CLINICAL STUDY PROTOCOL

A Phase 2 Study to Evaluate Safety and Efficacy of EB-001 Injections in Facial Scar Reduction After Undergoing Mohs Surgery

Study Number: EB001-SR201

IND Sponsor: Bonti, Inc.

Version Number:	2.0
Amendment:	1
Amendment 1 Date:	02 May, 2018
Original Protocol Date:	16 November, 2017

CONFIDENTIALITY STATEMENT

SUMMARY OF CHANGES RATIONALE

[redacted]

SIGNATURE PAGE

Approved 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 on clinical trials, Good Clinical Practice (GCP), and protection of human subjects

_____	_____	_____
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)
ATC	Anatomical Therapeutic Chemical
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
CRO	Contract Research Organization
DAS	digital abduction score
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
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
HBsAg	hepatitis B surface antigen
HC	heavy chain
HDL	high density lipoprotein
HEENT	head, eye, ear, nose, throat

Term	Definition
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
IM	Intramuscular
IRB	institutional review board
IUD	intrauterine device
LC	light chain
LDH	lactate dehydrogenase
LDL	low density lipoprotein
MCH	mean cell hemoglobin
MCHC	mean cell hemoglobin concentration
MCV	mean (red) cell volume
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified Intent to Treat
mL	Milliliter
mouse LD_{50}	lethal dose to 50% of mice after intraperitoneal injection
msec	millisecond
NA	not applicable
ng	nanogram
NOAEL	no observable adverse effects limit
OHRP	Office for Human Research Protections
PCV	packed cell volume
PI	principal investigator
POSAS	Patient and Observer Scar Assessment Scale
PR interval	time between the onset of atrial depolarization and the onset of ventricular depolarization
PRN	as-needed
RBC	red blood cell

Term	Definition
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
SCARS	Scar Cosmesis Assessment and Rating Scale
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
µg	microgram
UP	unanticipated problem
US	United States
VAS	Visual Analog Scale
WBC	white blood cell (Leukocyte)
WHO	World Health Organization

PROTOCOL SUMMARY

Study Number:
EB001-SR201

Study Title:
A Phase 2 Study to Evaluate Safety and Efficacy of EB-001 Injections in Facial Scar Reduction After Mohs Surgery

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

Study Objectives:
Safety Objective: To determine the safety and tolerability of single treatment of EB-001 when injected into forehead muscles underlying a surgical wound during Mohs surgery.

Efficacy Objective: To evaluate the efficacy of EB-001 intramuscular (IM) injection into the forehead muscles underlying the surgical wound in improving wound healing, and reducing scar formation.

Phase of Trial:
Phase 2

Clinical Hypothesis:
Safety: In patients undergoing Mohs surgery for skin lesions in the forehead area, a single treatment with EB-001 when injected into the muscles underlying the incision area will have an acceptable safety and tolerability profile.

Efficacy: In patients undergoing Mohs surgery for skin lesions in the forehead area, a single treatment with EB-001 when injected into the muscles underlying the incision area will improve wound healing and reduce scar formation.

Study Population:
Healthy subjects 18 to 75 years of age, inclusive, undergoing dermatological surgical procedures to remove single skin lesions in the forehead.

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)
- Urine pregnancy test for women of childbearing potential

Efficacy Measures:

- Scar assessment using a Visual Analog Scale (VAS)

[redacted]

Study Design:

This will be a randomized, placebo-controlled, single blind (to subject and study site personnel), parallel arm study with placebo or active treatment with IM injections. Subjects will be randomized to receive either a single dose (treatment) of EB-001 or placebo.

The study will be conducted at one center that specializes in dermatological surgical procedures. The study will include a visit for the surgical procedure (Day 1). Follow up visits will be scheduled at Days 2, 8, 30, and 90 (Table 1). The study will enroll approximately 12 subjects, randomly assigned to EB-001 or placebo in a 2:1 ratio for a total of 8 subjects in the EB-001 arm, and 4 subjects in the placebo arm (Figure 2).

Investigational (Study) Sites:

One dermatology site specialized in Mohs surgery.

[redacted]

Duration:

The expected duration for each subject participation is approximately 13 weeks from the day of surgery to the last visit.

Inclusion Criteria:

An individual must meet ALL the following criteria to participate in this study:

1. Between 18 and 75 years of age, inclusive
2. In good health, or with stable treated medical condition, as determined by the investigator.
3. Scheduled to undergo Mohs surgery to remove a single skin lesion in the forehead. This could be

5. Women of non-childbearing potential must be postmenopausal (at least 12 consecutive months of amenorrhea)
6. Women of childbearing potential must not be pregnant, lactating, or planning to become pregnant during the study
7. Women of childbearing potential agreeing to use either
    a. a highly effective method of contraception with failures rates less than 1% per year such as implant, intrauterine device (IUD), or sterilization from the day of dosing for 3 months (subjects who underwent sterilization must have initiated the procedure at least 3 months prior to the day of dosing) or
    b. dual methods of contraception with overall failures rates less than 1% per year such as injectable, pill, patch, ring, and diaphragm from the day of dosing for 3 months (subjects using oral contraception must have initiated treatment at least 2 months prior to the day of dosing)
8. Willing and able to complete and comply with procedures, protocol requirements and instructions, which includes completion of all required visits
9. Willing and able to sign and date IRB-approved informed consent
10. Able to speak, read, and understand the language of the informed consent form (ICF) and study questionnaires

Exclusion Criteria:

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

1. Pregnant or breast feeding, or planning a pregnancy
2. Body weight less than 50 kg (110 pounds)
3. Reported use of any botulinum toxin of any serotype within last 6 months before study drug administration
4. Anticipated use of any botulinum toxin of any serotype during the study
5. Known hypersensitivity to any botulinum toxin serotype
6. Known allergy or sensitivity to any of the components of the study treatments, or any materials used in the study procedures
7. Aminoglycoside intake within 48 hours prior to or during surgery
8. Pre-existing disorders of the neuromuscular junction (myasthenia gravis, Eaton-Lambert syndrome, or amyotrophic lateral Sclerosis)

9. Any uncontrolled medical condition that in opinion of investigator, puts subject at undue safety risk
10. Any clinically significant psychiatric condition that, in opinion of investigator, may interfere with study assessments or protocol compliance
11. Any cosmetic procedure, laser resurfacing treatment, or retinoid therapy in the forehead area in the past 30 days before study drug administration
12. Any eyebrow or eyelid ptosis at baseline as determined by the Investigator
13. History of hypertrophic scars or keloid formation or other wound abnormalities as assessed by the investigator
14. History of alcohol or drug abuse in the last 3 years, based on investigator judgement

[redacted]

Study Drug:

[redacted]

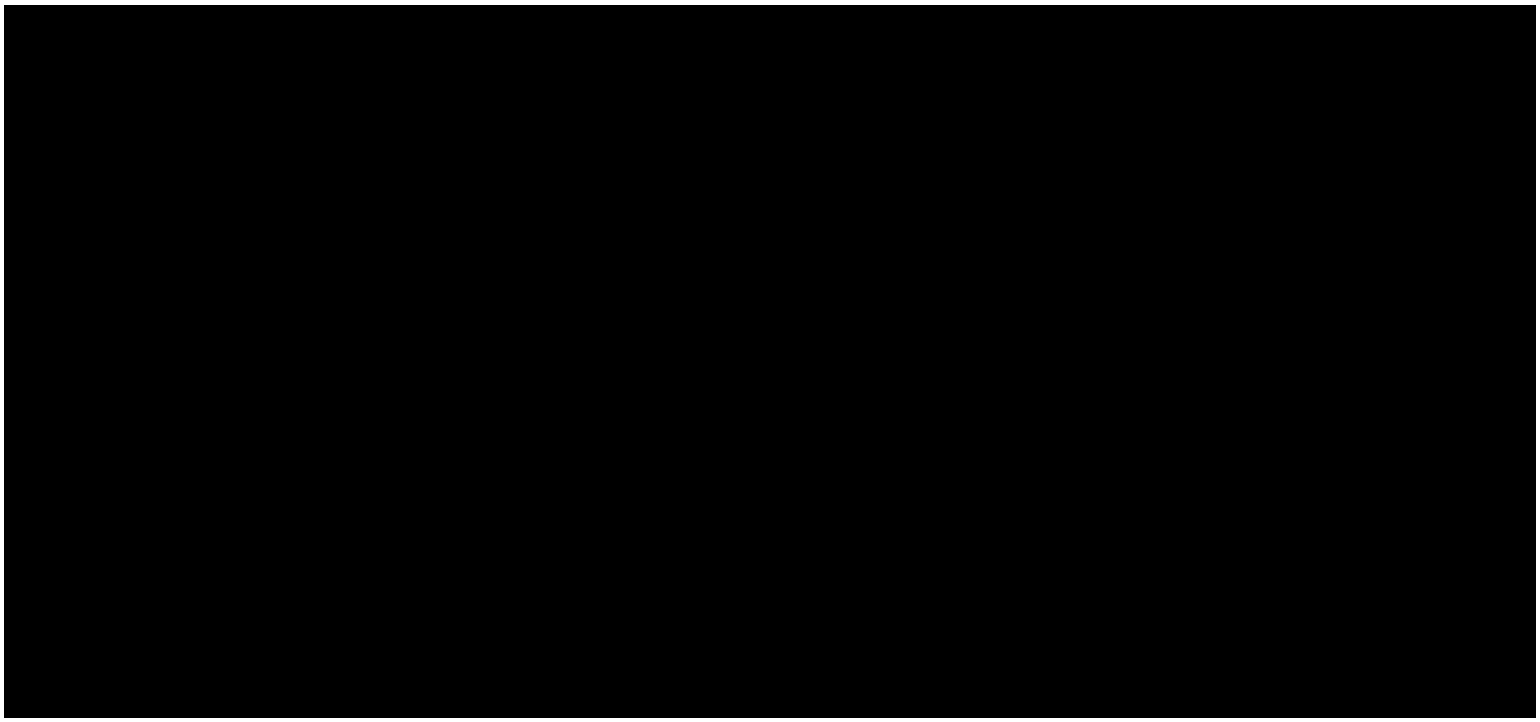
Placebo:

Preservative free, sterile saline solution 0.9% Sodium Chloride Injection, USP.

Dosage:

[redacted]

Figure 1 Injection Sites



Pre-Surgery Assessments:
Written informed consent form (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), immunogenicity sample collection, blood collection for human immunodeficiency virus (HIV) and hepatitis B and C, urine collection for drugs of abuse, and urine pregnancy test for premenopausal women.

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

Efficacy Assessments
Scar assessment using VAS,

Other Assessments
Standardized facial photography will be performed to aid efficacy assessments.

General Statistical Considerations:

Analysis will be performed when all patients have completed the Day 90 visit or exited early from the study. The statistical analysis plan detailing all analyses will be signed off before the primary database lock.

For efficacy analysis, modified intent to treat (mITT) population including all randomized and treated patients with at least one post-injection efficacy assessment will be used. The safety analysis will be performed using safety population including all randomized and treated patients. All analysis will be performed on "as treated" basis.

For main safety analysis, incidence of all adverse events, TEAEs, and serious adverse events will be summarized for each treatment group. The efficacy variables are scar assessment multiple scales. The data will be summarized by descriptive statistics and 95% confidence interval (based on t-test) for treatment group will also be presented.

The planned sample size will be approximately 12 subjects (8 for EB-001 and 4 for placebo, Figure 2). For this pilot study, no formal sample size computations were made.

All statistical analysis will be descriptive summary statistics.

Figure 2 Study Design of EB001-SR201