CLINICAL STUDY PROTOCOL

A Phase 2 Placebo-Controlled, Double Blind, Ascending Dose Cohort Study to Evaluate Safety and Efficacy of EB-001 Intramuscular (IM) Injections in Reducing Musculoskeletal Pain in Subjects Undergoing Elective Augmentation Mammoplasty (Breast Augmentation)

Study Number: EB001-MA201

IND Sponsor: Bonti, Inc.

[redacted]

CONFIDENTIALITY STATEMENT

SIGNATURE PAGE

Reviewed by:

[redacted]

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)
ANOVA	Analysis of Variance
ATC	Anatomical Therapeutic Chemical
AST (SGOT)	aspartate aminotransferase (= serum glutamic oxaloacetic transaminase)
AUC	Area under the curve
BMI	Body Mass Index
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
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
EU	European Union
F-U	follow up
FDA	Food and Drug Administration
FEV1	forced expiratory volume 1
FIH	first-in-human
FVC	forced vital capacity

Term	Definition
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
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
IUD	intrauterine device
IVRS	interactive voice 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
mITT	modified Intent to Treat
mL	Milliliter
mouse LD_{50}	lethal dose to 50% of mice after intraperitoneal injection
MRC	Medical Research Council

Term	Definition
MRSD	maximum recommended starting dose
Msec	Milliseconds
NA	not applicable
Ng	nano gram
NPRS	numerical pain rating scale
NPRS-A	NPRS administered after an activity
NOAEL	no observable adverse effects limit
OHRP	Office for Human Research Protections
PACU	post-anesthesia care unit
PAD	pharmacologically active dose
PCV	packed cell volume
PI	principal investigator
PFT	pulmonary function test
PGA	patient global assessment
PM	pectoralis major
PP	Per Protocol
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

Term	Definition
SD	Standard Deviation
SNAP	synaptosomal-associated protein
SOT	spread of toxin
SRC	Safety Review Committee
SUSAR	suspected unexpected serious adverse reactions
SVC	slow vital capacity
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
WBC	white blood cell (Leukocyte)
WHO	World Health Organization

PROTOCOL SUMMARY

Study Number:
EB001-MA201

Study Title:
A Phase 2 Placebo-Controlled, Double Blind, Ascending Dose Cohort Study to Evaluate Safety and Efficacy of EB-001 Intramuscular (IM) Injections in Reducing Musculoskeletal Pain in Subjects Undergoing Elective Augmentation Mammoplasty (Breast Augmentation)

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

Study Objectives:
Safety Objective: To determine the safety and tolerability of a single intraoperative treatment of EB-001 IM injections into the Pectoralis Major (PM) bilaterally in subjects undergoing breast augmentation with subpectoral implants.

Efficacy Objective: To evaluate the efficacy of intraoperative administration of EB-001 IM into the PM in bilaterally in reducing the pain and use of rescue pain medications in subjects undergoing breast augmentation with subpectoral implants.

Phase of Trial:
Phase 2

Clinical Hypothesis:
Safety: A single treatment of EB-001 IM injected into the PM bilaterally has an acceptable safety and tolerability profile at the tested doses in subjects undergoing breast augmentation with subpectoral implant placements.

Efficacy: A single treatment of EB-001 IM injected into the PM bilaterally reduces post-surgical musculoskeletal pain in subjects undergoing breast augmentation with subpectoral implants, at one or more of the doses tested in the study.

Study Population:
Healthy females 23 to 55 years of age, inclusive, undergoing primary, bilateral, cosmetic breast augmentation with subpectoral implants under general anesthesia (endotracheal or otherwise).

Outcome Measures:
Safety Measures:

- Incidence and severity of treatment emergent adverse events (TEAEs) and serious adverse events (SAEs)
- Assessment of AEs of special interest (post-operative dyspnea, tachypnea, tachycardia, pneumonia, atelectasis, and fever)
- 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, pulse oximetry and blood pressure)
- [redacted]
- Serum/urine pregnancy test for women of childbearing potential

Efficacy Measures:

Primary Efficacy Measures:

- Area under the curve (AUC) of subject's assessment of pain using the Numeric Pain Rating Scale (NPRS) between 16 and 96 hour post-surgery (AUC_{16-96}).

[redacted]

Study Design:

This will be a randomized, placebo-controlled, double blind, single ascending dose cohort study. The study will be conducted at up to two surgical centers that specialize in breast augmentation surgeries. The study will enroll up to 66 subjects (Figure 1).

[redacted]

[redacted]

[redacted]

The study will include a visit for screening and pre-surgical assessments. On the day of surgery (Day 1), eligible subjects will be admitted to an inpatient clinic and a single treatment of EB-001 IM will be given intraoperatively via IM injections into each PM. The subject will remain in-clinic and be assessed for 96 hours post-surgery. Follow up visits will be scheduled at Days 8, 15, and 29 (Table 2 and Table 3).

Investigational (Study) Sites:

It is expected that up to 2 clinical surgical sites will conduct the study and enroll up to 66 subjects, or up to 86 subjects if up to 5 additional cohorts are enrolled.

[redacted]

[redacted]

[redacted]

Duration:

The expected study duration for each subject includes up to 4 weeks in screening, and approximately 4 weeks from the day of surgery to the last visit, for a total duration of 8 weeks from the signing the Informed Consent Form (ICF) to the last study visit.

Inclusion Criteria:

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

1. Women 23 to 55 years of age, inclusive
2. Women who are in good health as determined by medical history, physical examination, clinical laboratory studies, ECGs, vital signs, and Investigator judgment

3. Scheduled to undergo primary breast augmentation under general anesthesia (endotracheal or otherwise) with:
   a. Sub-pectoral implants placement,
   [redacted]
4. American Society of Anesthesiologist (ASA) Physical Class 1-2
5. Women of non-childbearing potential or 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 confirmed sterilization and sterilization procedure at least 3 months prior to the day of dosing
   b. dual methods of contraception with overall failures rate 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 protocol requirements and instructions, which includes completion of all required visits, procedures and in-clinic stays until the end of the study
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. History of surgical procedure involving the breast, including, but not limited to, breast augmentation. History of minor localized breast biopsy is not exclusionary if it occurred at least 1 year prior to the screening visit, and if considered not clinically significant in the opinion of the investigator.
2. Pre-existing lung disease that could impact subject safety in the opinion of the investigator
3. History of smoking within the past two years

[redacted]

7. Documented diagnosis of chronic pain condition, or other painful pre-operative condition that, in the opinion of the investigator, may require analgesic treatment in the post-operative period (e.g. significant joint pain, neuropathic pain)

8. Known hypersensitivity to any botulinum toxin serotype or to any component of the formulation
9. Reported use of any botulinum toxin within 3 months prior to the date of surgery
10. Anticipated use of any botulinum toxin of any serotype during the study
11. Use of long acting opioids within 3 days or any opioid medication within 24 hours prior to surgery

[redacted]

16. History of alcohol or drug abuse in the last 3 years, based on investigator judgement
17. 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
18. Subject plans to donate blood or plasma from 30 days prior to screening until last follow-up visit (Day 29)
19. Reported pain score of 2 or more at screening on the 11-point scale NPRS-A following strength testing with PM activation

Study Drug:

[redacted]

Placebo:

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

Dosage:

The total dose of active drug [redacted] The injection paradigm will be provided in the injection technique and surgical manual.

Study drug injections will be performed [redacted]

Stopping Criteria for Dose Escalation:

Upon completion of Day 5 assessments for the last subject dosed in the prior sentinel group

[redacted]

The Medical Monitor or designee may request unblinding of treatment assignment with any of the criteria set forth above, and may discuss the treatment identity with the Investigator, before any further subjects are dosed.

Flexibility in Dose Adjustment:

If an intolerable dose is identified (based on one of the above 5 criteria), a lower dose may be evaluated as proposed by the SRC (Figure 1). 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. If the dose is an intermediary dose, a sentinel group consisting of 2 subjects (1 active: 1 placebo) will be dosed first. The SRC will review all available safety data of the prior sentinel group through at least Day 5 post-operatively, and 4 additional subjects (3 active: 1 placebo) will be dosed upon approval.

[redacted]

Screening:

Written informed consent form (ICF), demographics and baseline characteristics, inclusion/exclusion criteria, medical/surgical history, height, weight and BMI, complete physical and focused neurological examinations, prior and concomitant medications, 12-lead ECG, vital signs, 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, serum pregnancy test, strength testing and pain assessment (NPRS-A) with PM activation, and pulmonary function test (PFT; SVC, FVC and FEV1).

Safety Assessments:

Safety assessments will include collection and evaluation of TEAEs, physical and focused neurologic examinations (for potential SOT events), prior and concomitant medications, triplicate ECG, vital signs, clinical laboratory tests (serum chemistry, lipids, hematology, and urinalysis), medical/surgical history, serum/urine pregnancy [redacted] Safety assessments will also include collection and evaluation of TEAEs of Special Interest including post-operative dyspnea, tachypnea, tachycardia, pneumonia, atelectasis, and fever, which will be closely monitored.

Efficacy Assessments

- Overall pain scores at rest using the NPRS
  - NPRS is self-assessed by the study subject for their current pain according to an 11- point numeric pain rating scale (NPRS; 0 - 10) where 0 equates to no pain, and

10 equates to the worst pain imaginable.

- [redacted]

- PGA of pain control
  - Each subject will be asked the following question: Overall, please rate how well your pain has been controlled during the last 24 hours? Poor (0), Fair (1), Good (2),

or Excellent (3).

- Use of rescue medications over the post-surgical assessment periods
- [redacted]

[redacted]

General Statistical Considerations:

The final analysis will be performed when all subjects have completed Day 29 or exited early from the study.

Study Populations

The modified Intent to Treat (mITT) population will include all randomized patients who receive study drug. All efficacy analyses will be performed using this population. Analyses will be performed on subjects using their randomized treatment group.

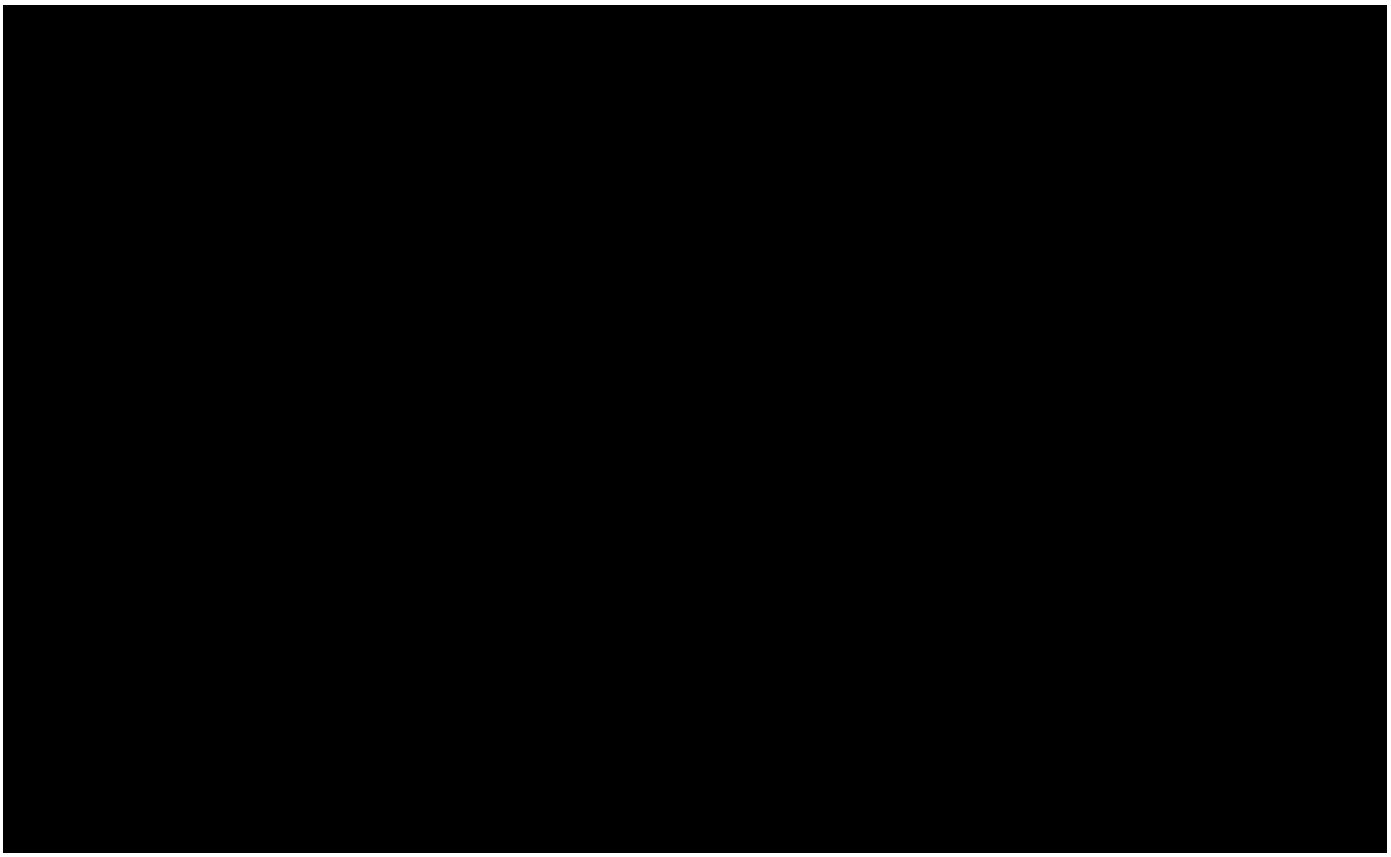
The Per Protocol (PP) population will include all subjects in the mITT population with no major protocol violations. The primary efficacy variable will also be analyzed using this population.

The Safety population will include all subjects exposed to any amount of study drug. All safety analyses will be performed using the safety population.

Sample Size

Subjects in each cohort will be randomly allocated to receive either EB-001 or placebo. [redacted]

All placebo subjects will be pooled for statistical analyses. All statistical analysis will be detailed in the statistical analysis plan (SAP), which will undergo formal sign off prior to database lock.



With at least 4 subjects receiving each dose level of EB-001 per cohort, an AE that occurs with a true frequency of 50% will be detectable with a 93.8% probability within a given cohort. Combined across all 6 cohorts, with up to 48 subjects receiving EB-001, an AE that occurs with a true frequency of 10% will be detectable with a 99.4% probability. The probability of detecting AEs is shown below (Table 1):

Table 1 Probability of Detecting Adverse Events that Occur at Various Frequencies

True Event Rate	Probability of Observing at Least 1 Event with 4 Completed Subjects	Probability of Observing at Least 1 Event with 48 Subjects
0.01	3.9%	38.3%
0.1	34.4%	99.4%
0.2	59.0%	>99%
0.5	93.8%	100%

Analyses

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, ECG measures, and pulmonary functions), including mean absolute change from baseline, will be summarized by treatment group.

Efficacy parameters including, but not limited to, AUC of overall pain assessment at rest, pain

assessment with passive and active arm abduction, amount of allowed rescue medications, and PGA of pain control will be summarized by treatment group. Statistical hypothesis testing will be performed, and one-sided p-values will be provided. The primary efficacy objective is to estimate the reduction of pain, assessed as an AUC for the NPRS pain scores over the 16-96 hour post-surgical period.

While this is not a formally powered study for efficacy analyses, efficacy data from the study will allow assessment of efficacy signal or trends, and exploration of the efficacious dose range. This will allow dose selection for future studies.

If a subject requests rescue medication, the pre-rescue pain NPRS and NPRS-A assessments will be carried forward for 4 hours. Handling of missing data for subjects who discontinue the study will be specified in the SAP.

Table 2 Schedule of Study Procedures, By Day

[redacted]