CLINICAL STUDY PROTOCOL

A Randomized, Double-Blind, Placebo-Controlled, Ascending Dose Cohort Study to Evaluate Safety and Efficacy of a Single Treatment Cycle of EB-001 in Subjects with Glabellar Frown Lines

Study Number: EB001-GL201

[redacted]

IND Sponsor: Bonti, Inc.

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Amendment:	1
Revised Final Date:	18 November 2016
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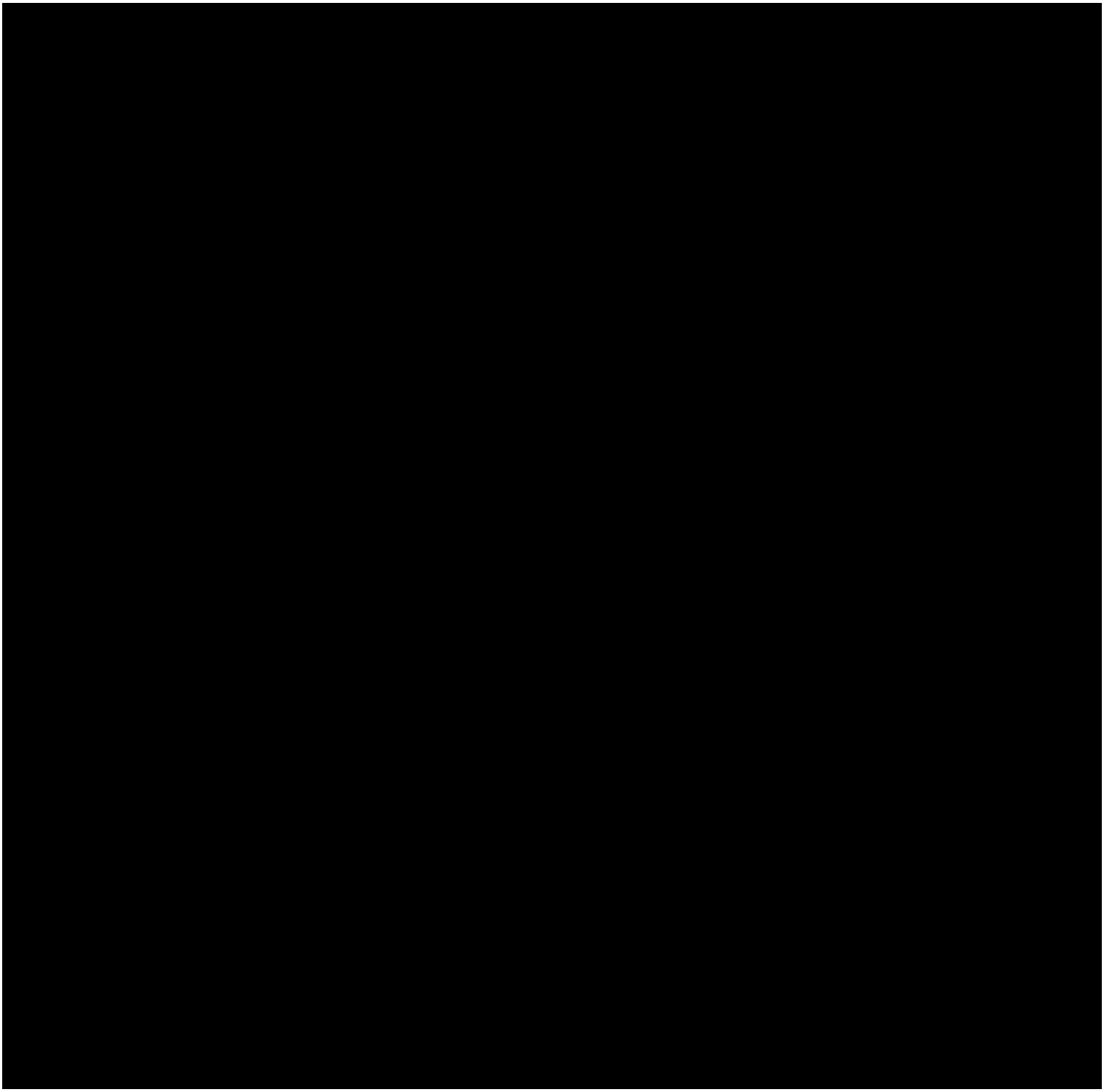
CONFIDENTIALITY STATEMENT

SIGNATURE PAGE

Prepared by:



STATEMENT OF COMPLIANCE

By signing below, I confirm that I have read this protocol and agree

- to assume responsibility for the proper conduct of the study at this site,
- to conduct the study according to the procedures described in this protocol and any future amendments,
- not to implement any deviation from, or changes to, the protocol without agreement of the sponsor and written approval from the Institutional Review Board or Independent Ethics Committee, except where necessary to eliminate an immediate hazard to subject(s), and
- that I am aware of and will comply with all applicable regulations and guidelines

_____	_____	_____
Investigator Printed Name	Signature	Date

_____	_____	_____
Investigator Printed Name	Signature	Date

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LIST OF ABBREVIATIONS AND GLOSSARY OF TERMS

Term	Definition
AE	adverse event
ALT (SGPT)	alanine aminotransferase (= serum glutamic pyruvic transaminase)
AST (SGOT)	aspartate aminotransferase (= serum glutamic oxaloacetic transaminase)
BoNT	botulinum neurotoxin
BoNT/A	botulinum neurotoxin serotype A
BoNT/E	botulinum neurotoxin serotype E
BP	blood pressure
BUN	blood urea nitrogen
CBL	change from baseline
CFR	Code of Federal Regulations
CMP	clinical monitoring plan
CRF	Case Report Form
CRO	Contract Research Organization
CTCAE	Common Terminology Criteria for Adverse Events
DAS	digital abduction score
DRT	Data Review Team
EB-001	botulinum neurotoxin serotype E drug product
ECG	electrocardiogram
eCRF	electronic case report form
ED50	effective dose to product 50% DAS effect
EDC	electronic data capture
EOS	end of study
ET	early termination
F-U	follow up
FDA	Food and Drug Administration
FIH	first-in-human
FWS	facial wrinkle scale
GCP	Good Clinical Practice
GGT	γ glutamyl transferase
GL	glabellar frown Lines
GLP	Good Laboratory Practices

Term	Definition
GMP	Good Manufacturing Practices
HBsAg	hepatitis B surface antigen
HC	heavy chain
HDL	high density lipoprotein
HED	human equivalent dose
HEENT	head, eye, ear, nose, throat
HIV	human immunodeficiency virus
HR	heart rate
HSA	human serum albumin
ICF	informed consent form
ICH	International Conference on Harmonization
ICH E6	International Conference on Harmonization Guidance for Industry, Good Clinical Practice: Consolidated Guidance
IEC	independent ethics committee
IM	intramuscular
IRB	institutional review board
IVRS	interactive voice response system
IWRS	interactive web response system
LC	light chain
LDH	lactate dehydrogenase
LDL	low density lipoprotein
M	molar
MCH	mean cell hemoglobin
MCHC	mean cell hemoglobin concentration
MCV	mean (red) cell volume
MedDRA	Medical Dictionary for Regulatory Activities
mL	milliliter
mouse LD_{50}	lethal dose to 50% of mice after intraperitoneal injection
MRSD	maximum recommended starting dose
msec	milliseconds
NA	not applicable
ng	nano gram
NOAEL	no observable adverse effects limit

Term	Definition
OHRP	Office for Human Research Protections
PAD	pharmacologically active dose
PCV	packed cell volume
PI	Principal Investigator
PR interval	time between the onset of atrial depolarization and the onset of ventricular depolarization
PRN	as-needed
RBC	red blood cell
RDW	red (cell) distribution width
RR interval	time elapsed between two consecutive R-waves
QRS duration	the interval from the beginning of the Q wave to the termination of the S wave, representing the time for ventricular depolarization
QT interval	interval representing the time for both ventricular depolarization and repolarization to occur
QTc	corrected QT (interval)
QT_cB interval	QTc interval using Bazett's correction (msec) = $QT/(RR)^{½}$, where the QT interval is measured in msec and the RR interval is measured in seconds
QT_cF interval	QTc interval using Fridericia's correction (msec) = $QT/(RR)^{⅓}$, where the QT interval is measured in msec and the RR interval is measured in seconds
SAE	serious adverse event/experience
SAP	statistical analysis plan
SNAP	synaptosomal-associated protein
SOT	spread of toxin
SUSAR	suspected unexpected serious adverse reactions
RR interval	time elapsing between two consecutive R waves in the electrocardiogram. It is used to assess the ventricular rate.
TCA	trichloroacetic Acid
TEAE	treatment emergent adverse event
UP	unanticipated problem
US	United States
WBC	white blood cell (Leukocyte)

PROTOCOL SUMMARY

Study Number:
EB001-GL201

Study Title:
A Randomized, Double-Blind, Placebo-Controlled, Ascending Dose Cohort Study to Evaluate Safety and Efficacy of a Single Treatment Cycle of EB-001 in Subjects with Glabellar Frown Lines

Investigational Drug Product:
EB-001 (Botulinum Neurotoxin Serotype E, BoNT/E) for injection.

Study Objectives:
To evaluate the safety and efficacy of EB-001 compared to placebo in subjects with glabellar frown lines (GL).

Phase of Trial:
Phase 2a

Clinical Hypothesis:
Safety: A single treatment cycle of EB-001 Intramuscular (IM) injections into the glabellar muscles (procerus and bilateral corrugator muscles) has an acceptable safety, immunogenicity, and tolerability profile at the tested dose range. Immunogenicity testing will be performed once methods have been developed.

Efficacy: A single treatment cycle of EB-001 IM injections, at one or more of the tested doses, is more effective than placebo in the treatment of GL assessed using the Facial Wrinkle Scale (FWS).

Study Population:
Males and Females 18-60 years old, with moderate to severe GL at maximum frown using the FWS.

Outcome Measures:
Safety Measures:

- Incidence and severity of treatment emergent adverse events (TEAEs) and serious adverse events (SAEs)
- Focused neurologic examination for potential spread of toxin (SOT)
- Incidence of abnormal findings in laboratory tests, electrocardiogram (ECG), physical exam, and vital signs (pulse rate, respiratory rate, and blood pressure)
- Pregnancy test for women of childbearing potential

Efficacy Measures:
Primary Efficacy Measures:

- Investigator's assessment of GL severity at maximum frown using the FWS. The FWS is a four-point scale that indicates severity of GL as follows: 0 = none, 1 = mild, 2 = moderate, or 3 = severe.

[redacted]

Study Design:
This will be the first-in-human (FIH), randomized, double-blind, placebo-controlled, ascending dose cohort study of EB-001.

A total of 7 ascending dose cohorts are planned for GL injections or up to 9 cohorts if 2 additional cohorts are evaluated. Each dose cohort will enroll a total of 6 subjects randomized to receive either EB-001 or placebo in a ratio of 5 (active): 1 (placebo).

Duration:
Expected duration is approximately 6 weeks for each subject from the day of study treatment to the follow-up visit, and approximately 10 weeks from signing ICF to the follow-up exit.

Inclusion Criteria:
In order to be eligible to participate in this study, an individual must meet ALL of the following criteria:

1. Signed and dated IRB-approved informed consent form (ICF).
2. Men or women between the ages of 18 and 60, inclusive.
3. Subjects in good health as determined by medical history, physical and focused neurological examinations, clinical laboratory studies, electrocardiograms (ECGs), vital signs, and Investigator's judgement.
4. Presence of bilaterally symmetrical GL of moderate to severe rating at maximum frown, as measured using FWS by both the Investigator and subject prior to study treatment.
5. Subjects with sufficient visual acuity without the use of eyeglasses (contact lens use acceptable) to accurately assess their facial wrinkles as determined by Investigator's judgement.
6. Women of child bearing potential must not be pregnant, lactating, or planning to become pregnant during the study.
7. Women of non-childbearing potential must be either postmenopausal (at least 12 consecutive months of amenorrhea) or surgically sterile (e.g., tubal ligation, hysterectomy, etc.).

8. Women of childbearing potential agreeing to use dual methods of contraception from the day of dosing until 3 months afterwards. Female subjects using oral contraception must have initiated treatment at least 2 months prior to the day of dosing.
9. Male subjects with partner(s) of childbearing potential agreeing to use dual methods of contraception from the day of dosing until 3 months afterwards, and to no sperm donation from day of dosing until 3 months afterwards.
10. Willing and able to complete protocol requirements and instructions, which include completion of all required visits.

Exclusion Criteria:

An individual who meets ANY of the following criteria will be excluded from participation in this study:

1. Any condition that precludes a subject's ability to comply with study requirements, including completion of the study visits or inability to read, understand, and/or self-assess GL severity using FWS.
2. Any uncontrolled systemic disease or other medical condition.
3. Any medical condition that may put the subject at increased risk with exposure to botulinum toxin of any serotype, including diagnosed myasthenia gravis, Eaton-Lambert syndrome, amyotrophic lateral sclerosis, or any other condition that might interfere with neuromuscular function.
4. Current or previous botulinum toxin treatment of any serotype.
5. Anticipated need for treatment with botulinum toxin of any serotype for any reason during the study (other than study treatment).
6. Known immunization or hypersensitivity to any botulinum toxin serotype.
7. Known allergy or sensitivity to any of the components of the study treatments, or any materials used in the study procedures.
8. Any of the following procedures or treatments occurring within the specified period prior to screening:
    - 3 months: Non-ablative resurfacing laser or light treatment, microdermabrasion, or superficial peels.
    - 6 months: Any facial cosmetic procedure with medium depth to deep facial chemical peels (e.g., trichloroacetic acid [TCA] and phenol), or mid facial or periorbital laser skin resurfacing.
    - 6 months: On topical retinoid therapy and/or topical hormone cream applied to the face, who have not been on a consistent dose regimen and are unable to maintain the same regimen for the study.
    - 12 months: Mid-facial or periorbital treatment with non-permanent soft tissue fillers.
    - 12 months: On oral retinoid therapy.
9. Prior periorbital surgery, facial lift (full face or mid face), brow lift, or related procedures (e.g., eyelid [blepharoplasty] and/or eyebrow surgery).
10. Prior mid face or periorbital treatment with permanent soft tissue fillers, synthetic implantation (e.g., Gore-Tex®), and/or autologous fat transplantation.

11. Marked facial asymmetry, dermatochalasis, deep dermal scarring, and/or excessively thick sebaceous skin.
12. The inability to substantially lessen facial rhytides (fixed lines) even by physically spreading them apart, as determined by the Investigator.
13. Permanent make-up that would interfere with the assessment of facial wrinkles.
14. Subjects who, in the Investigator's opinion, are unable or unwilling to maintain their standardized skin care regimen throughout the study period.
15. Any eyebrow or eyelid ptosis at baseline as determined by the Investigator.
16. Infection or skin disorder at the injection sites.
17. History of facial nerve palsy.
18. Recent history (within 6 months of screening) of alcohol or drug abuse based on the Investigator's judgement.
19. Anticipated need for surgery or overnight hospitalization during the study.
20. Current enrollment in an investigational drug or device study or participation in such a study within 30 days or 5 half-lives of the drug, whichever is longer, of entry into this study.

Study Drug:

[redacted]

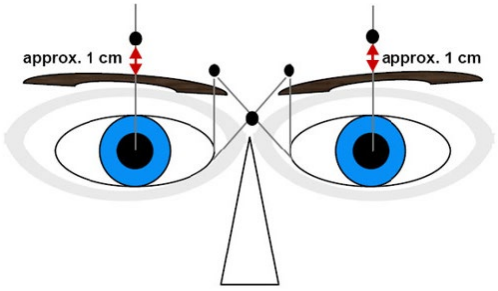
Placebo:

Sterile solution for injection with [redacted]

Dosage:

The total dose will be the specified amount of EB-001, or placebo, divided into 5 injections; 1 injection into procerus at midline and a single injection into each of the medial and lateral corrugators bilaterally (Figure S-1). Each subject will always receive 5 injections and the volume injected per site will be 0.1 mL. The spacing of injections into the lateral corrugators should be at or about 1 centimeter above the supraorbital ridge, which is known to minimize potential ptosis.

Figure S–1 Injection Sites



Starting Dose and Dose Escalation:

Dose escalation scheme is shown in Table S-1 below. Additional doses (cohorts) may be explored as defined below in Flexibility in Dose Adjustment.

[redacted]

[redacted]

[redacted]

[redacted]

Flexibility in Dose Adjustment:
If an intolerable dose is identified, a lower dose may be evaluated. This lower dose may be a repeat of the prior lower dose cohort or an intermediary dose between the intolerable dose and prior lower dose cohort.

Any dose cohort below the intolerable dose cohort may be repeated, if requested by the DRT, to better evaluate any finding at that dose level.

All dose escalation/adjustments or additional cohorts will be determined by the DRT up to a total of 9 dose cohorts for up to a total of 54 subjects.

Screening:
Written ICF, demographics, inclusion/exclusion criteria, medical history, physical and focused neurological examinations, height/weight, prior and concomitant medications, triplicate ECG, clinical laboratory tests (serum chemistry, lipids, hematology, urinalysis), immunogenicity sample collection, screens for human immunodeficiency virus (HIV) and hepatitis B and C, screens for alcohol and drugs of abuse, and serum pregnancy test.

Safety Assessments:
Adverse events, physical and focused neurologic examinations, prior and concomitant medications, triplicate ECG, vital signs, clinical laboratory tests, medical history, and serum/urine pregnancy test.

Efficacy Assessments
Investigator's and subject's assessment of the FWS with Photonumeric Guide at maximum frown and at rest.

Other Assessments
Standardized Facial Photography.

General Statistical Considerations:
The planned sample size will be approximately 42 subjects (35 for EB-001 and 7 for placebo) if all 7 cohorts are evaluated, or up to 54 subjects if additional 2 cohorts are evaluated. All

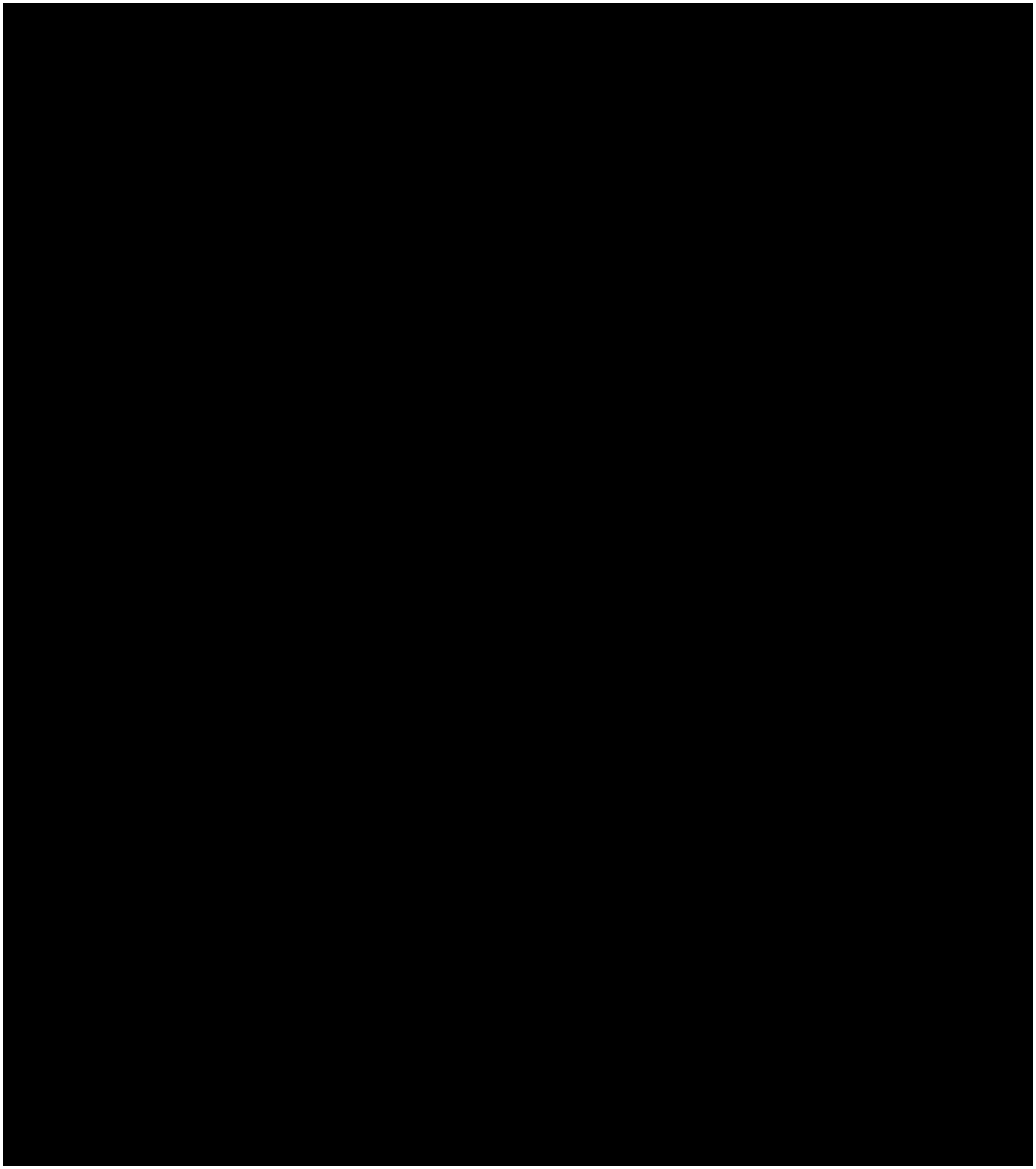
statistical analysis will be descriptive summary statistics. The placebo subjects will be pooled. The probabilities of observing at least 1 event detecting adverse events with given true event rate are shown in Table S-2:

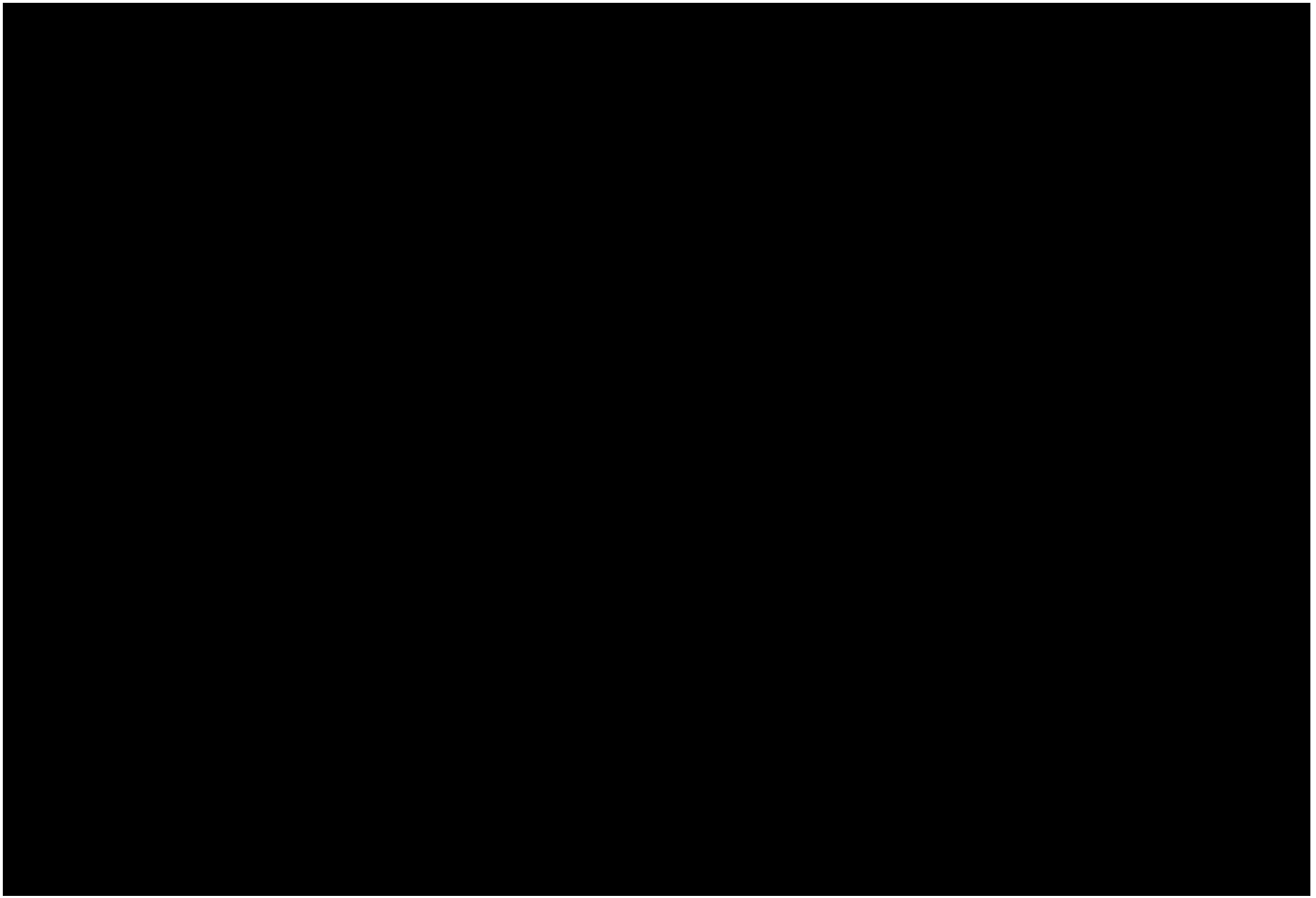
Table S–2 Probability of Detecting Adverse Events that Occur at Various Frequencies

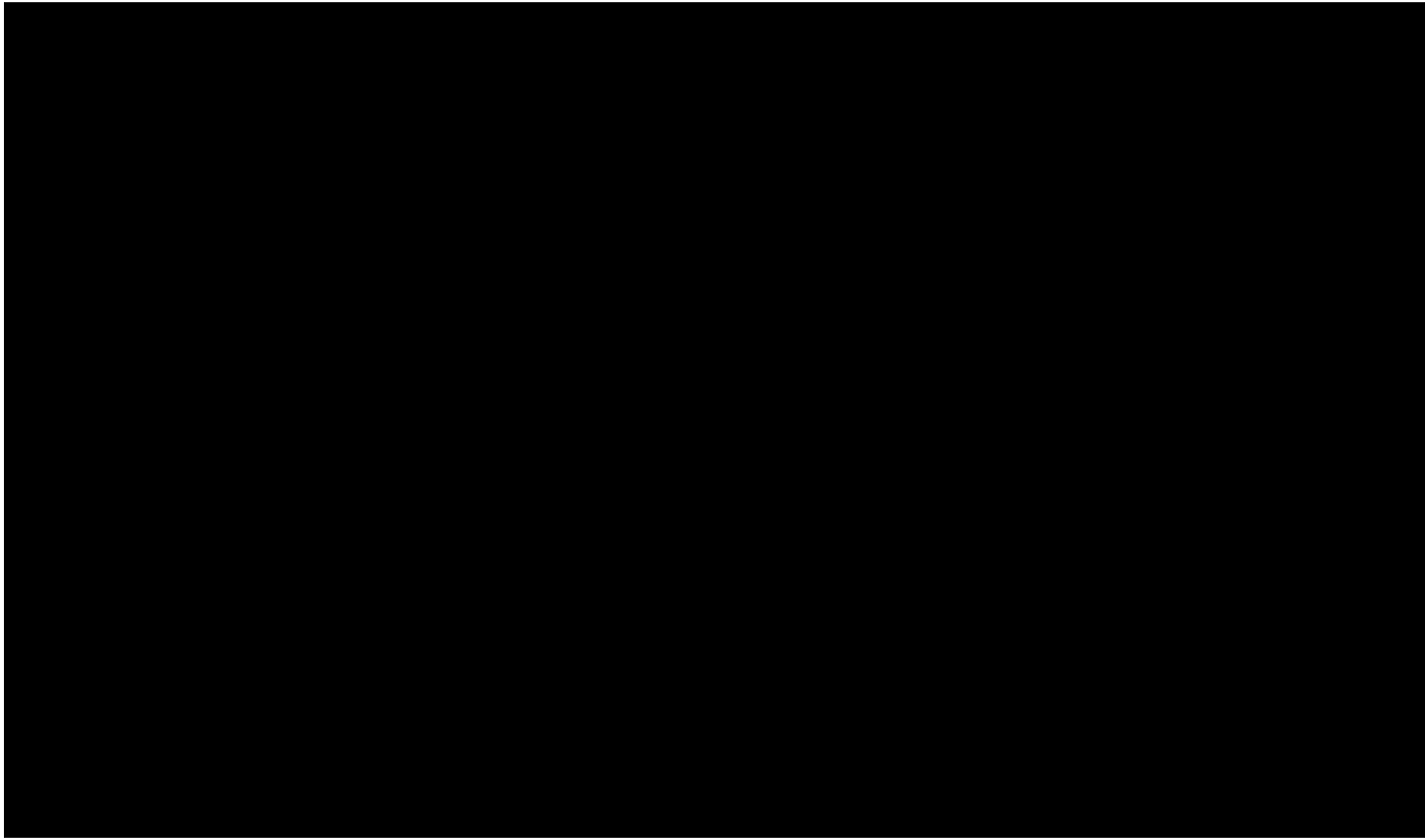
True Event Rate	Probability of Observing at Least 1 Event with 5 Completed Subjects	Probability of Observing at Least 1 Event with 35 Subjects
0.01	4.9%	29.7%
0.1	41.0%	97.5%
0.2	67.2%	>99%
0.5	96.9%	>99%

Demographic and baseline characteristics will be summarized. Safety will be assessed by summarizing the incidence of all adverse events, TEAEs, and serious adverse events. Other safety parameters (clinical laboratory parameters, vital signs, and ECG measures), including mean absolute change from baseline, will be summarized by treatment group. Efficacy will be assessed by summarizing the change from baseline of Investigator's and subject's assessment of GL severity at maximum frown and at rest using the FWS.

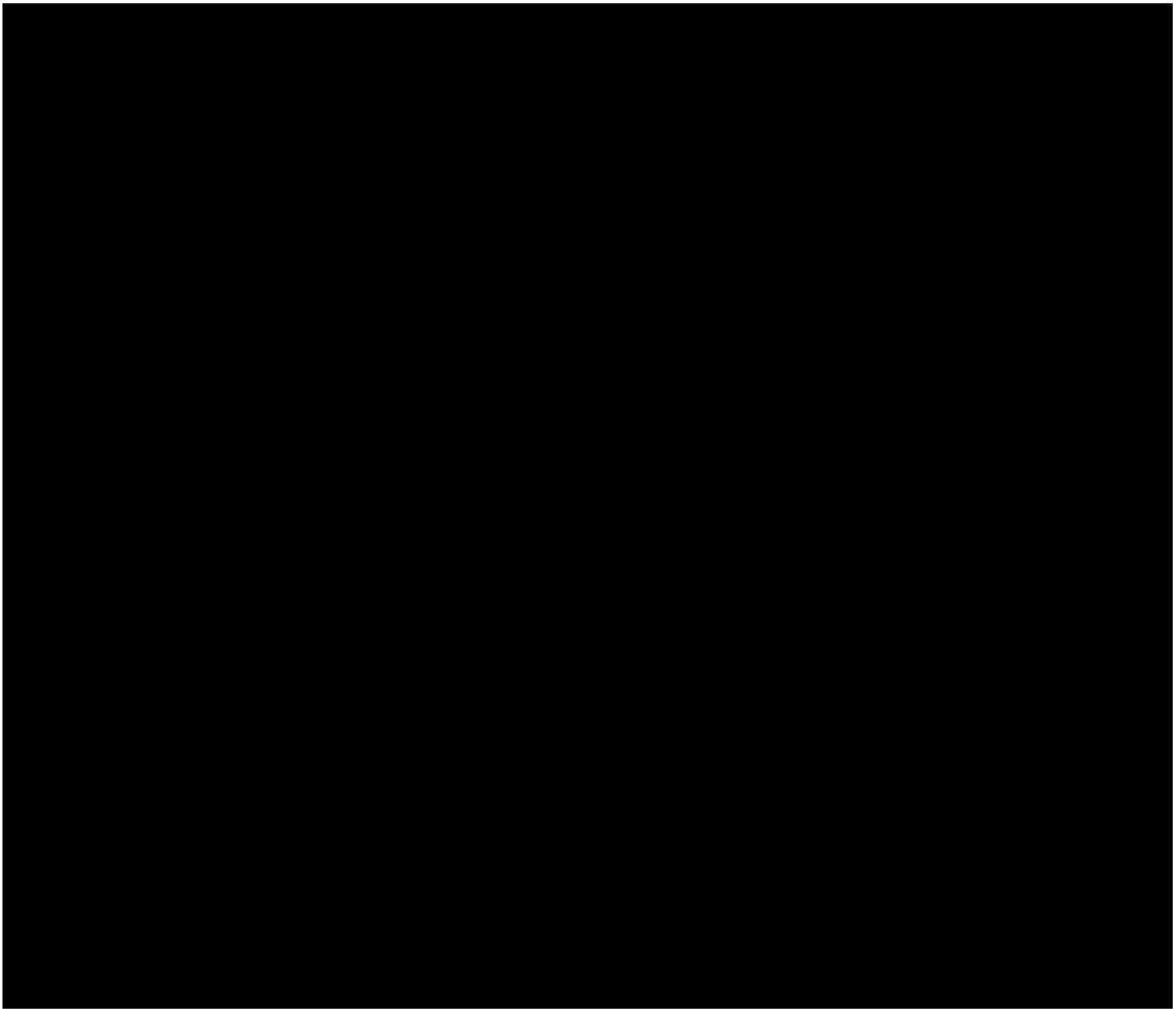
[redacted]







1 KEY ROLES



2 INTRODUCTION

2.1 Background Information

[redacted]

BoNT serotype E (BoNT/E, EB-001) has been previously studied in human subjects with

[redacted]

2.1.4 Nonclinical Evaluation of EB-001

EB-001 has been evaluated in a series of pharmacology and non-clinical toxicology studies

[redacted]

[redacted]

potency of EB-001 drug product is 22 Units per ng and the recommended dosage for the

[redacted]

2.2 Rationale

2.2.1 Study Rationale

This will be the FIH study of EB-001 to measure safety and efficacy in GL. Single doses of EB-001 administered through IM injection into procerus at midline and the medial and lateral corrugators will be assessed in healthy subjects with glabellar frown lines.

A total of 7 ascending dose cohorts are planned, or up to 9 cohorts if 2 additional cohorts are evaluated. Each dose cohort will enroll a total of 6 subjects randomized to receive either EB-001 or placebo in a ratio of 5 (active): 1 (placebo).

[redacted]

Table 1 Likely symptoms from spread of botulinum toxin

Body and Limbs Category	
• Decreased muscle tone • Loss of muscle function • Loss of muscle tone • Weakened reflexes • Lack of reflexes • Muscular weakness	• Muscle weakness of all four limbs • Partial loss of voluntary movement • Partial paralysis of one limb • Partial paralysis of one side of the body • Partial paralysis of the lower limbs • Pelvis muscle weakness
Brain Category	
• Inability to send signals from your brain to your body • Interruption between brain and nerves in muscle	
Eyes Category	
• Abnormal pupil reflex • Blurred vision • Double vision • Drooping of upper eyelid • Eyelid function irregularity • Inability to focus or maintain a clear image	• Partial loss of eye movement • Partial loss of eye muscle movement (eyelid) • Partial loss of eye muscle movement (vertical glaze)
Face Category	
• Loss of facial movement • Loss of feeling in face	• Loss of movement in face • Partial loss of feeling in face
Heart and Lungs Category	
• Difficulty breathing • Inflammation of the lungs • Shortness of breath	• Slowed breathing • Slow heart rate

Mouth Category	
• Difficulty speaking • Difficulty swallowing • Difficulty with motor skills (slurred speech, difficulty chewing and swallowing) • Dry mouth • Inability to move vocal cords	• Partial loss of facial motor functions (biting and chewing) • Partial loss of tongue movement • Speech impediment • Stuttering • Weakness of vocal cords
Stomach and Intestine Category	
• Bowel blockage • Constipation	• Unable to urinate completely

Another risk is the possibility of an allergic reactions to drugs and to product ingredients. If a subject has a very bad allergic reaction, death could occur. Likely signs or symptoms of allergic reactions (anaphylaxis) that could be life-threatening are:

- Rash.
- Difficulty in breathing or inability to breathe without assistance.
- Wheezing.
- Sudden drop in blood pressure (dizziness).
- Swelling around the mouth, throat, or eyes.
- Fast pulse.
- Sweating.
- Feeling of dread.

The events of serious allergic reactions have been rare in the case of botulinum neurotoxin serotype A (for example, Botox® Cosmetic Label).

Localized pain, infection, inflammation, tenderness, swelling, erythema, and/or bleeding/bruising may be associated with the injection.

2.3.2 Known Potential Benefits

Potential benefits to subjects in this study may include aesthetic improvement in appearance by reduction of GL at maximum frown and at rest.

3 OBJECTIVES AND PURPOSE

This will be the FIH study of EB-001 to evaluate safety and efficacy in GL.

The safety objective is whether a single treatment cycle of EB-001 IM injections into the glabellar muscles (procerus and bilateral corrugator muscles) has an acceptable safety, and tolerability profile at the tested dose range.

The efficacy objection is whether a single treatment cycle of EB-001 IM injections, at one or more of the tested doses, is more effective than placebo in the treatment of GL assessed using the FWS.

4 STUDY DESIGN AND ENDPOINTS

4.1 Description of the Study Design

This will be the FIH, multicenter, ascending dose cohort, randomized, double-blind, placebo-controlled, single treatment cycle study of EB-001 IM injections in subjects with moderate to severe GL at maximum frown using Facial Wrinkle Scale (FWS). Expected duration is approximately 6 weeks for each subject from the day of study treatment to the follow-up visit, and approximately 10 weeks from signing informed consent form (ICF) to the follow-up exit.

[redacted]

Placebo:

Sterile solution for injection [redacted]

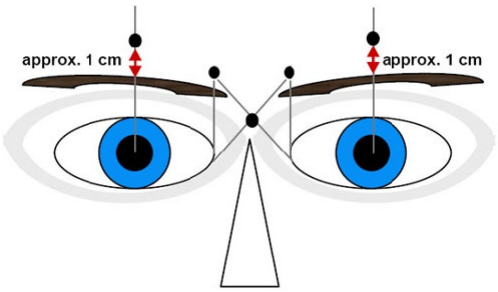
Dosage:

Subjects in each cohort will be randomized to receive either EB-001 or placebo, and each cohort will receive a different dose level of EB-001, which will generally be at a higher dose than the previous cohort, although dose modifications may be made depending on the safety and tolerability.

The total dose will be the specified amount of EB-001, or placebo, divided into 5 injections; 1 injection into procerus at midline and a single injection into each of the medial and lateral corrugators bilaterally (Figure 1). Each subject will always receive 5 injections and the volume injected per site will be 0.1 mL. The spacing of injections into the lateral corrugators should be at or about 1 centimeter above the supraorbital ridge, which is known to minimize potential ptosis.

There is no diet or water restriction throughout the study.

Figure 1 Injection Sites



[redacted]

[redacted]

4.1.1 Stopping Criteria

When there are 2 or more subjects experiencing intolerable treatment emergent adverse

[redacted]

Table 3 Toxicity Criteria

TEAE	Definition[1]
Serious adverse event	See Section 8.1.2
Related to spread of toxin[2]	CTCAE ≥Grade 2
Related to Laboratory and ECG parameters[3]	CTCAE ≥Grade 2
All others (other than the SOT or laboratory and ECG parameters)	CTCAE >Grade 2
Unspecified	If considered appropriate by the Medical Monitor and Investigator

[1] Unless considered to be unrelated to study medication
[2] FDA Draft Guidance, Upper Facial Lines: Developing Botulinum Toxin Drug Products (FDA 2014).
[3] To be confirmed by a repeat test

Flexibility in Dose Adjustment:

If an intolerable dose is identified (based on one of the above 3 criteria), a lower dose may be evaluated. This lower dose may be a repeat of the prior lower dose cohort or an intermediary dose between the intolerable dose and prior lower dose cohort.

Any dose cohort below the intolerable dose cohort may be repeated, if requested by the DRT, to better evaluate any finding at that dose level.

All dose escalation/adjustments or additional cohorts will be determined by the DRT up to a total of 9 dose cohorts for up to a total of 54 subjects.

4.1.2 Follow-up of Subjects Meeting Stopping Criteria

Subjects with any of the criteria in Table 3 will be monitored carefully, which may include the following (to be agreed upon by the Investigator and the Medical Monitor):

- Additional clinical laboratory tests and/or other investigations.
- Additional outpatient visits.
- Extended duration of follow-up.
- Obtaining a specialist's opinion.

4.2 Study Endpoints

4.2.1 Safety Endpoints

- Incidence and severity of TEAEs and serious adverse events (SAEs).
- Focused neurologic examination for potential SOT (See Appendix 1 for examination sheet).
- Incidence of abnormal findings in laboratory tests, electrocardiogram (ECG), physical examination, and vital signs (pulse rate, respiratory rate, and blood pressure).
- Serum/urine pregnancy test for women of childbearing potential.

4.2.2 Primary Efficacy Endpoint

- The primary endpoint is the Investigator's assessment of GL severity at maximum frown using the FWS.

The FWS is a four-point scale that indicates severity of GL as follows: 0 = none, 1 = mild, 2 = moderate, or 3 = severe (see Appendix 2 for sample FWS assessment sheet).

4.2.3 Secondary Efficacy Endpoints

- Investigator's assessment of GL severity at rest using the FWS.
- Subject's assessment of GL severity at maximum frown using the FWS.
- Subject's assessment of GL severity at rest using the FWS.

5 STUDY ENROLLMENT AND WITHDRAWAL

Prior to shipment of study drug and before subjects may be enrolled in the study, the Sponsor or designee requires a copy of the following critical documents:

- Institutional Review Board (IRB) / Independent Ethics Committee (IEC) approval of the protocol and the subject Information Sheet / Informed Consent Form (ICF);
- Signed and dated protocol signature page;
- Completed Food and Drug Administration (FDA) Form 1572 (central laboratories and any local laboratories for the study must be listed on the form);
- Up-to-date curricula vitae and medical licenses (if applicable) of the Principal Investigator (PI) and all Sub-Investigators listed on the FDA Form 1572;
- Signed financial disclosure forms for the Principal Investigator (PI) and all Sub-Investigators listed on the FDA Form 1572;
- Name, address, and membership of the IRB/IEC;
- Laboratory normal ranges and documentation of laboratory certification (or equivalent);
- Signed clinical study agreement;

All subjects must personally sign and date an IRB-approved ICF before any study procedures, including screening procedures, are performed. Subjects will be considered enrolled into the study only when they have received study drug.

5.1 Participant Inclusion Criteria

In order to be eligible to participate in this study, an individual must meet ALL of the following criteria:

1. Signed and dated IRB-approved informed consent form (ICF).
2. Men or women between the ages of 18 and 60, inclusive.
3. Subjects in good health as determined by medical history, physical and focused neurological examinations, clinical laboratory studies, electrocardiograms (ECGs), vital signs, and Investigator's judgement.
4. Presence of bilaterally symmetrical GL of moderate to severe rating at maximum frown, as measured using FWS by both the Investigator and subject prior to study treatment.
5. Subjects with sufficient visual acuity without the use of eyeglasses (contact lens use acceptable) to accurately assess their facial wrinkles as determined by the Investigator's judgement.
6. Women of child bearing potential must not be pregnant, lactating, or planning to become pregnant during the study.
7. Women of non-childbearing potential must be either postmenopausal (at least 12 consecutive months of amenorrhea) or surgically sterile (e.g., tubal ligation, hysterectomy, etc.).

8. Women of childbearing potential agreeing to use dual methods of contraception from the day of dosing until 3 months afterwards. Female subjects using oral contraception must have initiated treatment at least 2 months prior to the day of dosing.
9. Male subjects with partner(s) of childbearing potential agreeing to use dual methods of contraception from the day of dosing until 3 months afterwards, and to no sperm donation from day of dosing until 3 months afterwards.
10. Willing and able to complete protocol requirements and instructions, which includes completion of all required visits.

5.2 Participant Exclusion Criteria

An individual who meets ANY of the following criteria will be excluded from participation in this study:

1. Any condition that precludes a subject's ability to comply with study requirements, including completion of the study visits or inability to read, understand, and/or self-assess GL severity using FWS.
2. Any uncontrolled systemic disease or other medical condition.
3. Any medical condition that may put the subject at increased risk with exposure to botulinum toxin of any serotype, including diagnosed myasthenia gravis, Eaton-Lambert syndrome, amyotrophic lateral sclerosis, or any other condition that might interfere with neuromuscular function.
4. Current or previous botulinum toxin treatment of any serotype.
5. Anticipated need for treatment with botulinum toxin of any serotype for any reason during the study (other than study treatment).
6. Known immunization or hypersensitivity to any botulinum toxin serotype.
7. Known allergy or sensitivity to any of the components of the study treatments, or any materials used in the study procedures.
8. Any of the following procedures or treatments occurring within the specified period prior to screening:
    - 3 months: Non-ablative resurfacing laser or light treatment, microdermabrasion, or superficial peels.
    - 6 months: Any facial cosmetic procedure with medium depth to deep facial chemical peels (e.g., trichloroacetic acid [TCA] and phenol), or mid facial or periorbital laser skin resurfacing.
    - 6 months: On topical retinoid therapy and/or topical hormone cream applied to the face, who have not been on a consistent dose regimen and are unable to maintain the same regimen for the study.
    - 12 months: Mid-facial or periorbital treatment with non-permanent soft tissue fillers.
    - 12 months: On oral retinoid therapy.
9. Prior periorbital surgery, facial lift (full face or mid face), brow lift, or related procedures (e.g., eyelid [blepharoplasty] and/or eyebrow surgery).

10. Prior mid face or periorbital treatment with permanent soft tissue fillers, synthetic implantation (e.g., Gore-Tex®), and/or autologous fat transplantation.
11. Marked facial asymmetry, dermatochalasis, deep dermal scarring, and/or excessively thick sebaceous skin.
12. The inability to substantially lessen facial rhytides (fixed lines) even by physically spreading them apart, as determined by the Investigator.
13. Permanent make-up that would interfere with the assessment of facial wrinkles.
14. Subjects who, in the Investigator's opinion, are unable or unwilling to maintain their standardized skin care regimen throughout the study period.
15. Any eyebrow or eyelid ptosis at baseline as determined by the Investigator.
16. Infection or skin disorder at the injection sites.
17. History of facial nerve palsy.
18. Recent history (within 6 months of screening) of alcohol or drug abuse based on the Investigator's judgement.
19. Anticipated need for surgery or overnight hospitalization during the study.
20. Current enrollment in an investigational drug or device study or participation in such a study within 30 days or 5 half-lives of the drug, whichever is longer, of entry into this study.

5.3 Strategies for Recruitment and Retention

Sufficient subjects will be screened to allow for approximately 42 eligible subjects to be randomized at 2 US-based investigational sites.

Subjects will be mainly recruited via referrals. If radio, local print advertising, or any recruitment material is considered, prior Sponsor and IRB approval will be obtained. Potential subjects will be contacted via telephone for a preliminary screen of some of the inclusion and exclusion criteria. Only subjects who are able to provide voluntary informed consent will be admitted. Preliminarily eligible subjects will be invited to the clinic for complete screening, as set forth in the Schedule of Study Procedures.

5.4 Participant Withdrawal or Termination

5.4.1 Reasons for Withdrawal or Termination

Participants are free to withdraw from participation in the study at any time upon request for any reason without prejudice to his or her future medical care by the physician or at the institution. A subject may be terminated from the study for any of the following reasons:

- Withdrawal of informed consent.
- Entry into the study in violation of the protocol.
- Any AE, laboratory abnormality, or other medical condition or situation occurs such that the study doctor or study staff believes continued participation in the study would not be in the best interest of the participant.

- The participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation.
- Noncompliance with the protocol.
- At the discretion of the Investigator or Sponsor for any reason.

5.4.2 Handling of Participant Withdrawals or Termination

If a subject discontinues from the study prematurely, all efforts will be made to conduct early termination (ET) evaluations as thoroughly as possible up to the date of withdrawal at the time of discontinuation.

Subjects who discontinue from the study may be replaced unless it is due to one of the toxicity criteria in Table 3, in which situation subjects will not be replaced.

5.5 Premature Termination or Suspension of Study

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to Bonti. If the study is prematurely terminated or suspended, the PI will promptly inform the IRB and will provide the reason(s) for the termination or suspension.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants.
- Demonstration of efficacy that would warrant stopping.
- Insufficient compliance to protocol requirements.
- Data that are not sufficiently complete and/or evaluable.
- Determination of futility.

Study may resume once concerns about safety, protocol compliance, and/or data quality are addressed and satisfy the Sponsor, IRB and/or FDA.

6 STUDY AGENT

[redacted]

6.1.5 Dosing and Administration

See Section 4.1.

6.1.6 Route of Administration

Intramuscular

6.1.7 Starting Dose and Dose Escalation Schedule

See Section 4.1.

6.1.8 Dose Adjustments/Modification/Delays

If an intolerable dose is identified, a lower dose may be evaluated. This lower dose may be a repeat of the prior lower dose cohort or an intermediary dose between the intolerable dose and prior lower dose cohort.

Any dose cohort below the intolerable dose cohort may be repeated, if requested by the DRT, to better evaluate any finding at that dose level.

All dose escalation/adjustments or additional cohorts will be determined by the DRT up to a total of 9 dose cohorts for up to a total of 54 subjects.

6.1.9 Duration of Treatment

Expected duration is approximately 6 weeks for each subject from the day of study treatment to the follow-up visit, and approximately 10 weeks from signing ICF to the follow-up exit.

The entire study duration is expected to take approximately seven months from the first visit of the first subject (screening) to the last visit of the last subject.

6.1.10 Tracking of Study Kit and Dose

The Investigator will keep a record of the dates study drug kits received, the dose dispensed to each study subject from each kit. After dose is administered to the subject, the dispenser will collect and place the remaining vials back to the kit, and reseal it until CRA conducts final drug accountability which will be verified and reconciled on the Study Drug Kit Log and Study Drug Preparation Sheet. By the end of the study, the CRA upon conducting final drug accountability will instruct the dispenser or designee to ship any remaining study vials to the distribution center to be destroyed.

6.1.11 Replacement Procedures for Investigational Medicinal Product

Instructions for resupply shipments or replacement of study drug are referenced in the study manual(s).

6.2 Investigational Product Accountability Procedures

It is the responsibility of the Investigator to supervise accurate monitoring of the receipt, storage, dose preparation, and accounting of all study drug according to accepted medical and pharmaceutical practice. Copies of all invoices of study drug shipments must be retained. Accurate, original site records of study drug inventory and dispensing must be maintained using the forms provided study manual(s).

All study drug documentation must be maintained by the unblinded pharmacist or designated unblinded personnel. All disposition records must be made available for inspection by Sponsor or CRO upon request.

A Study Drug Kit Log will be provided for the accounting of study drug. Study Drug Kit Log forms will be provided for the accounting of study drug for each study subject and for maintaining the overall balance of vials. A reason(s) must be given for any amounts that are not accounted for.

Each site must keep all remaining study drug in the original vials until they are returned to the distribution center.

7 STUDY PROCEDURES AND SCHEDULE

7.1 Study Procedures/Evaluations

The principal Investigator and Sponsor must agree upon the format and content of the ICF before it is submitted to the IRB for approval. Written informed consent must be obtained from each subject prior to any study-related activities being conducted. The Investigator must retain all original signed and personally dated ICFs (together with any subsequent IRB-approved amended versions) in the subject's file. A copy of the original signed and dated ICF (and any amendments) must be given to the subject.

Subjects will be informed of findings (including AEs) from earlier cohorts if it is considered these could potentially affect the subject's willingness to participate or continue in the study. Depending on the nature, severity, and seriousness of these AEs, the ICF may be amended.

7.1.1 Study Specific Procedures

- Informed Consent
- Demographics
- Assessment of inclusion/exclusion criteria
- Medical history
- Assessment of adverse event
- Height and weight
- Complete physical and focused neurological examinations
- Mini Physical and focused neurological examinations
- Prior and concomitant medications
- 12-lead ECG
- Body temperature, respiration rate, blood pressure, and pulse rate
- Serum chemistry, Lipids, Hematology
- Urinalysis
- Immunogenicity sample collection
- Screens for HIV and hepatitis B and C
- Screens for alcohol / drugs of abuse
- Serum/urine pregnancy test
- Study drug administration
- Standardized Facial Photography
- Facial Wrinkle Scale – Subject Assessment
- Facial Wrinkle Scale – Investigator Assessment

7.1.1.1 Informed Consent

At the Screening Visit, prior to any procedures are performed, the site staff will obtain the signed ICF from each participant.

7.1.1.2 Demographics

At the Screening Visit, the site staff will be responsible for collecting the age, sex, ethnicity, and race.

7.1.1.3 Assessment of Inclusion/Exclusion Criteria

At the Screening and the Baseline (prior to dosing) Visits, the site staff will be responsible for reviewing the inclusion and exclusion criteria to determine the subject's eligibility for the study.

7.1.1.4 Medical History

At the Screening Visit, medical history of the subject will be conducted. Any untoward medical occurrence that occurs after signing ICF is considered AE.

7.1.1.5 Assessment of Adverse Event

Adverse events will be recorded beginning after signing the ICF until completion of the study until the final follow-up visit (Day 42), and will be evaluated by the Investigator for severity (using CTCAE version 4.03 criteria (CTCAE 2010)), seriousness, and attributability to study medication. Further details on AEs, including definitions, elicitation, and reporting are provided in Section 8.

7.1.1.6 Height and Weight

At the Screening Visit, subject height will be recorded. Height (cm) measured from the Screen Visit will be carried forward to Day 0. At the Screening and Baseline (prior to dosing) Visits, subject weight (kg, in indoor clothing, but without shoes) will be measured.

7.1.1.7 Complete Physical and Focused Neurological Examinations

At the Screening and the Baseline (prior to dosing) Visits, complete physical examinations (including but not limited to: dermatologic, head, eye, ear, nose, throat (HEENT), respiratory, cardiovascular, abdomen, lymph nodes, musculoskeletal) will be performed. Focused neurological examination will assess potential SOT per instructions in the Appendix 1.

7.1.1.8 Mini Physical and Focused Neurological Examinations

At Days 1, 2, 7, 14, 30 (EOS/ET), and 42 Visits, mini physical examination that is symptom-oriented will be performed. Focused neurological examination will assess potential SOT per instructions in the Appendix 1.

7.1.1.9 Prior and Concomitant Medications

At the Screening Visit, the Baseline Visit, and at all subsequent scheduled and unscheduled clinic visits, prior and concomitant medications will be assessed.

Medications taken within 30 days prior to the screening visit and up to the study drug administration will be considered to be prior medications. Concomitant medication is defined as any medication that is taken after the study drug administration (Day 0). Any use of prior and concomitant medications will be recorded on the Concomitant Medications electronic Case Report Form (eCRF). During the study, initiation of or change in concomitant medications to treat an AE must also be recorded on an AE eCRF for that AE.

7.1.1.10 12-Lead ECG

At the Screening Visit, Day 2 Visit, and Day 30 (EOS/ET) Visit, a standard 12-lead ECG will be recorded in the supine position after at least 5 minutes rest. All ECG measures will be performed in triplicate, with each consecutive measure approximately 1 minute apart. In addition, where applicable, ECGs will be performed prior to blood draws.

The definitive ECG assessments will be conducted by a central ECG-reading facility. The assessment of the ECG by the central ECG-reading facility will include heart rate (HR), ECG intervals/durations (RR interval, PR interval, QRS duration, QT interval, and QT_C interval using Fridericia's and Bazett's corrections [QT_cF and QT_cB intervals, respectively; see List of Abbreviations and Glossary of Terms), and assessments of the waveform. The tracings may be reviewed and reported both locally and by a blinded central reader. In the event that the clinical study site and the central reader disagree on the interpretation of the results, the central reader's interpretation will be considered final. The centrally reported ECG results will be used in the data analyses.

7.1.1.11 Body Temperature, Respiration Rate, Blood Pressure, and Pulse Rate

At the Screening Visit, Baseline Visit (Day 0), and at all subsequent scheduled clinic visits till Day 30 (EOS/ET) visit, vital signs including body temperature, respiration rate, blood pressure, and pulse rate will be recorded. In addition, where applicable, vital sign data will be collected prior to blood draws.

Body temperature taken either orally or aurally will be the same throughout the study. Respiration rate will be taken at a quiet resting state prior to blood pressure (BP) and pulse rate measurements. Supine blood pressure (BP; systolic and diastolic) and pulse rate will be evaluated after at least 5 minutes rest.

7.1.1.12 Serum Chemistry, Lipids, Hematology

At the Screening Visit, Day 7 Visit, and Day 30 (EOS/ET) Visit, samples for routine serum chemistry, lipids, and hematology will be collected (see Appendix 3 for specific tests). Fasting for serum chemistry and lipids will begin at midnight until testing.

The samples will be analyzed by a central laboratory (with the appropriate accreditations or certifications). If clinically indicated, tests may be taken at additional times. Any clinical laboratory findings considered to be clinically significant changes from screening will be recorded as an AE on the eCRF (unless the laboratory finding is a feature of a specific diagnosis, when only the diagnosis will be recorded). Any clinically significant abnormal values that persist will be followed until they have been resolved or the Investigator, in consultation with the Medical Monitor or designee, assesses them to be chronic or stable.

7.1.1.13 Urinalysis

At the Screening Visit, Day 7 Visit, and Day 30 (EOS/ET) Visit, urine samples for urinalysis will be collected (see Appendix 3 for specific tests).

The samples will be analyzed by a central laboratory (with the appropriate accreditations or certifications). If clinically indicated, tests may be taken at additional times. Any clinical laboratory findings considered to be clinically significant changes from screening will be recorded as an AE on the eCRF (unless the laboratory finding is a feature of a specific diagnosis, when only the diagnosis will be recorded). Any clinically significant abnormal values that persist will be followed until they have been resolved or the Investigator, in consultation with the Medical Monitor or designee, assesses them to be chronic or stable.

7.1.1.14 Immunogenicity Sample Collection

[redacted]

7.1.1.15 Screens for HIV and Hepatitis B and C

At the Screening Visit only, blood samples for testing HIV antibody, hepatitis B surface antigen, and hepatitis C antibody will be collected.

The samples will be analyzed by a central laboratory (with the appropriate accreditations or certifications). Any positive findings at the Screening will exclude subject from participating in the study.

7.1.1.16 Screens for Alcohol / Drugs of Abuse

At the Screening Visit, Baseline (prior to dosing) Visit, Day 7 Visit, and Day 30 (EOS/ET) Visit, urine samples for screening drugs of abuse and saliva samples for screening alcohol will be collected and performed (see Appendix 3 for specific tests).

The samples will be analyzed at the study site. Any positive findings at the Screening or Baseline Visit will exclude subject from participating in the study.

7.1.1.17 Pregnancy Test

At the Screening Visit, blood samples for pregnancy test for women of child bearing potential will be collected. The samples will be analyzed by a central laboratory (with the appropriate accreditations or certifications).

At the Baseline (prior to dosing) Visit and Day 30 (EOS/ET) Visit, urine samples for pregnancy test for women of child bearing potential will be collected. The samples will be analyzed at the study site. Any positive findings at the Screening or Baseline Visit will exclude subject from participating in the study. See Section 8.5.2 in the event of any positive findings during the study.

7.1.1.18 Study Drug Administration

At the Baseline Visit, upon conducting all specified pre-dose assessment and confirming subjects remain eligible for the study, study drug will be administered. Six subjects in a cohort will be treated with either EB-001 or placebo in a ratio of 5:1 in a double-blind manner.

7.1.1.19 Standardized Facial Photography

At the Baseline (prior to dosing) Visit, and at all subsequent scheduled clinic visits till Day 30 (EOS/ET) visit, standardized facial photographs will be taken per instructions in the study manual(s).

The facial photograph assessments will be conducted by a central facility. Results from the assessments will be used for reference purpose only and not be used to influence efficacy endpoint assessment at the site.

7.1.1.20 Facial Wrinkle Scale – Subject Assessment

At the Screening Visit, Baseline (prior to dosing) Visit, and at all subsequent scheduled clinic visits till Day 30 (EOS/ET) visit, FWS at maximum frown and at rest will be assessed by the subject. Subjects will be provided the Photonumeric Guide prior to self-assessment to assist and standardize grading of GL severity. The FWS is a four-point scale that indicates severity of GL as follows: 0 = none, 1 = mild, 2 = moderate, or 3 = severe (see Appendix 2 for sample FWS assessment sheet).

7.1.1.21 Facial Wrinkle Scale – Investigator Assessment

At the Screening Visit, Baseline (prior to dosing) Visit, and at all subsequent scheduled clinic visits till Day 30 (EOS/ET) visit, FWS at maximum frown and at rest will be assessed by the Investigator. Investigator will be provided the Photonumeric Guide prior to assessment to assist and standardize grading of GL severity. The FWS is a four-point scale that indicates severity of GL as follows: 0 = none, 1 = mild, 2 = moderate, or 3 = severe (see Appendix 2 for sample FWS assessment sheet).

7.2 Laboratory Procedures/Evaluations

7.2.1 Clinical Laboratory Evaluations

See Sections 7.1.1.12, 7.1.1.13, 7.1.1.14, 7.1.1.15, 7.1.1.16, and 7.1.1.17.

7.2.2 Specimen Preparation, Handling, and Storage

See Laboratory Manual for instructions of specimen preparation, handling, and storage.

7.2.3 Specimen Shipment

See Laboratory Manual for instruction of specimen shipment.

7.2.4 Volume of Blood Collected

The estimated total blood volume collected throughout the study for clinical laboratory and immunogenicity tests is summarized in Table 4 and is expected to be approximately 59.5 mL.

Table 4 Total Blood Volume Collected for Each Subject

Test	Blood Sample Volume	Number of Tests	Total Volume
Hematology[1]	4 mL	3	12 mL
Serum chemistry[1], Lipids, Serum pregnancy test[2]	8.5 mL	3	25.5 mL
HIV 1/O/2	5 mL	1	5 mL
HBsAG and HCV Ab	5 mL	1	5 mL
Serum samples for immunogenicity	4 mL	3	12 mL
TOTAL			59.5 mL

[1] Additional blood may be collected for safety laboratory tests, if clinically indicated

[2] Female of child bearing potential only

7.3 Study Schedule

7.3.1 Screening Visit (Days -30 to -1)

Screening (Visit 1, Days -30 to -1, inclusive) will include the procedures and evaluations set forth in Section 7.3.7.

7.3.2 Baseline Visit (Day 0)

Baseline measurements and confirmation of subject eligibility will take place on Day 0. Procedures and evaluations prior to and after dose administration are set forth in Section 7.3.7.

7.3.3 Follow-Up Visits (Days 1, 2, 7, AND 14)

Follow-up visits will take place on Days 1 (±2 hours), 2 (±4 hours), 7 (±12 hours), and 14 (±1 day). All procedures in each visit will be performed within the specified window. Procedures and evaluations for each follow-up visit are set forth in Section 7.3.7.

7.3.4 End of Study (Day 30) / Early Termination Visit

Subject is considered to have completed the study after procedures and evaluations of Day 30 (±2 days) are performed. All procedures will be performed within the specified window. End of study (EOS) visit will include procedures and evaluations set forth in Section 7.3.7.

In the event of early termination (ET), every attempt should be made to have subject return to the site to complete procedures and evaluations set forth in Section 7.3.7.

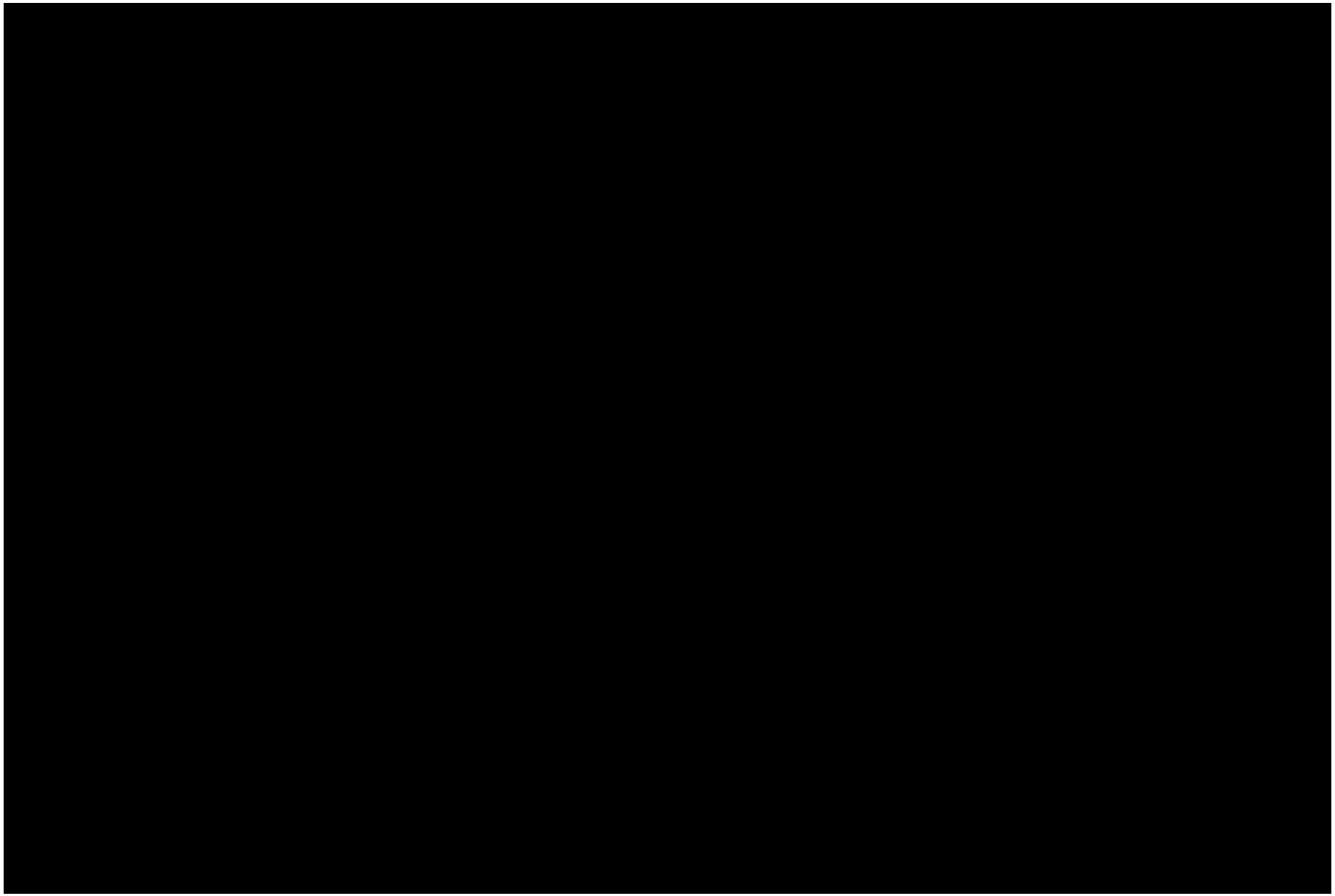
7.3.5 Final Follow-Up Visit

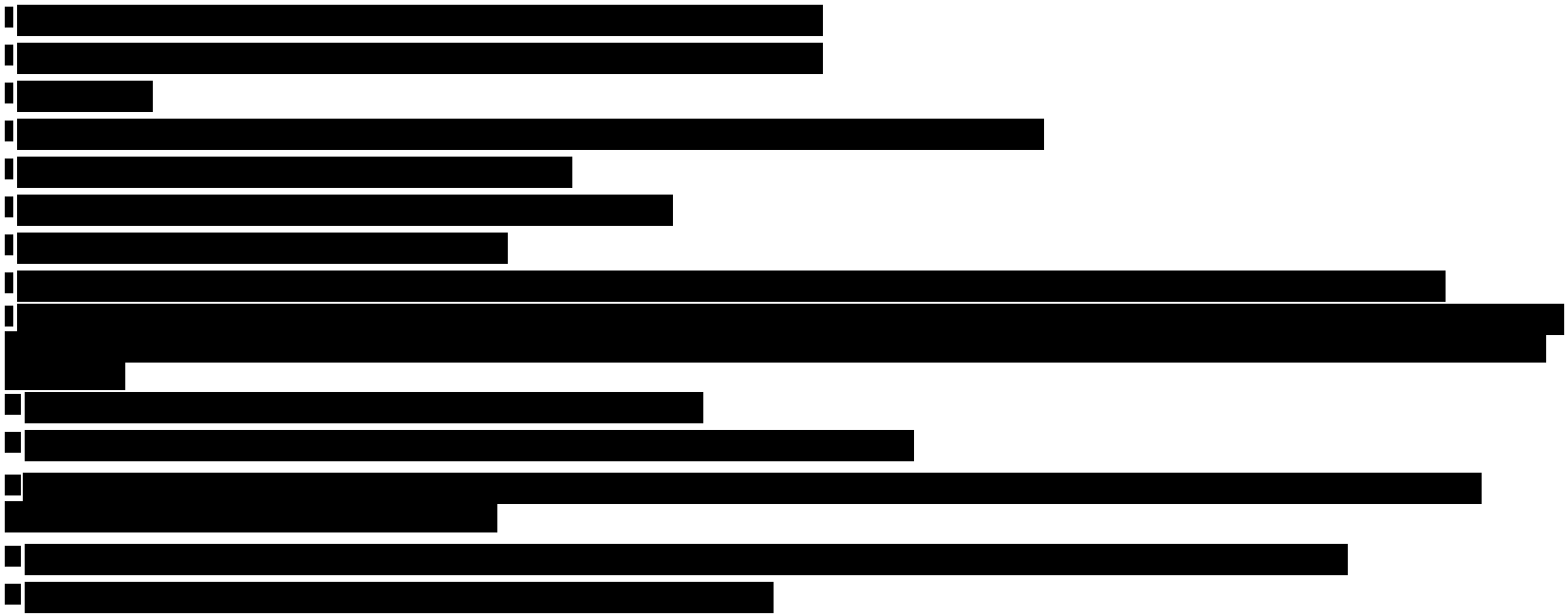
The final follow-up visit on Day 42 (±2 days) will include the procedures and evaluations set forth in Section 7.3.7. All procedures will be performed within the specified window.

7.3.6 Unscheduled Visit

Unscheduled Visit, at the discretion of the Investigator, may occur and appropriate procedures and evaluations will be conducted and documented in the eCRF.

7.3.7 Schedule of Events Table





7.4 Concomitant Medications and Treatments

Throughout the study, the following concomitant medications and treatments are allowed and will be recorded.

- Regular moisturizer or sunblock creams or lotions.
- Medications used for controlled systemic disease or other medical conditions.
- Vitamins and herbal medicines.
- Acetaminophen for symptomatic relief of pain on an as needed basis, as prescribed by the Investigator.

The Investigator must notify the Sponsor if participants take other concomitant medications during the study. The decision to allow the subject to be enrolled into the study or take medications during the study will be made jointly by the Sponsor and Investigator, based on their opinion that the use of the medication is unlikely to compromise the safety of the subject or the interpretation of the study data.

7.5 Prohibited Medications, Treatments, and Procedures

During the study, subjects may not use the following medications, or have following treatments/procedures performed until after the EOS Visit.

- Any topical retinoid therapy or topical hormone cream applied to the face unless they have been on a consistent dose regimen and maintained the same regimen for at least 6 months before enrollment.
- Any oral retinoid drugs within 12 months of enrollment.
- Any drugs used for skin conditions within 3 months of enrollment.
- Any non-ablative resurfacing laser or light treatment, microdermabrasion, superficial peels within 3 months of enrollment.
- Any facial cosmetic procedure with medium depth to deep facial chemical peels (e.g., trichloroacetic acid [TCA] and phenol), or mid facial or periorbital laser skin resurfacing within 3 months of enrollment.
- Any mid-facial or periorbital treatment with non-permanent soft tissue fillers within 12 months of enrollment.
- Any history of botulinum neurotoxin treatment of any serotype.

7.6 Subject Restriction

The following restrictions apply:

- Female of childbearing potential must agree to use dual methods of contraception from the day of dosing for 3 months. Female subjects using oral contraception must have initiated treatment at least 2 months prior to the day of dosing.

- Male subjects with partner(s) of childbearing potential must agree to use dual methods of contraception from the day of dosing for 3 months, and to no sperm donation from day of dosing until 3 months afterwards.
- Subjects must not donate blood or plasma from 30 days prior to Screening until the last follow-up visit (Day 42).
- Subjects should not consume more than moderate amount of alcohol per day (i.e., 1 drink per day for women or 2 drinks per day for men).

8 ASSESSMENT OF SAFETY

8.1 Specification of Safety Parameters

All of the following safety endpoints will be recorded on the eCRF.

- Incidence and severity of TEAEs and SAEs.
- Focused neurologic assessment for potential SOT.
- Incidence of abnormal findings in laboratory tests, ECG, physical examination, and vital signs (pulse rate, respiratory rate, and blood pressure).
- Urine pregnancy test for women of childbearing potential.

8.1.1 Definition of Adverse Events (AE)

Information about adverse events, whether reported by the subject, discovered by the Investigator by questioning/review of diary records or detected through physical examination, laboratory test or other means, will be collected and recorded on the adverse event form and followed-up as appropriate. Information about serious adverse events must be reported within 24 hours of obtaining knowledge of the event.

An adverse event (AE), defined according to International Committee on Harmonisation (ICH) Harmonized Tripartite Guideline E2A (FDA 1995), is any untoward medical occurrence in a subject or clinical trial subject administered a trial product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including a laboratory finding, for example), symptom, syndrome, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. Examples include:

- Any treatment-emergent signs and symptoms [events that are marked by a change from the subject's baseline/entry status (e.g., an increase in severity or frequency of pre-existing abnormality or disorder)];
- All reactions from study drug, abuse of drug, withdrawal phenomena, sensitivity, or toxicity to study drug;
- Apparently unrelated illnesses;
- Injury or accidents;
- Exacerbations of the underlying disease (indication),
- Extensions or exacerbations or symptomatology, subjective events reported by the subject, new clinically significant abnormalities in clinical laboratory, physiological testing, or physical examination.

The following is not considered an AE:

- Pre-planned procedure (documented as concomitant illness on the CRF at screening) unless the condition for which the procedure was planned has worsened from the first trial related activity after the subject has signed the informed consent form.
- Pre-existing conditions found as a result of screening procedures.

8.1.2 Definition of Serious Adverse Events (SAE)

In addition to the severity rating, each AE is to be classified by the Investigator as "serious" or "not serious." The seriousness of an event is defined according to the applicable regulations and generally refers to the outcome of an event. A serious adverse event (SAE) is one that meets one or more of the following:

- Is fatal.
- Is immediately life-threatening.
- Is permanently (or significantly) disabling.
- Requires hospitalization.
- Prolongs existing hospitalization.
- Is a congenital anomaly or birth defect (in an offspring).
- Is judged medically significant.

Definition of Life-threatening

Places the subject, in the view of the Investigator, at immediate risk of death from the event as it occurred. This does not include an adverse event, which, had it occurred in a more severe form, might have caused death.

Definition of Hospitalization

Hospitalization is defined by the Sponsor as a full admission to the hospital for diagnosis and treatment. This includes prolongation of an existing inpatient hospitalization.

Examples of visits to a hospital facility that do not meet the serious criteria for hospitalization include:

- Emergency room visits (that do not result in a full hospital admission).
- Outpatient surgery.
- Preplanned or elective procedures (See Section 8.1.2.1).
- Protocol procedures.

These events would not be reported as SAEs unless:

- The event triggering the hospital visit is an SAE as defined by other SAE criteria such as life-threatening, results in persistent or significant disability/incapacity or as per medical judgement of Investigator.
- Any other event fulfilling the definition of serious that develops as a result of the in-hospital procedure or extends the hospital stay is an SAE.

Definition of Disability

Disability is defined as a substantial disruption in a person's ability to conduct normal life functions.

Definition of Medically Significant

Important medical events (medically significant events) that may not result in death, be life-threatening or require hospitalization may be considered to be an SAE when, based upon appropriate medical judgement, they may jeopardize the subject or may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

An SAE may also include any other event that the Investigator, or Medical Monitor or designee judges to be serious, or that suggests a significant hazard, contraindication, side effect, or precaution.

8.1.2.1 Elective Procedures, and Surgeries

For the purposes of this Protocol, the following conventions will apply for SAE reporting of elective procedures, and surgeries:

A pre-scheduled elective procedure or a routinely scheduled treatment is not to be considered an SAE, even if the subject is hospitalized, provided the site stipulates that:

- The condition requiring the pre-scheduled elective procedure or routinely scheduled treatment was present before and did not worsen or progress between the subject's consent to participate in the clinical trial and the time of the procedure or treatment.
- The pre-scheduled elective procedure or routinely scheduled treatment is the sole reason for admission and intervention.

An untoward medical event occurring during the pre-scheduled elective procedure or routinely scheduled treatment must be recorded as an AE or a SAE. Record any concurrent medications on the eCRF.

8.1.3 Definition of Unanticipated Problems (UP)

The Office of Human Research Protection (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied.
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research).

- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

This study will use the OHRP definition of UP.

8.2 Classification of an Adverse Event

8.2.1 Severity of Event

AEs will be assessed according to the CTCAE version 4.03 (CTCAE 2010). AEs that do not have a corresponding CTCAE term will be assessed according to their impact on the participant's ability to perform daily activities as listed below.

- Mild (grade 1): The AE does not interfere in a significant manner with the subject's normal functioning level—it may be an annoyance.
- Moderate (grade 2): The AE produces some impairment of functioning, but is not hazardous to health—it is uncomfortable or an embarrassment.
- Severe (grade 3): The AE produces significant impairment of functioning or incapacitation and is a definite hazard to the subject's health.
- Life threatening (grade 4): Life threatening or disabling.
- Fatal (grade 5): Causes death of the participant.

These five categories are based on the Investigator's clinical judgement, which in turn depends on consideration of various factors such as the subject's reports, the physician's observations, and the physician's prior experience. Record the severity of the AE in the appropriate section of the AE page of the eCRF. The evaluation of severity is distinguished from the evaluation of "seriousness" (see Section 8.1.2). A severe event might not meet the criteria for seriousness and a serious event might be evaluated as mild. For example, a subject might have a **severe** headache that does not require hospitalization and is consequently **not serious**; or a subject might have a **mild** myocardial infarction that requires hospitalization and is therefore **serious**.

8.2.2 Relationship to Study Agent

The causality of each adverse event must be assessed and classified by the Investigator as "related" or "unrelated". An event is considered related if there is "a reasonable possibility" that the event may have been caused by the product under investigation (i.e., there are facts, evidence, or arguments to suggest possible causation).

Categories of attribution for "Related" events:

- Definitely related: There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out.

- Probably related: There is evidence to suggest a causal relationship, and the influence of other factors is unlikely.
- Possibly related: There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the study drug). However, the influence of other factors may have contributed to the event (e.g., the subject's clinical condition, other concomitant events).

Categories of attribution for "Unrelated" events:

- Unlikely related: There is little evidence to suggest there is a causal relationship. There is another reasonable explanation for the event.
- Not related: An AE will be considered "not related" to the use of the product if any of the following tests are met:
  - An unreasonable temporal relationship between administration of the product and the onset on the AE (e.g., the event occurred either before, or too long after administration of the product for it to be considered product-related);
  - A causal relationship between the product and the AE is biologically implausible (e.g., death as a passenger in an automobile accident);
  - A clearly more likely alternative explanation for the AE is present (e.g., typical adverse reaction to a concomitant drug and/or typical disease-related event).

Consider the following when assessing causality:

- Temporal associations between the agent and the event.
- Cessation or rechallenge.
- Compatibility with known class effect.
- Known effects of concomitant medications.
- Pre-existing risk factors.
- A plausible mechanism.
- Concurrent illnesses.

8.2.3 Expectedness

Sponsor will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study agent.

8.3 Time Period and Frequency for Event Assessment and Follow-up

The occurrence of an AE or SAE may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor. All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate eCRF. Information to be collected includes event description, dates and times of onset and resolution, clinician's assessment of severity, assessment of relatedness to study drug (assessed only by those with the training and authority to make a diagnosis), and action taken. All AEs occurring

while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE. UPs will be recorded in the data collection system throughout the study.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The Investigator will record all reportable events with start dates occurring any time after informed consent is obtained until the AE has resolved, stabilized, or a new chronic baseline has been established. At each study visit, the Investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

8.4 Reporting Procedures

8.5 Adverse Event Reporting

All AEs, *whether or not related to the study drug,* must be fully and completely documented on the AE eCRF and in the subject's medical notes. The following attributes must be assigned: event description, dates and times of onset and resolution, clinician's assessment of severity, assessment of relatedness to study drug (either related or not related), and action taken. The Investigator may be asked to provide additional follow-up information.

In the event that a subject is withdrawn from the study because of an AE, it must be recorded on the eCRF. The subject must be followed and treated by the Investigator until the AE has resolved, stabilized, or a new chronic baseline has been established.

The Investigator must report all observed AEs and all reported AEs. At each visit the Investigator will ask the subject a nonspecific question (e.g., "Have you noticed anything different since your last visit?") to assess whether any AEs have been experienced since the last report or visit. AEs will be identified and documented on the AE page of the eCRF in appropriate medical terminology. The severity and the relationship to the study drug will be determined and reported on the eCRF (see Sections 8.1.1 and 8.2.2).

Note that any intermittent or as-needed ("PRN") use of medication (and specifically any newly prescribed medication) during the course of a study may indicate the occurrence of an AE that may need to be recorded on both the AE page of the eCRF and the Concomitant Medication page.

8.5.1 Serious Adverse Event Reporting

The reporting of SAEs by Sponsor to the Regulatory Authorities is a regulatory requirement. Each Regulatory Authority has established a timetable for reporting SAEs based upon established criteria. It is the responsibility of the principal Investigator to report SAEs to the Sponsor within 24 hours.

All SAEs must be reported immediately (within 24 hours of discovery) to the Medical Monitor or designee. **Do not** delay in the reporting of a suspected SAE in order to obtain additional information. Any additional information, if collected, can be reported to the Sponsor as a follow-up to the initial report. SAEs will be reported using the SAE forms provided. Please remember to give details of the patient identification number or other appropriate terminology and ensure the narrative is comprehensive and includes a chronology and assessment of the event.

At a minimum, events identified by Bonti to require expedited reporting as serious, unexpected, and possibly related to study drug must be brought to the attention of the responsible IRB/IEC. For EU member States, Bonti or designee will provide reports of suspected unexpected serious adverse reactions (SUSARs) directly to the IECs, as required by local legislation. In all other countries, it is the Investigator's responsibility to provide these expedited reports to the responsible IRB/IEC. It is also the Investigator's responsibility to notify the responsible IRB/IEC regarding any new and significant safety information.

The process for reporting an SAE or study drug overdose is as follows:

- Complete an AE eCRF page.
- Complete an SAE form—this must include the patient identification number.
- Complete the narrative, which should be comprehensive and include a chronological description and assessment of the event.
- Complete the cover sheet.
- Call the Medical Monitor or designee for life-threatening or fatal events (see details that follow).
- Include results of any related laboratory tests or investigations, histopathologic examinations, or consultations with other healthcare professionals that serve to clarify the nature of the event, the cause of the event, or both.
- Email the cover sheet and the SAE form (within 24 hours of discovery) to the Medical Monitor or designee (see details that follow).

Follow-up information on a previously reported SAE should be processed using a new SAE form. Follow-up information includes additions, deletions, and corrections to the initial report. Previously signed, dated, and emailed forms should not be altered to provide follow-up SAE information of any type. The following must be done when providing follow-up information:

- Mark the box that indicates follow-up information is being provided.
- Fill out the dates on each page of the form that indicates this is a follow-up report.
- Restate the event as it appears on the initial report. If the event has changed, indicate, with parentheses, what the event was previously per the example below:

SERIOUS ADVERSE EVENT	Myocardial Infarction
Diagnosis or Sign/Symptom	(previously chest pain)

[redacted]

Bonti or designee will provide the Investigator with alternative contact information if the Medical Monitor will not be available.

These events should continue to be reported within 24 hours of discovery, particularly for life-threatening or fatal events, and the Investigator should continue to provide reports to the IRB/IEC, as required. In the event of any SAE (other than death), the patient will be instructed to contact the Investigator (or Medical Monitor or designee) using the telephone number provided in the ICF. All subjects experiencing an SAE will be seen by the Investigator or designee as soon as is feasible following the report of the SAE.

All SAEs will continue to be followed until the end of the Study or until such events have resolved or the Investigator, in conjunction with the Sponsor, deems them to be chronic or stable.

SAEs occurring up to 30 days after the study follow up period should be reported if in the judgement of the Investigator there is “a reasonable possibility” that the event may have been caused by the product.

8.5.2 Reporting of Pregnancy

Females that may be able to get pregnant will be required to take pregnancy test before study agent administration. The results of the pregnancy testing must be negative in order to be in the study.

All female subjects who may be able to get pregnant must agree to use dual methods of contraception from the day of dosing until 3 months afterwards. Female subjects using oral contraception must have initiated treatment at least 2 months prior to the day of dosing. All

male subjects with partner(s) of childbearing potential must agree to use dual methods of contraception from the day of dosing until 3 months afterwards, and to no sperm donation from day of dosing until 3 months afterwards.

In the event that a female subject does become pregnant at any time during the study, the Investigator must notify the Medical Monitor or designee within 48 hours of learning about the pregnancy.

The Investigator will be required to complete the Pregnancy Notification Form and any additional documents provided by the Sponsor, follow the subject through the pregnancy term, and report to the Medical Monitor or designee the course of the pregnancy, including perinatal or neonatal outcome.

Information on the status of the mother and the child will be forwarded to the Medical Monitor or designee using the Pregnancy Notification Follow-up Form. Any premature termination of the pregnancy will also be reported on this form.

Although pregnancy occurring in a clinical study is not considered to be an SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded as an AE and will be followed as such. A spontaneous abortion is considered to be an SAE.

8.6 Study Halting Rules

See Section 4.1.1.

8.7 Safety Oversight

The study Data Review Team (DRT) including the Investigators, Medical Monitor, Study Director as well as other *ad hoc* representatives as appropriate will regularly monitor all aspects of patient safety throughout this study. The DRT will review all available data in a blinded manner (may include: vital signs, ECGs clinical laboratory tests, incidence of SAE and TEAE) to assess the safety of each dose level of EB-001 prior to escalating to the next dose level.

9 CLINICAL MONITORING AND COMPLIANCE

The Sponsor representatives and regulatory authority inspectors are responsible for contacting and visiting the Investigator for the purpose of inspecting the facilities and, upon request, inspecting the various records of the study (e.g., eCRFs and other pertinent data), provided that subject confidentiality is respected.

The study monitor is responsible for inspecting the eCRFs at regular intervals throughout the study to verify the following: adherence to the protocol; completeness, accuracy, and consistency of the data; and adherence to local regulations on the conduct of clinical research. The monitor should have access to subject medical records and other study-related records needed to verify the entries on the eCRFs. The Investigator must agree to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

In accordance with ICH Good Clinical Practice (GCP) and the Sponsor audit plans, this study may be selected for an audit. Inspection of site facilities (e.g., pharmacy, drug storage areas, laboratories, etc.) and review of study-related records may occur in order to evaluate the trial conduct and compliance with the protocol, ICH GCP, and applicable regulatory requirements.

A separate clinical monitoring plan (CMP) should describe in detail who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed, and the distribution of monitoring reports. A CMP ordinarily should focus on preventing or mitigating important and likely risks, identified by a risk assessment, to critical data and processes. The types (e.g., on-site, centralized), frequency (e.g., early, for initial assessment and training versus throughout the study), and extent (e.g., comprehensive (100% data verification) versus targeted or random review of certain data (less than 100% data verification)) of monitoring activities will depend on a range of factors, considered during the risk assessment, including the complexity of the study design, types of study endpoints, clinical complexity of the study population, geography, relative experience of the PI and of the Sponsor with the PI, electronic data capture, relative safety of the study agent, stage of the study, and quantity of data.

10 STATISTICAL CONSIDERATIONS

10.1 Statistical and Analytical Plans

A formal statistical and analytical plan (SAP) will be completed prior to database lock and unblinding of the study data.

10.2 Statistical Hypotheses

All statistical analyses for all safety and efficacy endpoints will be descriptive summary statistics. Subjects who received placebo will be pooled across cohorts. Safety data will be evaluated by assessing the various dose groups of EB-001 versus the placebo group.

10.3 Analysis Datasets

The *safety set* will include all randomized subjects who received at least 1 dose of study drug and have at least 1 safety assessment thereafter.

The *efficacy set* will include all randomized subjects who received at least 1 dose of study drug and have at least 1 efficacy assessment thereafter.

10.4 Description of Statistical Methods

10.4.1 General Approach

Data will be summarized by dose of EB-001, across all subjects who received EB-001, and across all subjects who received placebo.

All continuous variables will be summarized using descriptive statistics of mean, median, standard deviation, minimum, and maximum. Categorical variables will be summarized using descriptive statistics of number and percentage of patients in each category.

10.4.2 Analysis of the Primary Efficacy Endpoint(s)

Baseline characteristics and change from baseline (CBL) of Investigator's assessment of GL severity at maximum using the FWS will be summarized using descriptive statistics, with details provided in patient listings.

[redacted]

10.4.4 Safety Analyses

10.4.4.1 Demographics and Baseline Characteristics

Demographic and baseline characteristics (medical history, physical examination, prior medications) will be summarized using descriptive statistics, with details provided in patient listings.

10.4.4.2 Prior and Concomitant Medications

All prior and concomitant medications will be assigned a generic name and a drug class based on the World Health Organization (WHO) Dictionary. Prior and concomitant medications will be listed and summarized by drug class.

10.4.4.3 Completion of the Study and Withdrawals

Withdrawals and the reason for withdrawal (AE(s), protocol non-compliance, lost to follow-up, failed to return, did not meet entrance criteria, voluntary withdrawal, and other reasons) will be tabulated. The number and percentage of subjects who complete the study and who withdraw from the study will be tabulated.

10.4.4.4 Tolerability Analysis

Tolerability will be assessed at each dose level of EB-001/placebo by tabulating the number and percentage of subjects who develop one or more of the toxicity criteria in Table 3. If 2 or more EB-001-treated subjects within a cohort at a particular dose level of EB-001 develop any of the intolerable toxicities specified in Table 3 and if these are considered to be related to EB-001, then that dose level will be considered an intolerable dose. The previous tolerated dose tested will be considered the highest tolerated dose (see Section 4.1.1).

10.4.4.5 Adverse Events

Adverse events will be classified into standard terminology using the Medical Dictionary for Regulatory Activities (MedDRA). Adverse events will be listed by event description (MedDRA-preferred term), dates and times of onset and resolution, clinician's assessment of severity, assessment of relatedness to study drug (either related or not related), and action taken. Additionally, data may be grouped for analysis by different levels of the MedDRA

hierarchy. The incidence of AEs, the incidence of treatment-related AEs, and the severity of AEs will be tabulated

Serious adverse events, treatment-related SAEs (with subsets for SAEs resulting in death and non-fatal SAEs) and subjects who withdraw due to an AE will be tabulated.

10.4.4.6 Clinical Laboratory Tests

Clinical laboratory test parameters will be listed for individual subjects. Baseline for clinical laboratory parameters will be defined as the last evaluation before dosing with study treatment. For each parameter, with the exception of urinalysis parameters, summary statistics, including mean absolute change from baseline, will be calculated for each measure and summarized; urinalysis results will be listed but not summarized. In addition, for leukocyte and lymphocyte counts, percentage change from baseline will be tabulated.

Each clinical laboratory test will be defined to be "Low", "Normal", or "High", according to the normal reference range from the clinical laboratory. The number and percentage of subjects who have a shift from within to outside the normal reference range (and vice versa) from baseline to each follow-up visit will be summarized.

Each clinical laboratory test will also be assigned to a grade based on the CTCAE v4.03 (CTCAE 2010). The number and percentage of subjects who have Grade 2, Grade 3, or Grade 4 laboratory value will be summarized.

10.4.4.7 Vital Signs

Vital signs results (including BP [systolic and diastolic], pulse rate, and body temperature) will be listed for individual subjects. Baseline for vital signs measurements will be defined as the last evaluation before dosing with study medication. Summary statistics, including mean change from baseline, will be determined for each measure and will be tabulated.

Vital signs will be reviewed for notable abnormalities according to the criteria in Table 6, and clinically notable vital sign abnormalities will be listed. The number and percentage of subjects who have a clinically notable vital sign abnormality will be summarized.

Table 6 Criteria for Clinically Notable Vital Sign Abnormalities

Parameter	High Threshold	Low Threshold
Systolic BP	>30 mmHg increase from baseline	>30 mmHg decrease from baseline
Diastolic BP	>20 mmHg increase from baseline	>20 mmHg decrease from baseline
Pulse rate	>120 beats/min and an increase in pulse rate of ≥15 beats/min from baseline	<40 beats/min and a decrease in pulse rate of ≥15 beats/min from baseline
Body temperature	>39.0°C (= >102.2°F)	<35.0°C (= <95.0°F)

10.4.4.8 Electrocardiograms

ECG intervals/durations (RR, PR, QT, QT_cF, and QT_cB intervals and QRS duration) and HR will be listed for individual subjects. Baseline for ECG intervals/durations will be defined as the mean of the triplicate values recorded on the last evaluation before dosing with study medication. Summary statistics, including mean change from baseline, will be determined for each measure and will be tabulated.

Electrocardiographic intervals and durations will be reviewed for notable abnormalities according to the criteria in Table 7, and clinically notable abnormalities will be listed. In addition, other ECG findings considered to be clinically significant (for example, rhythm disturbances, conduction abnormalities, T wave/ST segment abnormalities, etc.) will also be listed. The number and percentage of subjects who have a clinically notable ECG interval abnormality or other clinically significant ECG finding will be summarized.

Table 7 Criteria for Clinically Notable ECG Interval Abnormalities

Interval/Duration	High Threshold	Low Threshold
PR interval	PR interval ≥220 msec	PR interval ≤120 msec
QRS duration	QRS duration ≥120 msec and an increase in QRS duration of ≥20 msec from baseline	–
QT interval	QT interval >500 msec	–
QT_c intervals[1]	Males: QT_c interval ≥450 msec and an increase in QT_c interval of ≥60 msec from baseline or QT_c interval >500 msec	–
	Females: QT_c interval ≥470 msec and an increase in QT_c interval of ≥60 msec from baseline or QT_c interval >500 msec	

[1] Fridericia's and Bazett's corrections (QT_cF and QT_cB, respectively)

10.4.4.9 Physical and Focused Neurological Examinations

Findings of physical and focused neurological examinations will be listed for individual subjects and summarized.

For the evaluation of SOT terms, the criteria for Grading are:

- Grade 1 (Mild): Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2 (Moderate): Minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental Activities of Daily Living (ADL). Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
- Grade 3 (Severe or medically significant but not immediately life-threatening): Hospitalization or prolongation of hospitalization indicated; disabling; limiting self-

care ADL. Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden

- Grade 4 (Life-threatening consequences): Urgent intervention indicated.
- Grade 5 (Death related to AE).

[redacted]

10.4.4.11 Urine Drug Test

Results of urine drug test will be listed for individual subjects. Each test will be defined to be "negative" or "positive", according to the normal reference range from the clinical laboratory. The number and percentage of subjects who are "positive" or "negative" in each visit will be summarized.

10.4.4.12 Pregnancy Test

Results of pregnancy test will be listed for individual subjects. Each test will be defined to be "negative" or "positive", according to the normal reference range from the clinical laboratory. The number and percentage of subjects who are "positive" or "negative" in each visit will be summarized.

10.4.5 Planned Interim Analyses

No formal interim analysis is planned.

10.4.6 Exploratory Analyses

Exploratory analyses of efficacy as appropriate may be conducted.

10.5 Sample Size

This is the first human study to evaluate the safety and efficacy of EB-001, and therefore there are no data on which to base sample sizes. However, a sample size of 5 subjects per

cohort (n = 5 EB-001, n = 1 placebo) is considered to provide sufficient initial information on the estimation of the safety and tolerability of EB-001.

With 5 subjects receiving each dose level of EB-001 per cohort, an AE that occurs with a true frequency of 50% will be detectable with 96.9% probability within a given cohort. Combined across cohorts, with 35 subjects receiving EB-001, an AE that occurs with a true frequency of 10% will be detectable with greater than 97.5% probability. The probability of detecting AEs is shown in Table 8:

Table 8 Probability of Detecting Adverse Events that Occur at Various Frequencies

True Event Rate	Probability of Observing at Least 1 Event with 5 Completed Subjects	Probability of Observing at Least 1 Event with 35 Subjects
0.01	4.9%	29.7%
0.1	41.0%	97.5%
0.2	67.2%	>99%
0.5	96.9%	>99%

10.6 Measures to Minimize Bias

10.6.1 Enrollment/ Randomization/ Blinding Procedures

Subjects who meet the enrollment criteria will be enrolled into sequential cohorts. Patients are considered to be randomly assigned to the study when they are assigned to receive either EB-001 or placebo. Within each cohort, subjects will be randomly allocated to receive either EB-001 or placebo in a 5:1 ratio. The dosage level of EB-001 will not be randomized.

The study will be conducted in a double-blinded manner. Study drugs between EB-001 and the placebo vials will be identical in appearance. Study site personnel who prepare the study drug will not be involved in safety and efficacy assessment.

There will be an unblinded independent dispenser who will prepare and dispense EB-001 or placebo for administration in a blinded manner to subjects. The Investigator and site personnel, study subjects, and Sponsor personnel will be aware of the EB-001 dose level in each dose cohort; however, except for a limited number of Sponsor staff (see below), they will be unaware of whether subjects are receiving EB-001 or placebo until the study is formally unblinded.

10.6.1.1 Subject Numbering

Patients who have signed the ICF to begin screening procedures will be entered into the electronic data capture (EDC) system. The site will assign a 3-digit site-specific sequential screening number at that time. The unique patient identification number will consist of a

3-digit original site number followed by a 3-digit screening number. The patient will keep the same number throughout the study. Upon randomization, a unique 4-digit study-specific randomization number will be assigned by an Interactive Voice Response System (IVRS) or Interactive Web Response System (IWRS) system.

In the rare circumstance, where a patient is randomly assigned to treatment but does not receive the study drug, the study coordinator/research nurse must immediately inform the IVRS or IWRS that the study drug was not administered.

10.6.2 Evaluation of Success of Blinding

10.6.2.1 Blinding at the Study Site

Study treatment group information (active drug vs placebo) will remain blinded to the subject and also to all blinded members of the study team at the study site. There will be an unblinded independent dispenser who will prepare and dispense EB-001 or placebo for administration in a blinded manner to subjects. Study site personnel who prepare the study drug will not be involved in safety and efficacy assessment.

Investigators, coordinators, and nurses who are responsible for reviewing potentially unblinded medical data or who may have access to it (including all routine laboratory tests, imaging, and AEs) must not discuss any unblinded information or results with the site personnel responsible for blinded study assessments.

10.6.2.2 Blinding of Sponsor Personnel

During this study, staff of Bonti and designee will be blinded to treatment allocation, except as described in this section. The periodic DRT reviews will be performed in a blinded manner unless the data warrant unblinding due to safety concerns. It is assumed that the need to unblind a study subject's treatment assignment will occur in the setting of an SAE, and therefore, all procedures for the reporting of a SAE must be followed (see Section 8.5.1).

Procedures for emergency unblinding are described in Section 10.6.3. These procedures ensure that neither study blinded monitoring staff nor the Investigator and other site staff who are blinded have premature access to the study subjects' treatment assignments. Any personnel from Bonti and designee who become unblinded to study safety and efficacy data will be documented and no longer participate in day-to-day management of the study.

10.6.3 Breaking the Study Blind/Participant Code

An Investigator at a site may break the blind in the event of an immediate medical emergency, where knowledge of the study subject's treatment assignment (EB-001 or placebo) must be known in order to facilitate appropriate emergency medical treatment. In

these situations, the Investigator must first attempt to contact the Medical Monitor or designee before unblinding a subject's treatment identity in order to obtain concurrence that unblinding a study subject's treatment assignment is necessary. If circumstances preclude contacting the Medical Monitor or designee, each instance of unblinding must be reported to Sponsor within 24 hours. The Medical Monitor or designee may break the blind internally in the event of SAE(s), which require expedited reporting to regulatory authorities. Any other requests to reveal a subject's treatment identity must be requested of, and approved by the Medical Monitor or designee. If a study subject's treatment identity is unblinded by the study site, the unblinding must be reported to Bonti and documented on the eCRF as a deviation. If a subject's treatment identity is unblinded, the subject will be withdrawn from the study and will complete the Early Termination procedures describe in Section 5.4.

In an emergency situation in which the Investigator believes that the identity of a study subject's treatment assignment is necessary to treat the subject, the study subject's treatment assignment may be obtained from the 24-hour IVRS/IWRS. Details of the process to be followed and the telephone number are provided in the study manual(s) provided to the site. In the event that the IVRS/IWRS is used to perform a code break, Bonti or designee will be notified immediately by the IVRS/IWRS using an automated notification.

The Investigator or designee is responsible for ensuring that the instructions on how to perform a code break are stored safely, that their location is known, and that access is readily available to the relevant staff in case of an emergency.

11 SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

Each participating site will maintain appropriate medical and research records for this trial, in compliance with ICH E6 and regulatory and institutional requirements for the protection of confidentiality of participants.

The clinical site participating in this study are required to submit clinical data for each enrolled subject via an EDC system, using an eCRF. Site personnel will be trained on the EDC system before receiving access to the system. The Sponsor or designee is responsible for maintaining a record of all system users. The participants of the study will not be identified by name on any study documents to be collected by the Sponsor (see Section 13.4).

All clinical information requested in this protocol will be recorded on the eCRF provided by the CRO (or via other data collection methods, e.g. electronic laboratory data transfer). The principal Investigator is responsible for reviewing all eCRFs, verifying them for accuracy, and approving them via an electronic signature. Copies of the completed eCRFs, saved to disk in .pdf format, will be sent to the Investigator's site at the completion of the study.

Additional source data may include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, participant's memory aids or evaluation checklists, pharmacy dispensing records, recorded audio tapes of counseling sessions, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, photographic negatives, and participant files and records kept at the pharmacy, at the laboratories, and medico-technical departments involved in the clinical trial.

12 QUALITY ASSURANCE AND QUALITY CONTROL

See Section 9.

13 ETHICS/PROTECTION OF HUMAN SUBJECTS

13.1 Ethical Standard

The Investigator will ensure that this study is conducted in full conformity with Regulations for the Protection of Human Subjects of Research codified in 45 Code of Federal Regulations (CFR) Part 46, 21 CFR Part 50, 21 CFR Part 56, and/or the ICH E6.

13.2 Institutional Review Board

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Written approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether previously consented participants need to be re-consented.

13.3 Informed Consent Process

The Sponsor must review the draft ICF prepared by the Investigator prior to submission to the IRB for approval. An IRB-approved copy of the ICF will be forwarded to the Sponsor.

The ICF documents the study-specific information the Investigator provides to the subject and the subject's agreement to participate. Among other things, the Investigator will fully explain in layman's terms the nature of the study, along with the aims, methods, potential risks, and any discomfort participation may entail. The subject must sign and date the ICF before any study-related procedures are performed. The original and any amended signed and dated ICF(s) must be retained in the subject's file at the study site and a copy must be given to the subject.

13.4 Participant and Data Confidentiality

The Investigator must ensure that each subject's anonymity is maintained as described below. On the eCRFs or other documents submitted to the Sponsor, subjects must be identified by no more than their initials, date of birth, and a Subject Identification Number. Documents that are not for submission to the Sponsor (e.g., signed ICFs) should be kept in strict confidence by the Investigator in compliance with applicable regulations and ICH GCP E6 Guidelines (FDA 2015). Participant confidentiality is strictly held in trust by the participating Investigators, their staff, and the Sponsor(s) and their agents. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence.

No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the Sponsor.

The Investigator and institution must permit authorized representatives of the Sponsor, of regulatory agencies, and the IRB direct access to review the subject's original medical records for verification of study-related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are needed for the evaluation of the study. The Investigator is obligated to inform the subject in the ICF that the above named representatives may review study-related records from subjects.

13.4.1 Research Use of Stored Human Samples or Data

Samples and data collected under this protocol may be used to study the safety and efficacy of EB-001. All data and materials created from the samples will be the property of the Sponsor. Samples collected will be stored in either the laboratory of the Sponsor or the laboratory of a company contracted to work with the Sponsor with a proper tracking system. Access to study samples will be limited to laboratory personnel working for the Sponsor or contracted to the Sponsor, who are authorized to perform analyses.

Samples collected may be stored for up to 10 years after the end of the study (the end of the study occurs when a final study report is written).

13.5 Future Use of Stored Specimens

Additional tests may be conducted in case there are substances discovered about which we are not currently aware that might help us better understand or develop treatments for glabellar line, and/or for safety issues that may arise in the future.

During the conduct of the study, an individual participant can choose to withdraw consent to have biological specimens stored for future research. However, withdrawal of consent with regard to biosample storage will not be possible after the study is completed.

13.6 Protocol Amendments and Study Termination

Protocol amendments must be made only with the prior approval of the Sponsor. Agreement from the Investigator must be obtained for all protocol amendments and amendments to the ICF. The IRB must be informed of all amendments and give approval for any amendments before the changes are implemented to the study. The Investigator must send a copy of the approval letter from the IRB to the Sponsor.

Both the Sponsor and the Investigator reserve the right to terminate the study, according to the study contract. The Investigator should notify the IRB in writing of

the trial's completion or early termination and send a copy of the notification to the Sponsor.

14 DATA HANDLING AND RECORD KEEPING

14.1 Data Collection and Management Responsibilities

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site Investigator. The Investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. Black ink is required to ensure clarity of reproduced copies. When making changes or corrections, cross out the original entry with a single line, and initial and date the change. DO NOT ERASE, OVERWRITE, OR USE CORRECTION FLUID OR TAPE ON THE ORIGINAL.

Data reported in the eCRF derived from source documents should be consistent with the source documents or the discrepancies should be explained and maintained in the participant's official study record.

Clinical data (including AEs, concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into Axiom Fusion, a 21 CFR Part 11-compliant data capture system provided by the Axiom Real-time Metrics. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

14.2 Study Records Retention and Availability

The Investigator must make study data accessible to the study monitor, other authorized representatives of the Sponsor, and Regulatory Agency inspectors upon request. A file for each subject must be maintained that includes the signed ICF and the Investigator's copies of all source documentation related to that subject. The Investigator must ensure the reliability and availability of source documents from which the information on the eCRF was derived.

Investigators are required to maintain all study documentation, including copies of eCRFs, ICFs, and adequate records for the receipt and disposition of all study medications, for a period of 2 years following the FDA or other regulatory approval date of the drug, or until 2 years after the drug investigational program is discontinued, unless a longer period is required by applicable law or regulation. The Investigator must not discard any records unless given authorization by the Sponsor.

Subject identity information will be maintained for 15 years unless applicable law or regulation requires a longer period.

14.3 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol or GCP requirements. The non-compliance may be either on the part of the participant, the Investigator, or the study site staff. As a result of deviations, corrective actions may be developed by the site and implemented promptly.

These practices are consistent with ICH E6:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

All deviations must be addressed in study source documents and transcribed into the eCRF (as applicable). Protocol deviations must be sent to the local IRB per their guidelines. The site Investigator and study staff are responsible for knowing and adhering to their IRB requirements.

14.4 Publication and Data Sharing Policy

All publication and authorship rights are delineated in the Clinical Study Agreement.