring visits at each study site in order to ensure compliance to the protocol, applicable regulations, and ICH-GCP, and to ensure safety of the subjects and maintenance of adequate and accurate clinical records. A dedicated close-out visit will also be conducted at each site.

Monitoring functions will be performed in compliance with GCP and the study specific Monitoring Plan. The PI agrees to allow the site monitors, and other authorized Sponsor personnel, access to the clinical supplies, the investigational agent dispensing and storage area, subject medical records, laboratory data, and other source documentation of the study subjects.

Source Document worksheets for all subjects and eCRFs will be reviewed in detail by the site monitor to ensure data integrity. If errors or omissions are found in the course of a data audit, or if clarification of data is required, the eCRFs and/or worksheets in question will be corrected by the study coordinator and confirmed/signed for by the PI, as appropriate. Data clarification or query forms may be generated for omissions or clarifications, to be completed and returned to the site monitor.

The dates of monitoring visits will be recorded by the site monitor in a sign-in log to be kept at the site. The Sponsor expects that, during monitoring visits, the study coordinator and PI will be available, the source documentation will be available, and a suitable environment for on-site visits will be provided for review of study-related documents.

The PI and assisting staff must agree to cooperate with the site monitor to resolve any problems, errors, or possible misunderstandings concerning any data discrepancies detected in the course of these monitoring visits.

As part of the supervision of the study progress other Sponsor personnel may accompany the site monitor on visits to the study site.

14.2.3 Audit and Inspection

According to ICH Guidelines on GCP, the Sponsor (or its designate) may audit the investigational site to compare raw data, source data, and associated records with the interim (if applicable) or final report of the study to assure that data have been accurately reported.

The PI must accept that regulatory authorities may conduct an inspection to verify compliance of the study with GCP. The PI should notify the Sponsor and the CRO no later than 24 hours upon notification of being audited by the FDA or IRB.

14.3 Protocol Deviations

A protocol deviation is any noncompliance with the clinical study protocol or GCP. The noncompliance may be either on the part of the subject, the PI, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly. It is the responsibility of the site to use continuous vigilance to identify and promptly report deviations to the CRO.

All deviations from the protocol must be addressed in study subject source documents. A completed copy of the Protocol Deviation Form must be maintained in the regulatory file, as well as in the subject's source document. Protocol deviations must be sent to the IRB per its guidelines.

The protocol must be rigorously adhered to; however, exceptions will be made in emergency situations when the protection, safety, and well-being of the subject requires immediate intervention based on the judgment of an Investigator.

Protocol deviations are termed as Major or Minor, as defined below:

- **Minor Protocol Deviation:** any difference or departure in the conduct of a study from the criteria and/or procedures prescribed in the IRB approved protocol which does not affect the subject's rights, safety, welfare, and/or the integrity of the study and resultant data. deviations may result from action or inaction of the subject, investigator, or staff.
    1. Deviation has no substantive effect on the risks to research subjects;
    2. Deviation has no substantive effect on the value of the data collected (i.e., the deviation does not confound the scientific analysis of the results);
    3. Deviation did not result from willful or knowing misconduct on the part of the investigator(s) and;
    4. The deviation did not result in or require any substantive action to be taken or result in any change to the subject's condition or status (i.e., did not affect the subject's participation in any way, did not result in a change to the subject's emotional or clinical condition, did not cause an adverse experience or require a change to the clinical care of the subject, etc.)
- **Major Protocol Deviation:** Any difference or departure from the criteria and/or procedures prescribed in the IRB approved protocol that affects the subject's rights, safety, welfare, increases the risk/benefit ratio, or compromises the integrity of the study's data.
    1. Deviation resulted in or required a substantive action to be taken or resulted in a change to the subject's condition or status;
    2. Deviation has harmed or posed a significant risk of substantive harm to research subjects;
    3. Deviation has damaged the scientific integrity of the data collected for the study;

4. Deviation is evidence of willful or knowing misconduct on the part of the investigator(s);
5. Deviation involves serious or continuing noncompliance with federal, state, or local research regulations;
6. There have been repeated minor protocol deviations from the same investigator/research staff;
7. There has been a failure to follow action ordered to correct minor protocol deviations.

14.4 COVID-19 and Potential Study Interruption

Guidance for managing COVID-19 study interruption is provided in Appendix A.

15 DATA HANDLING AND RECORD KEEPING

15.1 Source Data

The site is required to maintain adequate and accurate medical records designed to record all observations and other data pertinent to the study for each study subject. Source documentation is generally considered to be the document on which the information or data point was first recorded. Source documentation may include a subject's medical records, hospital charts, clinic charts, and the site's study files as well as the results of diagnostic tests such as X-rays, laboratory tests, and electrocardiograms.

Source Document Worksheets will be prepared by the CRO for this purpose and serve as part of the source record for a subject's study-related data. The Source Document Worksheets will allow for the collection of the following information and allow for verification of subject identity throughout the study:

a. Subject's name;
b. Subject's contact information;
c. The date that the subject entered the study and the subject number assigned;
d. The study title and/or the protocol number of the study and the Sponsor's name;
e. A statement of the ICF process and the date that informed consent, HIPAA, and California Experimental Research Subject's Bill of Rights (if applicable) were signed;
f. Records of previous aesthetic treatments and/or therapies;
g. Dates of all subject visits;
h. Effectiveness evaluations;
i. Safety evaluations;
j. All prescription and non-prescription concurrent medications, therapies, and treatments (up to 14 days prior to enrollment through the final study visit) and any changes to the list of medications;
k. Occurrence and status of any AEs;
l. The date the subject exited the study, and a notation as to whether the subject completed the study or reason for discontinuation;
m. The results of urine pregnancy testing, if performed.

Pertinent records related to the study (e.g., the subject's medical chart) will be made available to the Sponsor representative on request with due precaution to protect the privacy of the subject. If applicable (i.e., SAE reporting), personal identifying information (except subject initials) will be redacted on any photocopies of relevant medical records and replaced with the unique subject number before submission to the Sponsor. The PI will protect the confidentiality of all subjects' records within applicable federal, state, and local laws.

A subject identification code list will be maintained in order to allow unambiguous identification of each subject included in the study. This list should contain the subject's full name, date of birth, dates of participation and identification number as per local regulations.

The PI must agree to supply all details to Sponsor auditor(s) and/or regulatory authorities, ensuring the data is held confidentially at the site after completion of the study. A note will be made in the

hospital or clinical medical records, if appropriate, that the subject is participating in a clinical study.

The eCRF and subjects' medical records will be reviewed by the CRO, representatives from the study Sponsor, the IRB, and/or the FDA to the extent permitted by regulations.

15.2 Case Report Form

In this study the case report form will be an eCRF. The study coordinator must complete the eCRF for each subject within a timely manner of the visit occurring.

The site monitor will review the completed eCRF for accuracy, completeness, and consistency with source documentation (i.e., medical records, source document worksheets, etc.). The site monitor will submit requests for correction/clarification of data (e.g., queries) as well as the data manager to the study coordinator when inconsistencies are identified during monitoring and source data verification or during the data review and edit check process.

All corrections and alterations of eCRF data must be made by the study coordinator in a timely manner and according to the instructions provided. Completed eCRFs for each visit (i.e., those reviewed by the CRO and with no remaining queries) should then be reviewed and electronically signed by the PI. In order to review and electronically sign the eCRF, the PI will have his/her own login that will allow them to view only the data that they have generated.

A full audit trail detailing corrections and alterations made to the eCRF will be maintained.

Upon study completion, a softcopy of the eCRF for each subject will be provided to the site.

15.3 Archiving of Study Documentation

An Investigator or Sponsor may withdraw from the responsibility to maintain records for the period required and transfer custody of the records to any other person who will accept responsibility for them under 812.140 and including the requirements of 812.145. Notice of a transfer shall be given to FDA no later than 10 working days after transfer occurs.

Custody of the records may be transferred to another responsible party, acceptable to the Sponsor, who agrees to abide by the retention policies. Written notice of transfer must be submitted to the Sponsor. The Investigator must contact the Sponsor prior to disposing of any study records.

An Investigator or Sponsor shall maintain the records required by the U.S. Code of Federal Regulations, Title 21, Part 812.140 during the investigation and for a period of 2 years after the latter of the following two dates: The date on which the investigation is terminated or completed, or the date that the records are no longer required for purposes of supporting a premarket approval application or a notice of completion of a product development protocol.

Completed eCRFs will be transferred to the Sponsor. The Investigator will retain copies of each eCRF. All source documents, records, and reports will be retained by the study site in accordance with 21 CFR 812.140 (d).

All primary data or copies thereof (e.g., laboratory records, CRFs, data sheets, correspondence, photographs, and computer records), which are a result of the original study observations, and are necessary for the reconstruction and evaluation of any study report, will be retained at the study site.

16 FINANCING AND INSURANCE

A separate financial agreement (Clinical Trial Agreement) will be made between Evolus, Inc. and the PI at each site.

The study is covered under a Evolus, Inc. liability insurance policy. The certificate of insurance will be provided upon request.

17 REPORTING AND PUBLICATION OF RESULTS

Neither the complete nor any part of the results of the study carried out under this protocol, nor any of the information provided by the sponsor for the purposes of performing the study, will be published or passed on to any third party without the consent of the Study Sponsor. Any Investigator involved with this study is obligated to provide the Sponsor with complete test results and all data derived from the study.

The Investigator agrees to the unrestricted use of results of the study for the purposes of national and international registration, publication, and information for medical and pharmaceutical professionals by the Sponsor. If required, the authorities will be notified of the Investigator's name, address, qualifications, and extent of involvement.

This study will be posted on www.clinicaltrials.gov. Authorship and manuscript composition will reflect joint cooperation between Investigators and Sponsor personnel. As this study involves multiple centers, no individual publication will be allowed prior to completion of the final report of the multicenter study except as agreed with the Sponsor.

18 REFERENCES

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3. Rzany B-J, et. al. A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Single-Dose, Phase III, Non-Inferiority Study Comparing PrabotulinumtoxinA and OnabotulinumtoxinA for the Treatment of Moderate to Severe Glabellar Lines in Adult Patients. Aesth Surg J 2019, 1–16 DOI: 10.1093/asj/sjz110
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19 APPENDICES

APPENDIX A: ADJUSTMENT OF VISITS AND ASSESSMENTS DUE TO COVID-19

1. General Guidance

Subject safety and preserving the integrity of the data are of the highest priority. Any federal, state, and local rules, guidances, or laws shall be followed.

Study visits and procedures should be followed per-protocol whenever possible. Any specific changes in study conduct that deviate from the protocol should be communicated to the sponsor via reporting to the site's Clinical Research Associate (CRA), Clinical Project Manager (CPM), and IRB, as applicable. All protocol deviations which occur as a result of COVID-19 disruptions (including remote visits), will be differentiated from other deviations, and must be documented on the appropriate reporting forms/source document, and clearly annotated "protocol deviations due to COVID-19 illness/restrictions/etc.". If the subject is unable or unwilling to come to the site due to COVID-19, the PI needs to ask for the reasons and document them in the source documents.

The PI is responsible for ensuring subjects' safety and for monitoring all active subjects per protocol. PI must ensure that study subjects are kept informed of changes to the study and monitoring plans that could impact them.

Should a subject develop any symptoms that could be related to COVID-19 or any other acute infection disease, the subject will be instructed to:

- Contact the PI as soon as possible
- Contact their general physician to be examined and determine the course of action according to the standard of care.

The PI or designee will follow-up with the subject as needed but at least within 72 hours of awareness to obtain an update on the subject's health and to obtain information on whether COVID-19 has been diagnosed or not. If the subject has been diagnosed with COVID-19, the event will be reported as an AE.

2. Adjustment of Study Visits

Telemedicine is understood as a possible solution due to COVID-19 disruption and it is not mandatory; if the situation allows it, study visits should be done in person.

On-site Study Visit: If the local situation allows for conduct of on-site study visits, the PI and study personnel must take all necessary steps/precautionary measures at the site to minimize or eliminate immediate hazards of viral transmission within and/or outside the clinical site premises.

Before any research activities occur on-site, both subjects and research staff should be screened for symptoms or risk of COVID-19 infection. Subjects should be pre-screened by phone before their on-site study visit.

If the local situation only allows for completion of some study procedures, the PI will prioritize the research activities that absolutely require an in-person visit in order to maintain the viability and integrity of the research (e.g., Treatment Visit). The PI may consider conducting the other assessments (e.g., medical history review, directed questionnaire) using telemedicine to minimize

subject time on site and risk of exposure at the site. However, all efforts should be made to conduct all assessments at the scheduled visits, if possible.

Remote Study Visit: If the local situation does not allow for an on-site study visit to be conducted or if a subject does not wish to come to the study site due to COVID-19 disruption, a remote study visit may be conducted via video conferencing in lieu of an on-site visit. Phone call may also be used to perform some assessments if a subject has no video conferencing capabilities.

The PI or study personnel who will conduct remote visits must be trained on how to conduct real-time video conferencing visits. Also, procedures should be put in place to maintain the subject's privacy, as would be done for a clinical visit:

- **Before the scheduled date of the visit:**
  - The site personnel should determine if the subject can accommodate for video conferencing (e.g., internet access, PC, smartphone, video conference apps, etc.).
  - The PI or site personnel conducting the remote visit should obtain the subject's verbal consent before proceeding with the visit and document it in the source document. The PI or personnel should also explain to the subject how the visit will be conducted.
  - A test call may also be completed with the subject prior to the appointment.
- **On the day of the scheduled visit:**
  - Both the investigator/site delegate and the subject should confirm their respective identities with one another before engaging in a real-time video conference visit. For example, the site personnel will state their name and role and the subject may be identified by using two subject identifiers (e.g., name and date of birth) and a photo ID.
  - The date and time of the real-time video interaction, the location of the subject, and the location of the PI or site personnel conducting the remote visit should be documented in the source document.
  - Remote collection of data by PI or delegate will be conducted as described in Section 3 below.

3. Adjustment of Study Assessments

Informed consent: The following process will be followed for consenting a prospective subject remotely:

- Each subject will be provided with a copy of the IRB-approved consent form to aid in the consent discussion before the consent process begins. The consent form may be provided to a prospective subject by mail or e-mail.
- The PI and/or site delegate will participate in the consent process via video conference. All parties must introduce themselves and their role in the consenting process.
- The consent form provided to the subject will be reviewed in detail and the subject will be invited to ask any questions and to have them addressed by the study team.
- If the subject is interested in joining the research study, the subject will be asked to sign the consent document. The personnel conducting the consent process must verify that the

subject physically signed the consent document by viewing via video conference and then obtain a photo or scanned copy of the signed consent form before proceeding with study assessments.

- In order to obtain the required signatures from the PI and person conducting the consent process on the same day, the site will either sign a separate copy of the informed consent form or ask the subject to send a copy of the signed ICF by e-mail.
- The site should ensure to obtain all signature pages from the subject and to document the consent process in the source document. The site should also file in the source document all signed components as one combined document and provide a copy to the subject.

Inclusion/Exclusion Criteria: The list of inclusion/exclusion criteria may be reviewed via video conference or phone call with the subject to confirm that they are eligible for the study.

For potential subjects in a high-risk population for COVID-19 (e.g., 60 years old and older, with comorbidities such as diabetes, cardiovascular disease, respiratory system issues, etc.), deferring participation should be considered to minimize risks of exposure.

UPT (if applicable): UPTs cannot be conducted remotely.

Demographics: Demographic information may be collected via video conference or phone call from the subject at a remote screening visit.

Medical History and Concomitant Medications: Medical history and concomitant medications may be reviewed via video conference or phone call at each remote visit.

Randomization: Randomization is performed before treatment. Therefore, subjects will be required to present themselves at the clinic for randomization.

IP Treatment Session: IP cannot be administered remotely. Therefore, subjects will be required to present themselves at the clinic for the IP treatment session.

Vital Signs, Physical Exam, Safety Laboratories, ECG: Subjects will be required to present themselves at the clinic for assessment of vital signs, physical examinations, clinical labs, and ECGs.

Brow Area Photography: Subjects will be required to present themselves at the clinic for photography sessions of the brow area.

Directed Review of Systems: Subjects will be required to present themselves at the clinic for the directed review of systems.

Adverse Events: AEs may be reviewed remotely via video conference or phone call with the subject at each remote study visit. Any AE/SAE (including suspected / confirmed COVID-19 cases) elicited by a subject during a remote visit / phone call must be immediately captured, and all attempts should be done to capture the necessary clinical and medical information. Reporting of AEs and SAEs to the Sponsor and IRB should follow the protocol procedure and IRB requirements.

Investigator Assessments (GLS, GAIS): The primary effectiveness endpoint will be based on the GLS as assessed by the Investigator. As such, the Investigator assessment of the GLS cannot be conducted remotely and subjects will be asked to travel to the clinic in order for the Investigator to perform a live GLS assessment. If this is impossible, GLS may be conducted remotely via video

conference; however, such data collected will not be part of the primary effectiveness endpoint analysis and will be used as supportive data only. The GAIS may be conducted remotely via video conference or phone call with the subject.

Subject Assessments (GLS, GAIS, Subject Satisfaction, Clinical Interview, Directed Questionnaire): All subject assessments may be conducted remotely via video conference or phone call with the subject at each remote visit. Subjects will be interviewed by the study coordinator who will record responses into the source document worksheets. In order to perform the GAIS, the subject's Baseline photo will also be provided by email.

APPENDIX B: DECLARATION OF HELSINKI

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI
Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington 2002 (Note of Clarification on paragraph 29 added)
55th WMA General Assembly, Tokyo 2004 (Note of Clarification on Paragraph 30 added)
59th WMA General Assembly, Seoul, October 2008

A. INTRODUCTION

1. The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. Medical research involving human subjects includes research on identifiable human material or identifiable data.

2. It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.

3. The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."

4. Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

5. In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society.

6. The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic and therapeutic procedures and the understanding of the aetiology and pathogenesis of disease. Even the best proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility, and quality.

7. In current medical practice and in medical research, most prophylactic, diagnostic and therapeutic procedures involve risks and burdens.

8. Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need special protection. The particular needs of the economically and medically disadvantaged must be recognized. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be subject to giving consent under duress, for those who will not benefit personally from the research and for those for whom the research is combined with care.

9. Research Investigators should be aware of the ethical, legal and regulatory requirements for research on human subjects in their own countries as well as applicable international requirements. No national ethical, legal or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this Declaration.

B. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

10. It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject.

11. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and on adequate laboratory and, where appropriate, animal experimentation.

12. Appropriate caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

13. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator, the sponsor or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any serious adverse events. The researcher should also submit to the committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects.

14. The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration.

15. Medical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given consent.

16. Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the subject or to others. This does not preclude the participation of healthy volunteers in medical research. The design of all studies should be publicly available.

17. Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians should cease any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results.

18. Medical research involving human subjects should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject. This is especially important when the human subjects are healthy volunteers.

19. Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.

20. The subjects must be volunteers and informed participants in the research project.

21. The right of research subjects to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the subject, the confidentiality of the patient's information and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

22. In any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail.

The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subject's freely-given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.

23. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress. In that case the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship.

24. For a research subject who is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the investigator must obtain informed consent from the legally authorized representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons.

25. When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorized representative.

26. Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population. The specific reasons for involving research subjects with a condition that renders them unable to give informed consent should be stated in the experimental protocol for consideration and approval of the review committee. The protocol should state that consent to remain in the research should be obtained as soon as possible from the individual or a legally authorized surrogate.

27. Both authors and publishers have ethical obligations. In publication of the results of research, the investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Sources of funding, institutional affiliations and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

28. The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic or therapeutic value. When medical research is combined with medical care, additional standards apply to protect the patients who are research subjects.

29. The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.

30. At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study.

31. The physician should fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study must never interfere with the patient-physician relationship.

32. In the treatment of a patient, where proven prophylactic, diagnostic and therapeutic methods do not

exist or have been ineffective, the physician, with informed consent from the patient, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the physician's judgment it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed.

APPENDIX C: GLABELLAR LINE SCALE (GLS) AT MAXIMUM FROWN

APPENDIX D: GLOBAL AESTHETIC IMPROVEMENT SCALE (GAIS)

GAIS Grade	Score	Description
Much Improved	**2**	Marked improvement in appearance
Improved	**1**	Improved in appearance, but would like more
No Change	**0**	The appearance is essentially the same as the original condition
Worse	**-1**	The appearance is worse than the original condition
Much Worse	**-2**	The appearance is much worse that the original condition

APPENDIX E: SUBJECT SATISFACTION SCALE (SSS)

SSS Grade	Score	Description
Very Satisfied	**2**	I am very satisfied with the treatment
Satisfied	**1**	I am satisfied with the treatment
Indifferent	**0**	I am indifferent with the treatment
Unsatisfied	**-1**	I am unsatisfied with the treatment
Very Unsatisfied	**-2**	I am very unsatisfied with the treatment