NCT03429556

Study ID: EB001-ABD201

Title: A Phase 2 Study to Evaluate Safety and Efficacy of EB-001 Intramuscular (IM) Injections in Reducing Musculoskeletal Pain in Subjects Undergoing Elective Abdominoplasty Surgery

Protocol Amendment 4: 28 September 2018

CLINICAL STUDY PROTOCOL

A Phase 2 Study to Evaluate Safety and Efficacy of EB-001 Intramuscular (IM) Injections in Reducing Musculoskeletal Pain in Subjects Undergoing Elective Abdominoplasty Surgery

Study Number: EB001-ABD201

IND Sponsor: Bonti, Inc.

Version Number:	5.0
Amendment:	4
Amendment 4 Date:	28 September, 2018
Amendment 3 Date:	09 May, 2018
Amendment 2 Date:	20 April, 2018
Amendment 1 Date:	16 March, 2018
Original Protocol Date:	09 February, 2018

CONFIDENTIALITY STATEMENT

Amendment 4 changes from Amendment 3 include:

- As per FDA feedback
  - Update study design with regard to dosing rationale, dosing regimen, and sample size
  - [redacted]
  - Apply study stopping criteria to all cohorts and stages of the study
  - Include statement on how to manage subjects who develop adverse effects indicative of spread of toxin
  - Update dosage of allowed rescue medication
  - Add criteria of when opioid rescue medications can be administered
  - Add muscle relaxants as prohibited medication
  - Specify that the subject, investigator and site staff are blinded, only sponsor is unblinded
- Change in allowable use of rescue medication during surgery, and in the first 12 hours following injection.
- Administrative changes are to:
  - Update of title page and headers throughout
  - Update of typographic errors

Amendment 3 changes from Amendment 2 include:

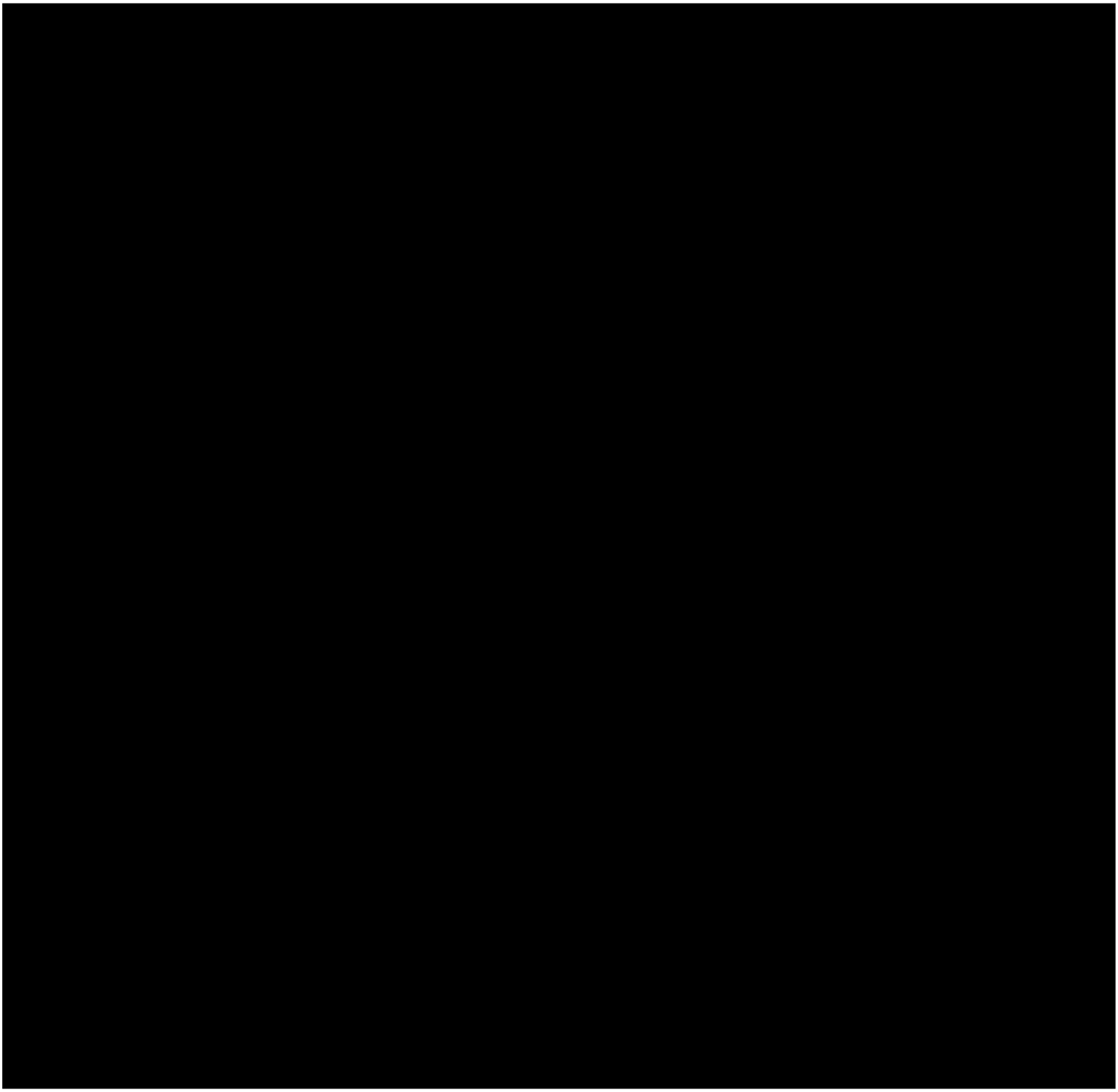
- Increase of one additional cohort in Stage 1 from 3 to 4.
- [redacted]
- Increase of sample size of optional cohort in Stage 1 from 8 to up to 42 subjects.
- Administrative changes are to:
    - Update of title page and headers throughout
    - Update of typographic errors

Amendment 2 changes from Amendment 1 include:

- Study design change of Stage 1 from a double-blind manner to a single-blind manner.
- Change of sample size of each cohort in Stage 1 from 6 to 8 (2 additional placebo subjects: 1 in the sentinel group and 1 in the rest of the cohort.
- Handling participant exceeding allowed rescue medication separately from early terminated participant
- Administrative changes are to:
    - Update of title page and headers throughout
    - Update of typographic errors

Amendment 1 changes from original protocol include:

- Addition of secondary efficacy measures: Over the period of time X to 96 hours post-surgery ($AUC_{t\text{-}96}$), whereas X is any time during confinement
- Revision of NPRS-A: Pain assessment after sitting up in the bed unassisted at an angle of approximately 45 degrees or more, swinging legs out, putting feet down, standing up, and walking approximately 10 feet
- [redacted]
- Revision and addition of exclusion criteria
  6. Unacceptable risk of deep vein thrombosis (DVT) as deemed by the investigator
  7. Past major surgery (more than 45 minutes) within the last 6 months
  8. History of blood clots, either DVT or pulmonary embolism
  9. Current or past malignancies (excluding skin cancer, but not melanoma) within the last 12 months
- Addition of NPRS-A data collection term prior to rescue medication usage: In the event subjects can not perform NPRS-A due to intolerable pain, this assessment may be omitted.
- Addition of warm packs for upper back pain
- Addition of assessment window of ±2 hours in various assessments.
- Addition of compression calf sleeves
- Revision of NPRS and NPRS-A collection time: NPRS and NPRS-A scores will be recorded by Subjects daily, in the morning (10:00 ±4 hours), in a take-home diary beginning on the day after discharge (Day 5) through EOS/ET.
- Administrative changes are to:
  - Update of title page and headers throughout
  - Update of typographic errors



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

TABLE OF CONTENTS

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

LIST OF TABLES

[redacted]

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
DVT	deep vein thrombosis
EB-001	botulinum neurotoxin serotype E drug product
ECG	electrocardiogram
eCRF	electronic case report form
[redacted]	[redacted]
EDC	electronic data capture
EOS	end of study
ET	early termination
EU	European Union
FDA	Food and Drug Administration
FEV1	forced expiratory volume 1
FVC	forced vital capacity
GCP	Good Clinical Practice

Term	Definition
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
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
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
[redacted]	[redacted]
Msec	Milliseconds
NA	not applicable
Ng	nano gram
NPRS	numerical pain rating scale

Term	Definition
NPRS-A	NPRS administered after an activity
NOAEL	no observable adverse effects limit
OHRP	Office for Human Research Protections
PACU	post-anesthesia care unit
PCV	packed cell volume
PI	principal investigator
PFT	pulmonary function test
PGA	patient global assessment
PM	pectoralis major
[redacted]	[redacted]
PP	Per Protocol
PR interval	time between the onset of atrial depolarization and the onset of ventricular depolarization
PRN	as-needed
RA	Rectus abdominus muscle
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
SD	Standard Deviation
SNAP	synaptosomal-associated protein
SOT	spread of toxin
SRC	Safety Review Committee

Term	Definition
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.
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-ABD201

Study Title:
A Phase 2 Study to Evaluate Safety and Efficacy of EB-001 Intramuscular (IM) Injections in Reducing Musculoskeletal Pain in Subjects Undergoing Elective Abdominoplasty 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 a single intraoperative treatment of EB-001 IM injections into the rectus abdominus (RA) muscles in subjects undergoing elective abdominoplasty surgery.

Efficacy Objective: To evaluate the efficacy of intraoperative administration of EB-001 IM into the RA muscles in reducing the pain and use of rescue pain medications in subjects undergoing elective abdominoplasty surgery.

Phase of Trial:
Phase 2

Clinical Hypothesis:
Safety: A single treatment of EB-001 IM injected into the RA muscles has an acceptable safety and tolerability profile at the tested doses in subjects undergoing elective abdominoplasty surgery.

Efficacy: A single treatment of EB-001 IM injected into the RA muscles reduces post-surgical musculoskeletal pain in subjects undergoing elective abdominoplasty surgery, at one or more of the doses tested in the study.

Study Population:
Healthy males or females 23 to 55 years of age, inclusive, undergoing elective abdominoplasty surgery (Full length plication from xyphoid to pubis, removal of skin/fat flap) under general anesthesia (endotracheal or otherwise) without liposuction.

Outcome Measures:


[redacted]

<u>Efficacy Measures:</u> Primary
Efficacy Measures:

- Area under the curve (AUC) of subject's assessment of pain using the Numeric Pain Rating Scale (NPRS) between 12 and 96 hours post-surgery ($AUC_{12\text{-}96}$).

Secondary Efficacy Measures:

- AUC assessment of overall pain profile using NPRS:
  - Over the first 96 hours post-surgery ($AUC_{0\text{-}96}$)
  - Over the first 72 hours post-surgery ($AUC_{0\text{-}72}$)
  - Over the first 48 hours post-surgery ($AUC_{0\text{-}48}$)
  - Over the first 24 hours post-surgery ($AUC_{0\text{-}24}$)
  - Over the period of 12 to 24 hours post-surgery ($AUC_{12\text{-}24}$)
  - Over the period of time X to 96 hours post-surgery ($AUC_{t\text{-}96}$), whereas X is any time during confinement
- Pain assessment at rest after discharge using NPRS at Days 6 through 29.
- Pain assessment after sitting up in the bed unassisted at an angle of approximately 45 degrees or more, swinging legs out, putting feet down, standing up, and walking approximately 10 feet using NPRS-A (NPRS administered after an activity) over the first 96 hours and at Days 8, 15, 29.
- Patient global assessment (PGA) of pain control
- Use of rescue medications over various postsurgical periods

<u>Study Design:</u>
This will be a two-stage study. The study will be conducted at up to two surgical centers that specialize in elective abdominoplasty surgeries. The study will include a screening visit to determine subject eligibility. On the day of surgery, subjects will be admitted to an inpatient clinic for 5 days post-operatively (Days 1-5) (Table 1 and Table 2). Intraoperatively, a single dose of EB-001 IM will be given via IM injections into each RA muscles per the surgical procedure manual. Follow up visits will be scheduled at days 8, 15, and 29.

The first stage will be a placebo-controlled, double blinded (to subject, investigator, and site staff), single ascending dose cohort study. The study is stratified by ethnicity (Hispanic and non-Hispanic) starting from Cohort 2. Six cohorts (3-8 subjects per cohort) will be dosed at 6 ascending doses of EB-001. An optional Cohort 7 may be considered. Clinical staff at the sponsor will be unblinded to drug assignment.

[redacted]

[redacted]

Cohorts Added in Amendment 4 (September 2018):

[redacted]

The second stage will be a randomized, placebo-controlled, double-blind, parallel 3-arm study (Sponsor will also be blinded). In this stage, there will be 2 doses of EB-001 (to be determined by the SRC after last dosing of last subject of Stage 1) and placebo in a 1:1:1 ratio for a total of 66 subjects stratified by ethnicity (Hispanic and non-Hispanic). SRC will meet periodically to review safety data.

Investigational (Study) Sites:

It is expected that up to 2 clinical surgical sites will conduct the study and enroll approximately 90-98 subjects.

[redacted]

Duration:

The expected study duration for each subject includes up to 45 days in screening, and approximately 4 weeks from the day of surgery to the last visit, for a total duration of up to approximately 10 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. Men or women 23 to 55 years of age, inclusive
2. Men or 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 elective abdominoplasty surgery with full length plication from xyphoid to pubis, and removal of skin/fat flap under general anesthesia

(endotracheal or otherwise) without liposuction
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. Men 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.
9. 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
10. Willing and able to sign and date IRB-approved informed consent
11. 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 prior major abdominal surgery as judged by 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
4. Pre-existing disorders of the neuromuscular junction (myasthenia gravis, Eaton-Lambert syndrome, or amyotrophic lateral Sclerosis)
5. Any past or current medical condition that in opinion of investigator, puts subject at undue safety risk for surgical complications or for use of the investigational product
6. Unacceptable risk of deep vein thrombosis (DVT) as deemed by the investigator
7. Past major surgery (more than 45 minutes) within the last 6 months
8. History of blood clots, either DVT or pulmonary embolism
9. Current or pst malignancies (excluding skin cancer, but not melanoma) within the last 12 months
10. History of diabetes
11. Any clinically significant psychiatric condition that, in opinion of investigator, may interfere with study assessments or protocol compliance

12. History of alcohol or drug abuse in the last 3 years, based on investigator judgement
13. Slow vital capacity that is below 80% of normal value for respective race, age, height, and gender or below 2.5 L of absolute volume
14. Pulse oximetry below 95%
15. Body weight less than 50 kg (110 pounds) or a Body Mass Index (BMI) of ≥ 32
16. 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)
17. Known hypersensitivity to any botulinum toxin serotype or to any component of the formulation
18. Reported use of any botulinum toxin within 3 months prior to the date of surgery
19. Anticipated use of any botulinum toxin of any serotype during the study
20. Use of long acting opioids within 3 days or any opioid medication within 24 hours prior to surgery
21. Aminoglycoside intake within 48 hours prior to or during surgery
22. Use of anti-depressant or anti-psychotic medications in the past 3 months
23. 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
24. Subject plans to donate blood or plasma from 30 days prior to screening until last follow-up visit (Day 29)
25. Reported pain score of 2 or more at screening on the 11-point scale NPRS-A following an activity after and walking approximately 10 feet.

[redacted]

Dosage:
The total dose of active drug will be the specified amount of EB-001 [redacted]. Each dose will be administered into the RA muscles per instructions in the surgical procedure manual. The injection paradigm will be the same for each cohort in Stage 1 and each arm in Stage 2.

Study drug injections will be performed intraoperatively under general anesthesia, under direct visualization of the RA muscles. Intramuscular needle placement, types of needles used, and additional instructions for study drug administration are referenced in the study manual(s).

Safety Oversight:
The safety and tolerability data for each patient will be monitored throughout the study in a

blinded fashion by the medical monitor, investigator(s) and the SRC. In the event a patient experiences unacceptable safety event(s) as determined by the investigator(s) and/or the SRC, treatment of that subject shall be discontinued.

The study Safety Review Committee (SRC) 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.

In the first stage of the study, the SRC will review all available safety data in a blinded manner to assess the safety of each dose level of EB-001 prior to escalating to the next dose level.

In the second stage of the study, the SRC will meet on a regular ongoing basis (further details provided in SRC charter document) to review all available data in a blinded manner to assess the safety of EB-001.

[redacted]

Flexibility in Dose Adjustment of Stage 1:

In the first stage of the study, 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. 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 6 additional subjects (5 active: 1 placebo) will be dosed upon approval.

In addition, if the SRC deems appropriate, before an intolerable dose is identified, a repeat dose, or a dose not exceeding the planned dose of the next cohort may be evaluated.

If a repeat or lower dose (i.e., any dose at or lower than prior highest dose evaluated without meeting stopping criteria) is considered, subjects may be dosed without implementing sentinel dosing strategy.

All dose escalation/adjustments or additional cohorts and corresponding sample size will be determined by the SRC. [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) following an activity after walking for

approximately 10 feet, and pulmonary function test (PFT; SVC, FVC and FEV1).

[redacted]

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.
  - Pain assessment starts once the subject is awake and lucid from surgery at every 2 hour timepoint (±15 minutes) until 96 hours (time of discharge). Time 0 is the time of intraoperative drug administration.
  - NPRS assessments scheduled between 00:00 and 06:00 may be skipped if the subject is sleeping except for the 12 hour pain assessment if it falls between 00:00 and 06:00.
  - On the mornings (10:00 ±4 hours) of Days 6-29 (inclusive), subjects will be encouraged to record their worst pain at rest since the last assessment of their pain intensity in their take home Pain Assessment Diary.
- Pain assessment using NPRS-A
  - After completing the overall pain assessment at rest, the investigator will ask the subjects to sit up in the bed unassisted at an angle of approximately 45 degrees or more, swing legs out, put feet down, stand up, and walk for approximately 10 feet. Subjects will then be asked to rate their level of worst pain when performing the activities using the NPRS-A. Pain assessments for NPRS-A will be conducted every 8 hours on Day 1, and every 6 hours on Day 2 and after.
  - NPRS-A assessments scheduled between 00:00 and 06:00 may be skipped if the subject is sleeping except for the 12-hour pain assessment if it falls between 00:00 and 06:00.
  - At visits on Days 8, 15, and 29, the NPRS-A assessment will be performed.
- 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

- In the event rescue medication is used, pain assessments using NPRS and NPRS-A will be recorded immediately prior to administering rescue medication.

[redacted]

General Statistical Considerations:

The final analysis will be performed when all patients have completed Day 29 visit or exited early from the study. The statistical analysis plan detailing all analyses will be signed off before the final database lock.

Study Populations

For efficacy analysis, modified intent to treat (mITT) population will include all randomized and treated patients with at least one post-injection pain score. 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 will be allocated to receive either EB-001 or placebo in a 1:1 ratio in Cohorts 1-3, a 4:1 ratio in Cohort 4, a 2:1 ratio in Cohort 5, a 3:1 Ratio in Cohort 6, and a 5:1 ratio in Optional Cohort 7 in Stage 1 stratified by ethnicity (Hispanic and non-Hispanic) starting from Cohort 2. The planned total sample size in Stage 1 will be up to 40-58 subjects (up to 24-39 for EB-001 and up to 16-19 for placebo) (Figure 1).

Subjects in each arm of Stage 2 will be randomly allocated to receive either EB-001 or placebo. The planned total sample size will be 66 subjects (44 for EB-001 and 22 for placebo) in Stage 2 stratified by ethnicity (Hispanic and non-Hispanic) (Figure 1).

Sample size of this study is not based on formal computations. However, 22 for active and 22 for placebo provide ~67% power to detect the difference. This power is based on one-sided alpha of 0.05, a mean baseline maximum pain score of 7.5, AUC12-96 ~440 with no drug effect, the delta AUC of 110 (drug and placebo difference), and SD of 170 AUC12-96.

[redacted]

Demographic and baseline characteristics will be summarized.

Safety will be assessed by summarizing the incidence of all adverse events, TEAEs, and serious adverse events in the Safety population. 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.

The primary efficacy variable is the Area under the Curve (AUC) of subject's NPRS assessment between 12 and 96 hours post-surgery (AUC12-96). The primary efficacy variable will be summarized by treatment group. The Secondary Efficacy Measures include AUC assessment of overall pain profile using NPRS for various time duration. Secondary efficacy variables also include: NPRS at Days 6 through 29, NPRS-A over the first 96 hours and at Days 8, 15, 29, patient global assessment (PGA) of pain control, and use of rescue medications over various postsurgical periods. The statistical analyses for primary and secondary variables will be outlined in detail in the final SAP.

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.

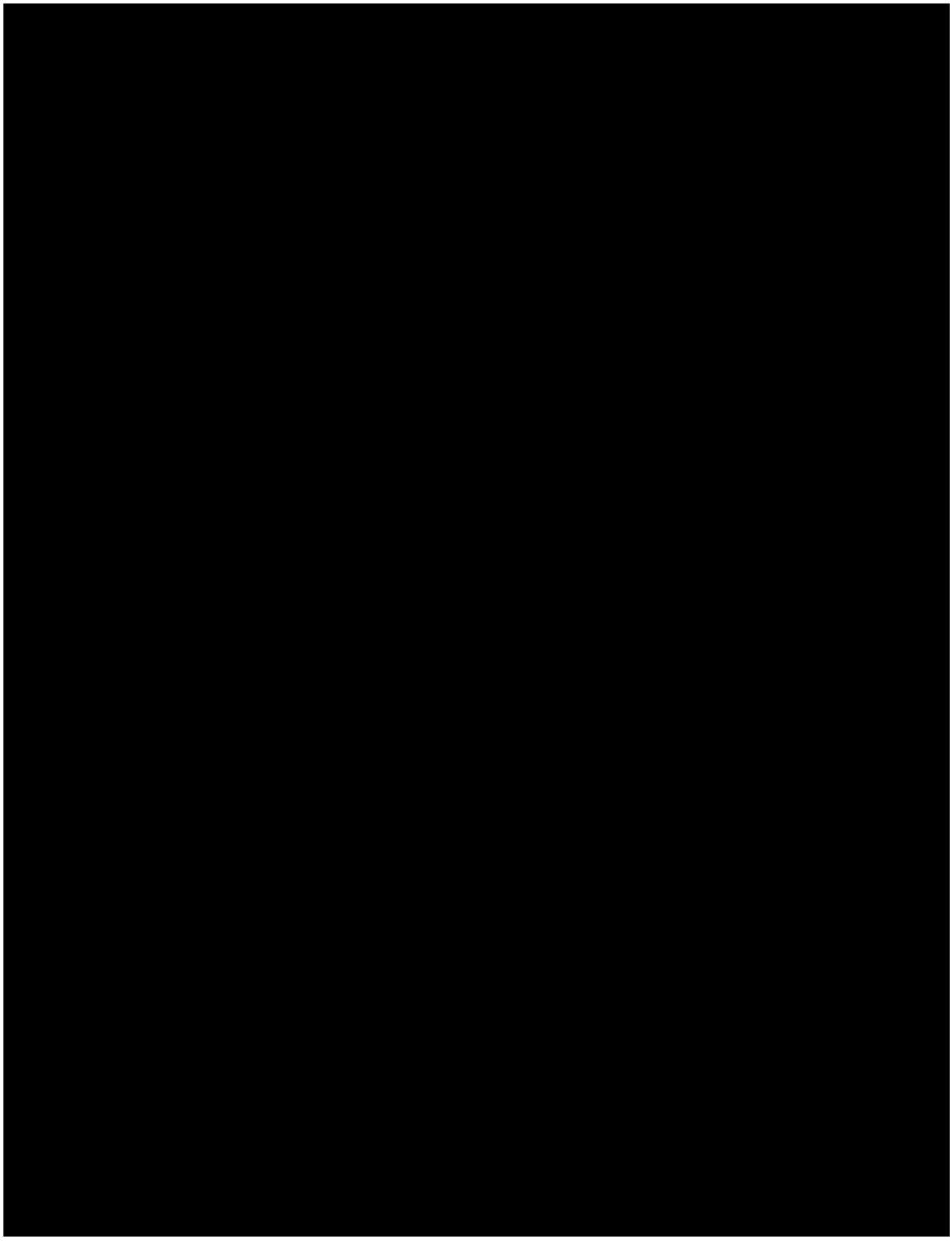
If a subject requests rescue medication, the pre-rescue pain NPRS and NPRS-A assessments will be carried forward for 4 hours. Handling of missing data for subjects who discontinue the study will be specified in the SAP.

[redacted]

[redacted]

[redacted]

[redacted]



[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]

[redacted]

[redacted]

2.2 Rationale

2.2.1 Study Rationale

BoNT serotype E (BoNT/E) has been previously studied in human subjects with injection into the extensor digitorium brevis foot muscle (Eleopra et al. 1998; Eleopra et al. 2002). These studies suggested a distinct clinical profile for BoNT/E versus the BoNT/A toxins, with faster onset and more limited duration of effect. IM administration of EB-001 bilaterally into pectoralis muscles during surgery has the potential to decrease post-operative focal musculoskeletal pain in the chest, including muscle spasm, pain and sensation of tightness. The efficacy is expected to start early in post-surgical period and is expected to last approximately 2-4 weeks.

[redacted]

Musculoskeletal pain is defined as pain originating from the skeletal muscles, tendons or ligaments due to focal injury in these structures. In subjects undergoing mammoplasty with sub-pectoral implant placement, the pectoralis major muscle is manipulated in order to form a sub-pectoral pocket for placement of the implant. Similarly, the RA muscle is stretched during plication in abdominoplasty. This manipulation of the RA muscles results in localized pain, muscular spasm, tenderness, and upper chest tightness or heaviness. Intramuscular injection of EB-001 is thought to reduce pain by relaxing the injured muscle, and by decreasing tension on the RA muscles and its tendons.

[redacted]

[redacted]

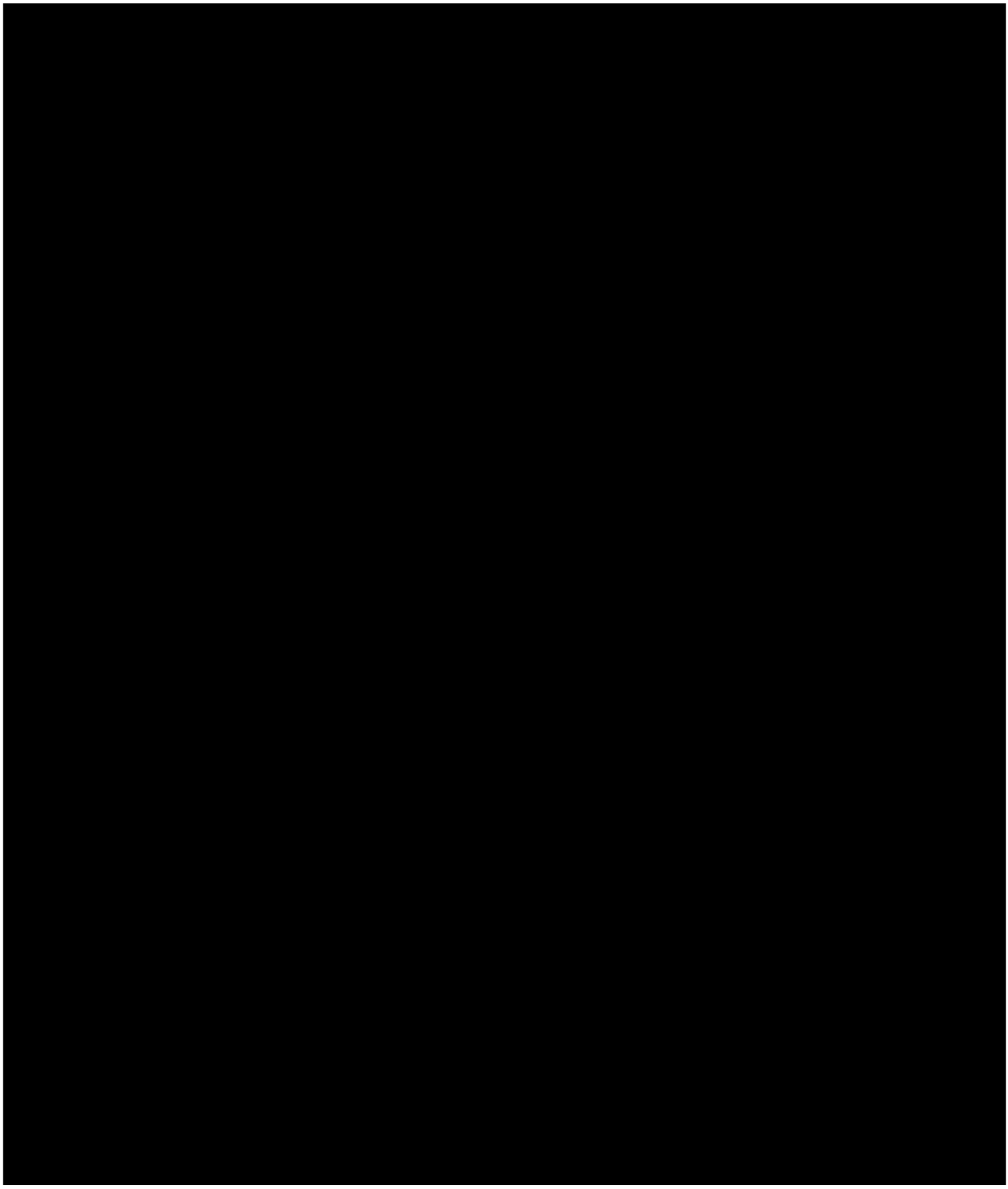


Table 3 Likely Symptoms of Botulinum Toxin Poisoning or Overdose

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

The safety evaluations in this protocol related to potential spread of toxin were based on the extensive knowledge about the systemic manifestations of botulism. It is well established that hematogenous spread of botulinum toxin leads to classic descending flaccid paralysis that starts with cranial nerve manifestations (Sobel, 2005, Gaware, 2011) followed by symmetrical descending flaccid paralysis that may progress to respiratory compromise (Sobel, 2005). The earliest symptoms of botulism are typically diplopia and ptosis followed by facial or pharyngeal muscle paralysis progressing to upper and then lower extremity weakness, and finally appearance of respiratory symptoms due to diaphragm weakness. This classic progression of symptoms and signs suggests that SOT effects in the face would manifest before extremity weakness and respiratory symptoms. This is the basis for the focused neurological exam aimed at detecting SOT. In the event of systemic toxicity with EB-001, the muscle paralytic effect is expected to begin recovering approximately 1 week following dosing. In contrast, the muscle paralytic effect of Botulinum Toxin Type A is long, lasting up to several weeks to months.

Another risk is the possibility of an allergic reactions to drugs and to product ingredients. If a subject has a severe 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

Documented events of serious allergic reactions have been rare in the case of botulinum neurotoxin serotype A (for example, see 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 be decreased pain following abdominoplasty and a decrease in the use of opioid medications post-surgery.

3 OBJECTIVES AND PURPOSE

This study will evaluate the safety and efficacy of EB-001 in decreasing the post-surgical pain in patients undergoing elective abdominoplasty surgery.

The safety objective is to determine the safety and tolerability of a single intraoperative

treatment of EB-001 IM injections into the RA muscles in subjects undergoing elective abdominoplasty surgery.

The efficacy objective is to evaluate the efficacy of intraoperative administration of EB-001 IM into the RA muscles in reducing the pain and use of rescue pain medications in subjects undergoing elective abdominoplasty surgery.

4 STUDY DESIGN AND ENDPOINTS

4.1 Description of the Study Design

This will be a two-stage study. The study will be conducted at up to two surgical centers that specialize in elective abdominoplasty surgeries and enroll up to 39-57 subjects in Stage 1 and 66 subjects in Stage 2 (Figure 1), with up to 67-82 subjects exposed to active drug. The study will include a screening visit to determine subject eligibility. On the day of surgery, subjects will be admitted to an inpatient clinic for 5 days post-operatively (Days 1-5) (Table 1 and Table 2). Intraoperatively, a single dose of EB-001 IM will be given via IM injections into the RA muscles per the surgical procedure manual. Follow up visits will be scheduled at days 8, 15, and 29.

The first stage will be a placebo controlled, single-blind (to subject and staff at study sites), single ascending cohort study stratified by ethnicity (Hispanic and non-Hispanic) starting from Cohort 2. Six cohorts (3-8 subjects per cohort) will be dosed at 6 ascending doses of EB-001. An optional Cohort 7 may be considered.

Cohort 1 sentinel group (3 subjects; 1 active: 2 placebo) [redacted] The rest of the cohort (5 subjects; 3 active: 2 placebo) will be dosed at the same dose after review of all available data by the Safety Review Committee (SRC) is conducted, with safety data through at least Day 5 post-operatively.

Cohort 2 sentinel group (3 subjects; 1 active: 2 placebo) [redacted] after review of all available safety data from the prior cohort through at least Day 5 post-operatively. The rest of the cohort (5 subjects; 3 active: 2 placebo) will be dosed after review of all available data by the SRC is conducted, with safety data through at least Day 5 post-operatively.

Cohort 3 sentinel group (3 subjects; 1 active: 2 placebo) [redacted] after review of all available safety data from the prior cohorts through at least Day 5 post-operatively. The rest of the cohort (5 subjects; 3 active: 2 placebo) will be dosed after review of all available data by the SRC is conducted, with safety data through at least Day 5 post-operatively.

Cohort 4 group (5 subjects; 4 active: 1 placebo) [redacted] after review of all available safety data from the prior cohort through at least Day 5 post-operatively.

Cohort 5 group (3 subjects; 2 active: 1 placebo) [redacted] after review of all available safety data from the prior cohort through at least Day 5 post-operatively.

Cohort 6 sentinel group (2 subjects; 1 active: 1 placebo) [redacted] after review of all available safety data from the prior cohorts through at least Day 5 post-operatively. The rest of the cohort (6 subjects; 5 active: 1 placebo) will be dosed after review of all available data by the SRC is conducted, with safety data through at least Day 5 post-operatively.

Optional Cohort 7 (up to 18 subjects; 15 active: 3 placebo) will be dosed at a dose previously assessed after review of all available safety data from the prior cohorts through at least Day 5 post-operatively.

In the event an intolerable dose is identified, a lower (intermediary) dose may be evaluated as proposed by the SRC. 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. See further details in Flexibility in Dose Adjustment of Stage 1.

The second stage will be a randomized, placebo-controlled, double blind, parallel 3-arm study. In this stage, there will be 2 doses of EB-001 (to be determined by the SRC after last dosing of last subject of Stage 1) and placebo in a 1:1:1 ratio for a total of 66 subjects stratified by ethnicity (Hispanic and non-Hispanic). SRC will meet periodically to review safety data.

Investigational (Study) Sites:
It is expected that up to 2 clinical surgical sites will conduct the study and enroll approximately 105-123 subjects.

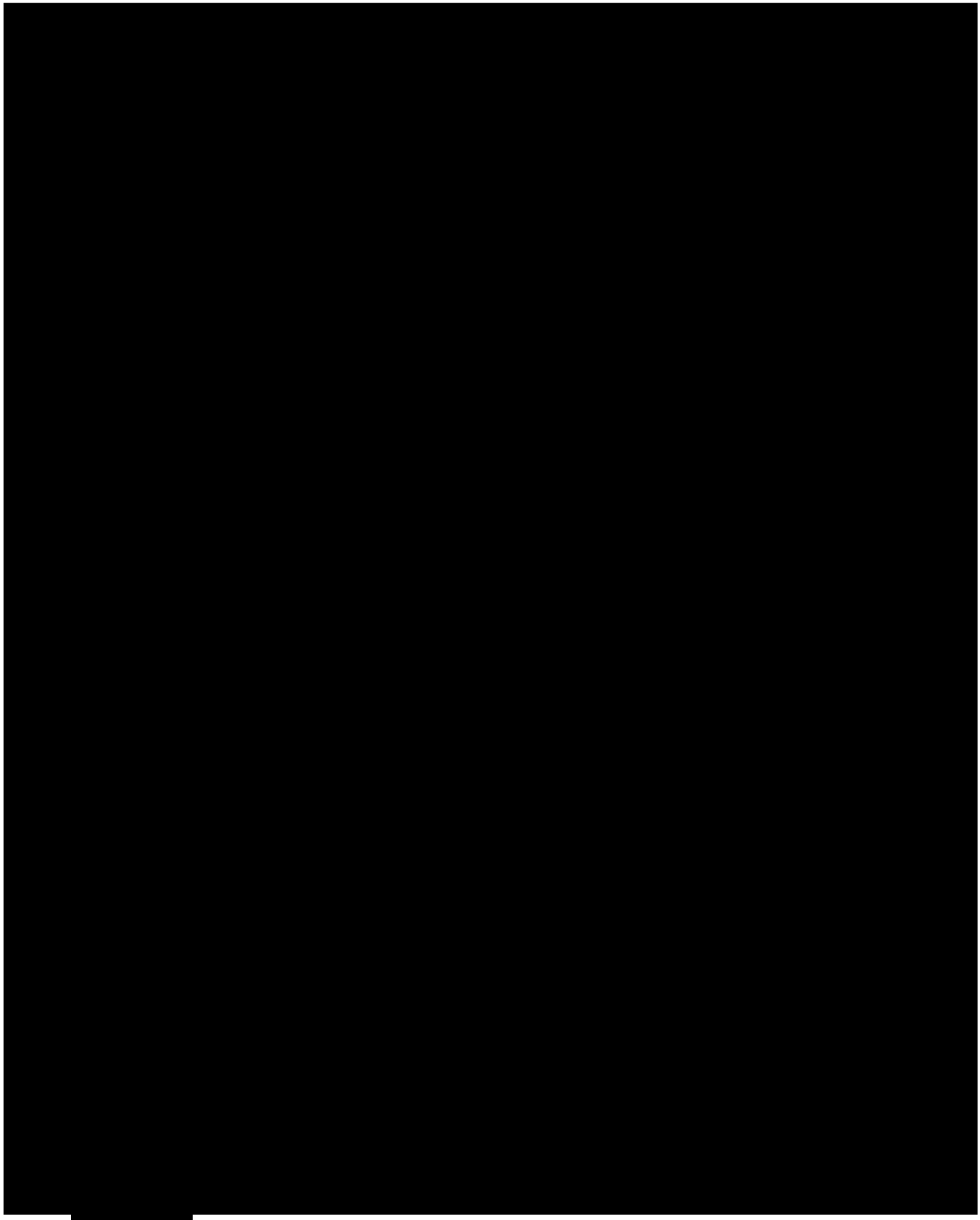
[redacted]

Placebo:
[redacted]

Dosage:
The total dose of active drug will be the specified amount of EB-001 [redacted]. Each dose will be administered into the RA muscles per instructions in the surgical procedure manual. The injection paradigm will be the same for each cohort.

Study drug injections will be performed intraoperatively under general anesthesia, under direct visualization of the RA muscles. Intramuscular needle placement, types of needles used, and additional instructions for study drug administration are referenced in the study

manual(s).



[redacted]

Table 4 Toxicity Criteria

TEAE	Definition[1]
Serious adverse event	See Section 8.1.2
TEAEs related to spread of toxin, including PFTs	SOT: FDA Draft Guidance: Upper Facial Lines: Developing Botulinum Toxin Drug Products[2] ≥Grade 2 SVC: SVC on PFT with a reduction of greater than 40% relative to baseline pre-dose measure and the absolute SVC less than 2 L at 96 hours (Day 5) post-dose or later, when confirmed by a repeat SVC approximately 4 hours later.
Post-operative TEAEs of Special Interest	Tachypnea, tachycardia, and fever according to the Guidance for Vaccine Trials in Healthy Volunteers[3] ≥Grade 2 Pneumonia or atelectasis diagnosed clinically and confirmed by chest x-ray Dyspnea with a clinical diagnosis of moderate or worse severity
TEAEs related to Laboratory and ECG parameters[4]	Guidance for Vaccine Trials in Healthy Volunteers[3] ≥Grade 2
All others TEAEs (other than the SOT, post-operative TEAEs of Special Interest, or laboratory and ECG parameters)	Guidance for Vaccine Trials in Healthy Volunteers[3] ≥Grade 3

[1] Unless considered to be unrelated to study medication
[2] FDA Draft Guidance, Upper Facial Lines: Developing Botulinum Toxin Drug Products (FDA 2014).
[3] Guidance for Industry: Toxicity Grading Scale for Health Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (FDA 2007)
[4] To be confirmed by a repeat test

Flexibility in Dose Adjustment of Stage 1:

In the first stage of the study, 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. 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 6 additional subjects (5 active: 1 placebo) will be dosed upon approval.

In addition, if the SRC deems appropriate, before an intolerable dose is identified, a repeat dose, or a dose not exceeding the planned dose of the next cohort may be evaluated.

If a repeat or lower dose (i.e., any dose at or lower than prior highest dose evaluated without meeting stopping criteria) is considered, subjects may be dosed without implementing sentinel dosing strategy.

All dose escalation/adjustments or additional cohorts and corresponding sample size will be determined by the SRC. [redacted]

[redacted]

4.2 Study Endpoints

[redacted]

4.2.2 Primary Efficacy Endpoint

- Area under the curve (AUC) of subject's assessment of pain using the Numeric Pain Rating Scale (NPRS) between 12 and 96 hours post-surgery ($AUC_{12\text{-}96}$).

4.2.3 Secondary Efficacy Endpoints

- AUC assessment of overall pain profile using NPRS:
  - Over the first 96 hours post-surgery (AUC_{0-96})
  - Over the first 72 hours post-surgery (AUC_{0-72})
  - Over the first 48 hours post-surgery (AUC_{0-48})
  - Over the first 24 hours post-surgery (AUC_{0-24})
  - Over the period of 12 to 24 hours post-surgery (AUC_{12-24})
  - Over the period of time X to 96 hours post-surgery (AUC_{t-96}), whereas X is any time during confinement
- Pain assessment at rest after discharge using NPRS at Days 6 through 29.
- Pain assessment after sitting up in the bed unassisted at an angle of approximately 45 degrees or more, swinging legs out, putting feet down, standing up, and walking approximately 10 feet using NPRS-A (NPRS administered after an activity) over the first 96 hours and at Days 8, 15, 29.
- Patient global assessment (PGA) of pain control
- Use of rescue medications over various postsurgical periods

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. Men or women 23 to 55 years of age, inclusive
2. Men or 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 elective abdominoplasty surgery with full length plication from xyphoid to pubis, and removal of skin/fat flap under general anesthesia (endotracheal or otherwise) without liposuction
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. Men 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.
9. 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
10. Willing and able to sign and date IRB-approved informed consent
11. Able to speak, read, and understand the language of the informed consent form (ICF) and study questionnaires

5.2 Participant Exclusion Criteria

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

1. History of prior major abdominal surgery as judged by 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
4. Pre-existing disorders of the neuromuscular junction (myasthenia gravis, Eaton-Lambert syndrome, or amyotrophic lateral Sclerosis)

5. Any past or current medical condition that in opinion of investigator, puts subject at undue safety risk for surgical complications or for use of the investigational product
6. Unacceptable risk of deep vein thrombosis (DVT) as deemed by the investigator
7. Past major surgery (more than 45 minutes) within the last 6 months
8. History of blood clots, either DVT or pulmonary embolism
9. Current or pst malignancies (excluding skin cancer, but not melanoma) within the last 12 months
10. History of diabetes
11. Any clinically significant psychiatric condition that, in opinion of investigator, may interfere with study assessments or protocol compliance
12. History of alcohol or drug abuse in the last 3 years, based on investigator judgement
13. Slow vital capacity that is below 80% of normal value for respective race, age, height, and gender or below 2.5 L of absolute volume
14. Pulse oximetry below 95%
15. Body weight less than 50 kg (110 pounds) or a Body Mass Index (BMI) of ≥ 32
16. 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)
17. Known hypersensitivity to any botulinum toxin serotype or to any component of the formulation
18. Reported use of any botulinum toxin within 3 months prior to the date of surgery
19. Anticipated use of any botulinum toxin of any serotype during the study
20. Use of long acting opioids within 3 days or any opioid medication within 24 hours prior to surgery
21. Aminoglycoside intake within 48 hours prior to or during surgery
22. Use of anti-depressant or anti-psychotic medications in the past 3 months
23. 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
24. Subject plans to donate blood or plasma from 30 days prior to screening until last follow-up visit (Day 29)
25. Reported pain score of 2 or more at screening on the 11-point scale NPRS-A after walking approximately 10 feet

5.3 Strategies for Recruitment and Retention

A sufficient number of subjects will be screened to allow for approximately 90-98 eligible subjects to be randomized at up to 2 US-based investigational sites.

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, signed written 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 (except for exceeding limit of allowed rescue medication; specified below in Section 5.4.3).
- At the discretion of the Investigator or Sponsor for any reason.

5.4.2 Handling of Participant Withdrawal 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 participation, or who are discontinued prior to completing study participation, will be asked to complete ET procedures, including:

- Assessment of AEs
- Assessment of AEs of Special Interest including post-operative dyspnea, tachypnea, tachycardia, pneumonia, atelectasis, and fever
- Height, weight, and BMI
- Mini-physical and focused neurological examinations
- Prior and concomitant medications
- 12-lead ECG
- Body temperature, respiration rate, blood pressure, pulse oximetry, and pulse rate
- Serum chemistry, Lipids, and Hematology
- Urinalysis
- Immunogenicity sample collection
- Pregnancy test
- Postoperative wound assessment

- Overall assessment of pain at rest using NPRS (if prior to the 96-hr assessment)
- Pain assessment using NPRS-A after sitting up in the bed unassisted at an angle of approximately 45 degrees or more, swinging legs out, putting feet down, standing up, and walking approximately 10 feet (if prior to the 96-hr assessment)
- Patient global assessment (PGA) of pain control
- Pulmonary function test (SVC, FVC, and FEV1)
- Use of rescue medications
- Collection of take-home diaries (if applicable)

5.4.3 Handling of Participant Exceeding Allowed Rescue Medication

Subjects who exceed limit of allowed rescue medication, considered noncompliance with the protocol specified in Section 5.4.1 due to lack of efficacy, will be followed, not early terminated, with regard to all safety assessments per protocol. They at all subsequent visits will be asked to complete protocol-specified assessments, with the exception of efficacy assessments as follows:

- NPRS
- NPRS-A
- Collection of take-home pain assessment diary

5.5 Replacement of Subjects

Up to 4 (or up to 1 subject per cohort) subjects in Stage 1 who discontinue from the study may be replaced (unless the discontinuation is due to one of the toxicity criteria in Section 4.1.1 when subjects will not be replaced). Up to 9 subjects (or up to 3 subjects per cohort) in Stage 2 who discontinue from the study will be replaced (unless the discontinuation is due to safety reasons when subjects will not be replaced).

5.6 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. Bonti may also choose to suspend or terminate the study at any time for any of the reasons as noted below. 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.

[redacted]

6.1.5 Dosing and Administration

See Section 4.1.

6.1.6 Route of Administration

The study drug will be administered as intramuscular (IM) injections.

6.1.7 Starting Dose and Dose Escalation Schedule

See Section 4.1.

6.1.8 Dose Adjustments/Modification/Delays in Stage 1

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. 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. In addition, if the SRC deems appropriate, before the intolerable dose is identified, a lower or repeat dose without exceeding the dose of the next planned cohort may be evaluated.

6.1.9 Duration of Treatment

Expected duration is approximately 4 weeks for each subject from the day of study treatment to the End of Study Visit on Day 29, or up to approximately 10 weeks from signing ICF to the follow-up exit.

6.1.10 Tracking of Study Vials and Dose

The Investigator will keep a record of the dates study drug vials received, the dose dispensed to each study subject from each vial. After dose is administered to the subject, the dispenser will return the vial for storage in the pharmacy until CRA conducts final drug accountability which will be verified and reconciled on the Study Drug 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. Instructions for study drug preparation, dispensing and record keeping are referenced in the study manual(s).

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).

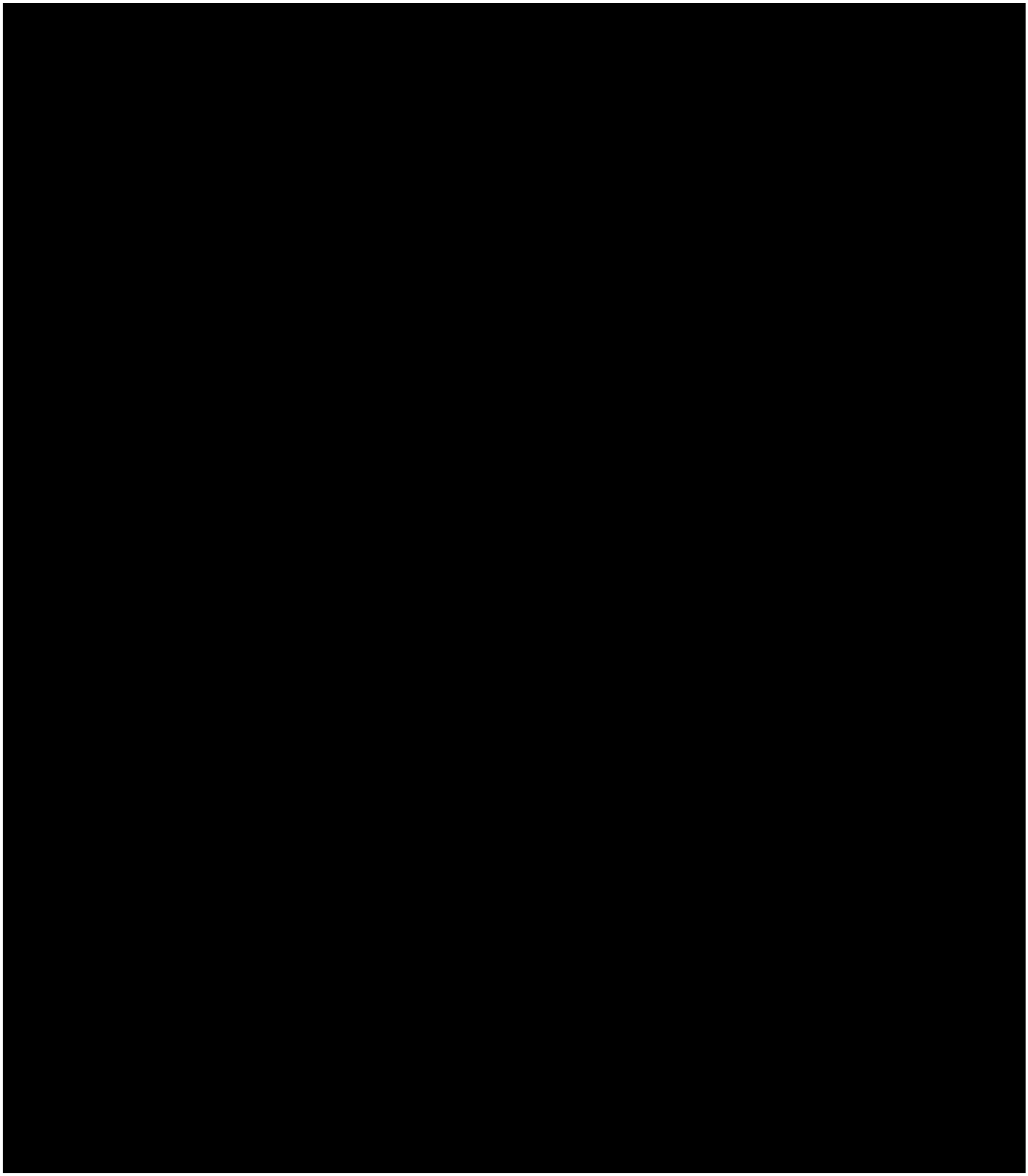
6.2 Investigational Product Accountability Procedures

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 Log will be provided for the accounting of study drug. Study Drug 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.



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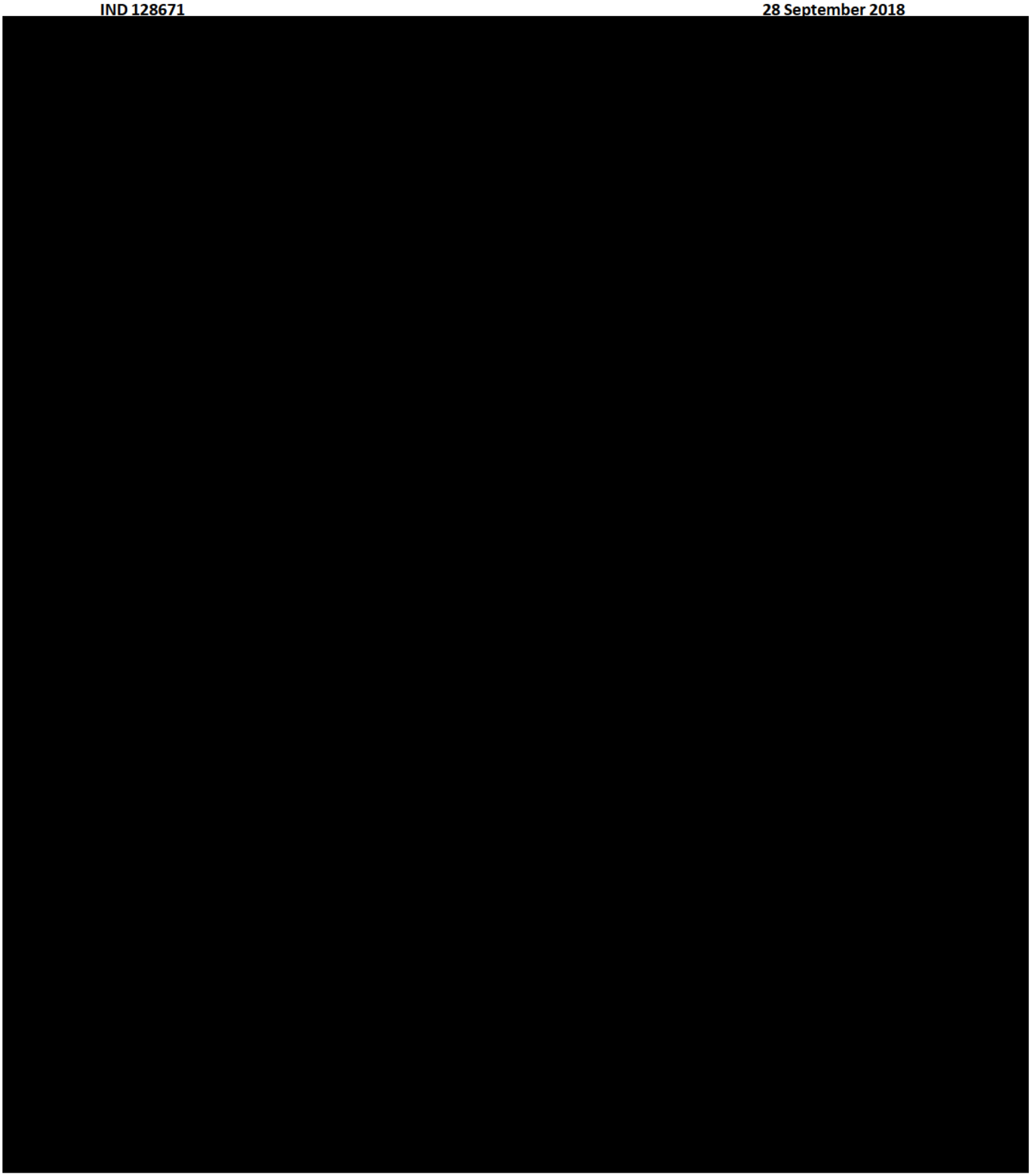


[redacted]

[redacted]

[redacted]

3).

7.1.1.25 Overall Assessment of Pain at Rest Using NPRS

Subjects will assess their overall pain level at rest since the last assessment using an 11-point NPRS, where 0 is no pain, and 10 is the worst pain imaginable (Appendix 4).

Assessments will be made every 2 hours (±15 minutes) post-dose after the subject is awake and lucid from surgery, until discharge. NPRS assessments scheduled between 00:00 and 06:00 may be skipped if the subject is sleeping. However, the 12-hour pain assessment must be completed even when the assessment falls between 00:00 and 06:00. Assessments will also be made after subjects are discharged on Days 6-29, and will be entered into the Pain Assessment Diary (see Section 7.1.1.31.1).

In the event rescue medication is used, an assessment of pain using the NPRS prior to administering rescue medication will be recorded.

7.1.1.26 Pain Assessment after Walking (NPRS-A)

At baseline prior to surgery, and then every 8 hours (±15 minutes) post-dose on Day 1, and every 6 hours on day 2 and after, after the subject is awake and lucid from surgery until discharge, the Investigator will ask subjects to sit up in the bed unassisted at an angle of approximately 45 degrees or more, swing legs out, put feet down, stand up, and walk approximately 10 feet. Subjects will then be asked to rate their level of worst pain when performing the activities using the NPRS-A, on an 11-point numerical scale, where 0 means no pain and 10 means the worst pain imaginable (Appendix 5) while they were walking.

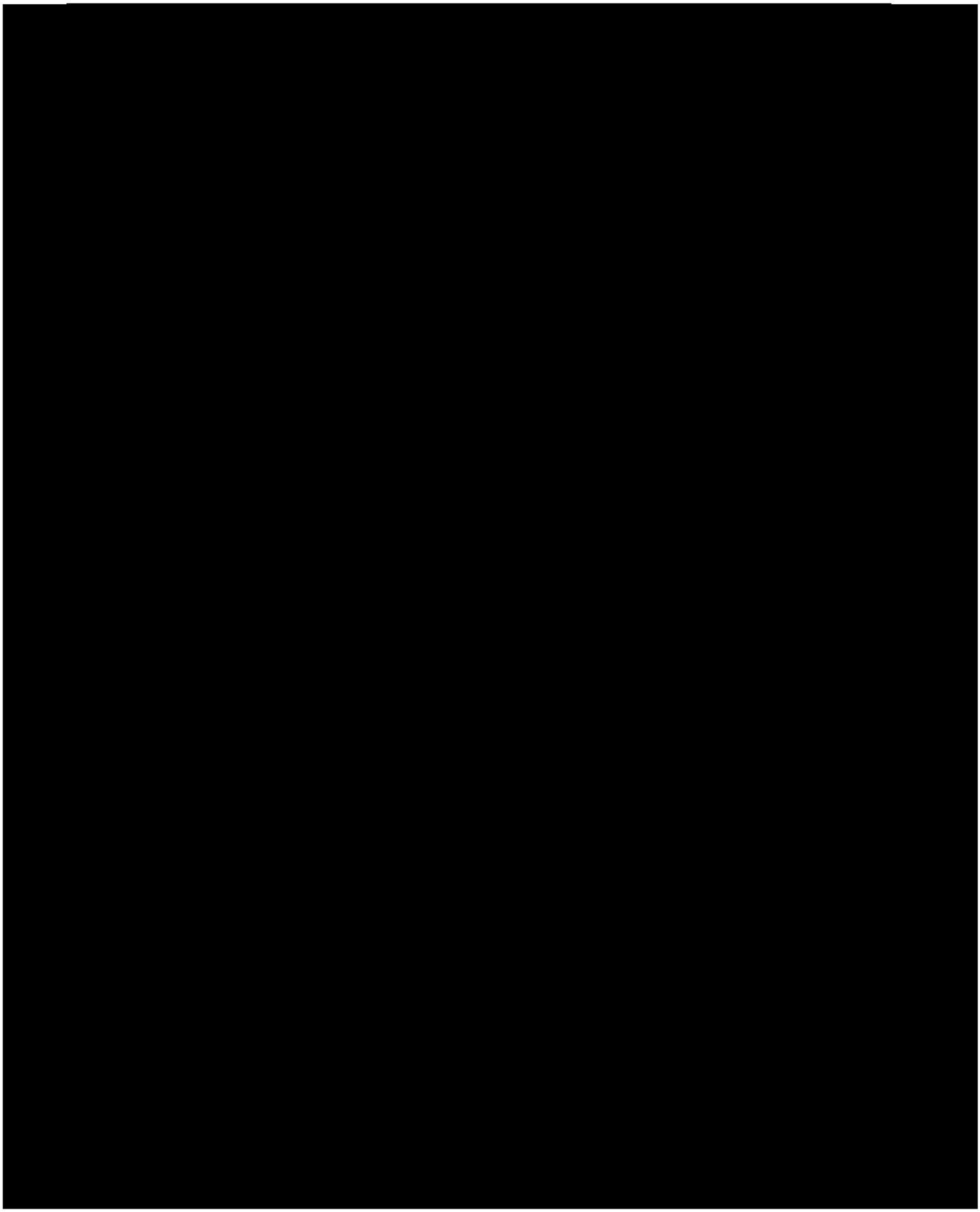
NPRS-A assessments scheduled between 00:00 and 06:00 may be skipped if the subject is sleeping. However, the 12-hour pain assessment must be completed even when the assessment falls between 00:00 and 06:00. Assessments will also be made at each follow up visit on Days 8, 15, and 29.

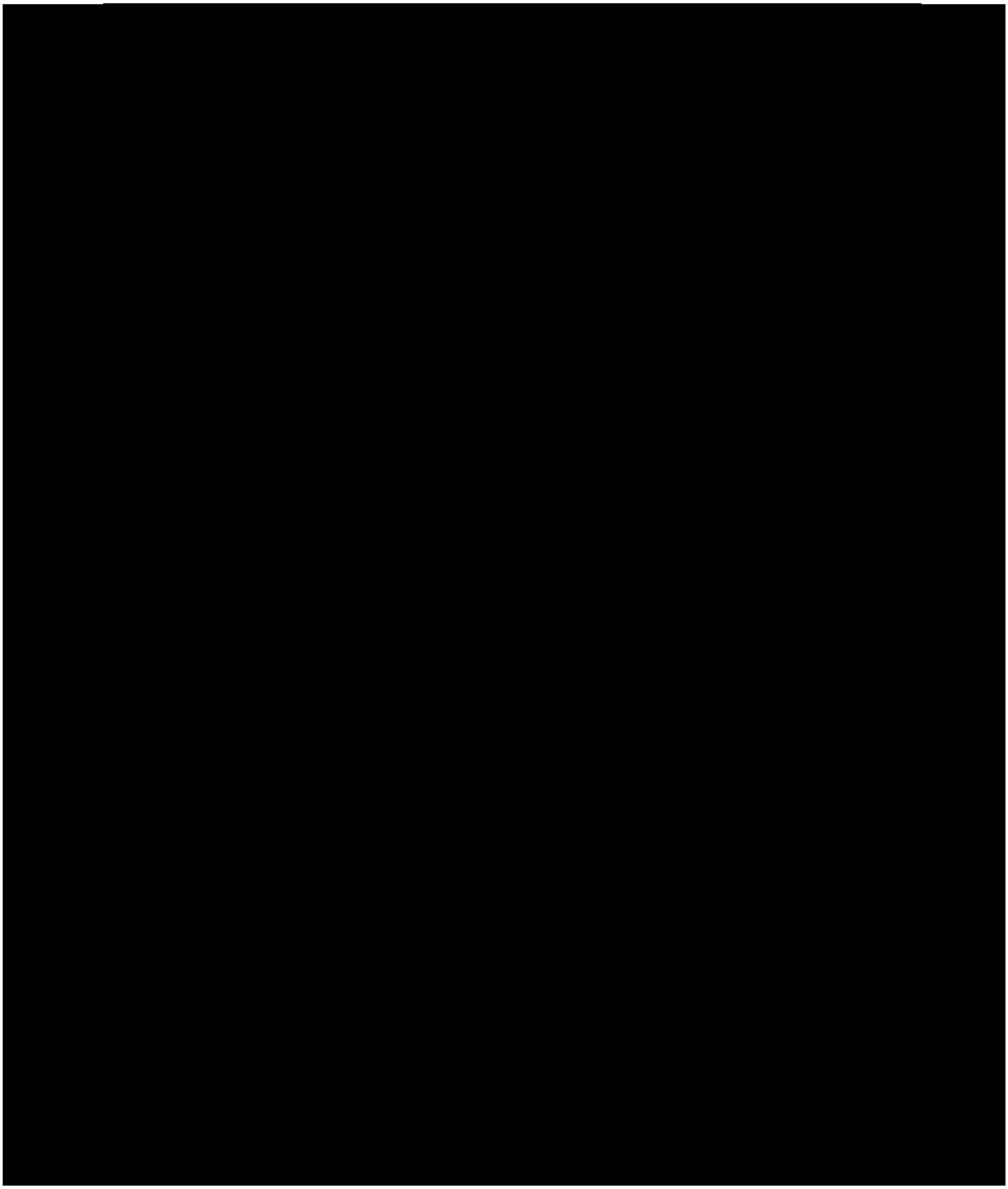
In the event rescue medication is used, an assessment of pain using the NPRS prior to administering rescue medication will be recorded. If subjects can not perform NPRS-A prior to taking rescue medication due to intolerable pain, this assessment may be omitted.

7.1.1.27 Patient Global Assessment (PGA) of Pain Control

The PGA will be evaluated at 96±2 hours (Days 5), and on Days 8, 15, and 29 (EOS/ET), using a 4-point categorical scale (Poor (0), Fair (1), Good (2), Excellent (3) (Appendix 6). Each subject will be asked the following question: “Overall, how well your pain has been controlled during the last 24 hours?” (Rothman 2009)

[redacted]





value should be recorded in the e-CRF. The largest FVC and largest FEV1 should be selected and reported in the eCRF, even if not from the same spirogram.

7.1.1.31 Take-home Diaries

Subjects will be encouraged to maintain two take-home diaries from discharge through EOS/ET, a Pain Assessment Diary and a Rescue Medication Diary. On Day 5, prior to discharge, site staff will review the diaries with subjects to ensure they understand how to complete them. Subjects will take the diaries home.

At follow-up visits on Days 8, 15 and 29, subjects will return with their diaries, and site staff will review them for completion. Subjects will return home with both diaries at the end of the visit on Days 8 and 15. Both diaries will be collected by the site at the EOS/ET visit (if applicable).

7.1.1.31.1 Pain Assessment Diary

On the mornings of Days 6-29 (inclusive), subjects will be encouraged to record their worst pain at rest (NPRS) and worst pain when sitting up in the bed unassisted at an angle of approximately 45 degrees or more, swinging legs out, putting feet down, standing up, and walking approximately 10 feet (NPRS-A) since the last assessment of their pain intensity in their take-home Pain Assessment Diary.

These scores will be captured once each in the morning (10:00 ±4 hours) using an 11-point NPRS and NPRS-A, where 0 is no pain, and 10 is the worst pain imaginable. Subjects will be encouraged to record additional pain assessment scores prior to taking rescue medication (Refer to Section 7.1.1.31.2). Completion of the Pain Assessment Diary will start on Day 6 (Appendix 7).

7.1.1.31.2 Rescue Medication Diary

Subjects will be encouraged to record all rescue medication usage in their take-home Rescue Medication Diary. See Section 7.2 for details regarding allowable rescue medication. Subjects will be instructed to complete an entry in their Pain Assessment Diary prior to taking rescue medication. Completion of the Rescue Medication Diary will start immediately following discharge on Day 5. In the event rescue medication is taken by the subject following discharge on Day 5, subjects will be encouraged to record their pain scores prior to taking the rescue medication (Appendix 8). In the event subjects can not perform NPRS-A due to intolerable pain, this assessment may be omitted.

[redacted]

[redacted]

7.3 Laboratory Procedures/Evaluations

7.3.1 Clinical Laboratory Evaluations

See Sections 7.1.1.14, 7.1.1.15, 7.1.1.16, 7.1.1.17, 7.1.1.18, and 7.1.1.19.

7.3.2 Specimen Preparation, Handling, and Storage

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

7.3.3 Specimen Shipment

See Laboratory Manual for instruction of specimen shipment.

7.3.4 Volume of Blood Collected

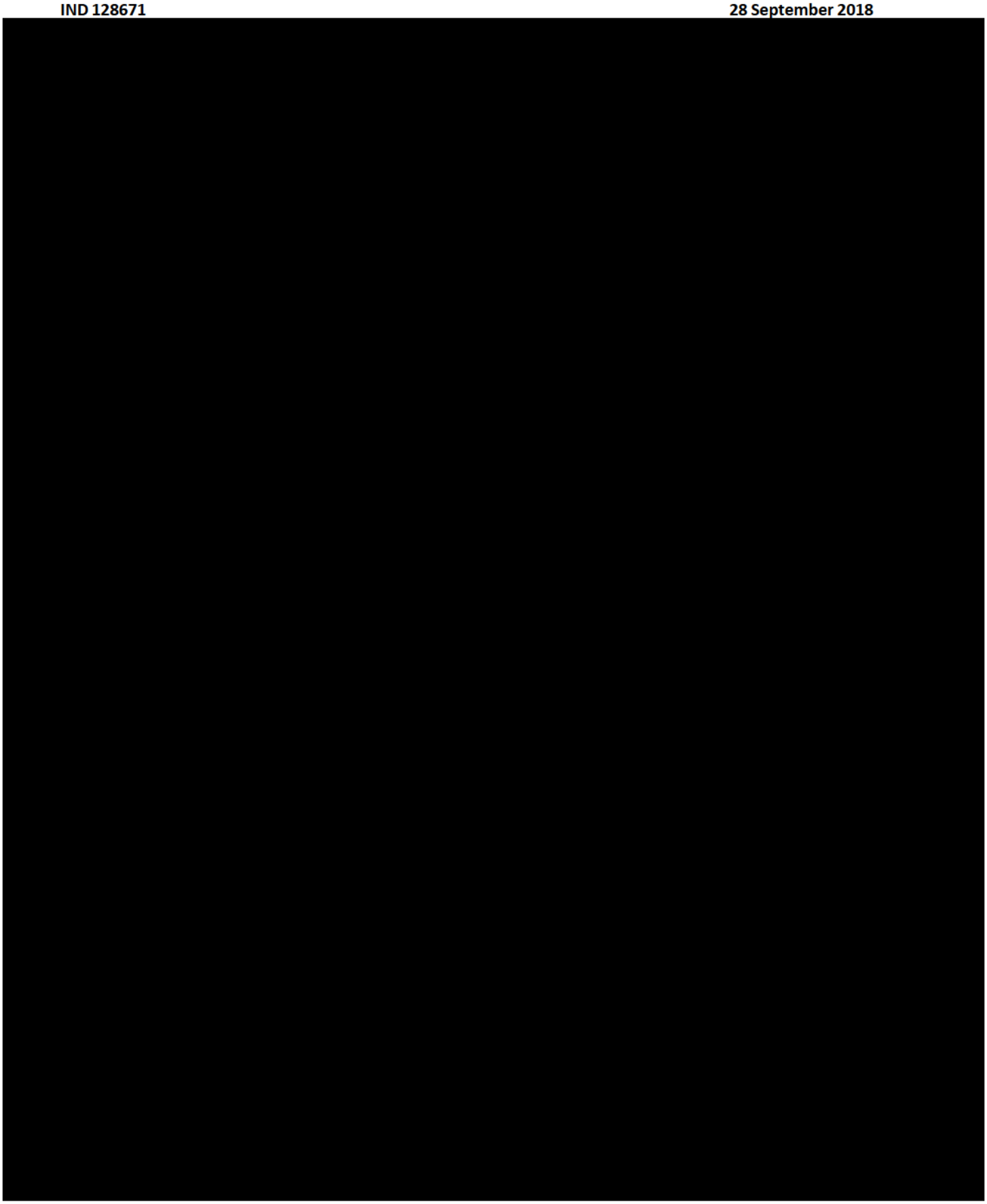
The estimated total blood volume collected throughout the study for clinical laboratory and immunogenicity tests is summarized in Table 5 and is expected to be approximately 72 mL.

Table 5 Total Blood Volume Collected for Each Patient

Test	Blood Sample Volume	Number of Tests	Total Volume
Hematology[1]	4 mL	4	16 mL
Serum chemistry[1], Lipids, Serum pregnancy test[2]	8.5 mL	4	34 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			72 mL

[1] Additional blood may be collected for safety laboratory tests, if clinically indicated
[2] Female of child bearing potential only

[redacted]



7.6 Prohibited Medications, Treatments, and Procedures

During the study, subjects may not use the following medications, or have following treatments/procedures performed in postoperative period throughout the EOS Visit.

- Any analgesics other than those specified in Section 7.5
- Use of botulinum neurotoxin treatment of any serotype
- Use of aminoglycosides
- Use of skeletal muscle relaxants
- Antiemetic's may be used to treat nausea, but may not be used prophylactically
- Ice may not be used as a non-medication therapy

7.7 Subject Restrictions

The following restrictions apply:

- Women of childbearing potential must agree to use either
  - a highly effective method of contraception with failures rates less than 1% per year such as implant, 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
  - 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).
- Men 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.
- Subjects must not donate blood or plasma from 30 days prior to Screening until the last follow-up visit (Day 29).

[redacted]

[redacted]

8.1.1 Definition of Adverse Events (AE)

Information about adverse events including those of Special Interest, 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, 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. Post-operative dyspnea, tachypnea, tachycardia, pneumonia, atelectasis, and fever are AEs of Special Interest, and will be closely monitored. Other examples of AEs 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

A life-threatening event 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 to participation in the research
- Research placing 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 Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (FDA 2007). Adverse events including those of Special Interest that do not have a corresponding term in the Guidance may be considered a systemic illness (Illness or clinical adverse event (as defined according to applicable regulations)), and will be assessed according to their impact on the participant's ability to perform daily activities as listed below:

- Mild (Grade 1): No interference with activity
- Moderate (Grade 2): Some interference with activity not requiring medical intervention
- Severe (Grade 3): Prevents daily activity and requires medical intervention
- Potentially Life threatening (Grade 4): ER visit or hospitalization

These four 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 including those of Special Interest, *regardless of relatedness 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)

All SAEs must be reported immediately (within 24 hours of discovery) by email to the Medical Monitor or designee. Calls related to SAEs should first be directed to the Medical Monitor or designee.

[redacted]

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

These events will 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 either a highly effective method of contraception with failures rates less than 1% per year or dual methods of contraception with overall failures rates less than 1% per year from the day of dosing until 3 months afterwards. Female subjects who underwent sterilization must have initiated the procedure at least 3 months prior to the day of dosing. Female subjects using oral contraception must have initiated treatment at least 2 months prior to the day of dosing.

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 Report/Outcome 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 Report/Outcome 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 SRC 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 SRC 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.

8.8 Risk Management of Prolonged Respiratory Compromise

Subjects may develop adverse effects indicative of spread of toxin, including a potentially prolonged course of respiratory compromise. If there were to be a significant respiratory event, the study site is located inside an acute care hospital. All subjects have access 24/7 to a fully-functional code blue team (including personnel expert in managing airways and respiratory emergencies). In addition, the study site is located 100 yards from the hospital emergency room so subjects can be quickly and easily transferred after stabilization by the code team.

If there is any significant respiratory event in the study i.e., profound hypoxia, respiratory depression, sedation etc., the study site and staff will follow usual standard of care which may include verbal and physical stimulation, high flow oxygen via face mask or big-mask, airway management, and calling for the hospital code team for immediate transfer to the emergency room once stabilized, if required. Subjects who do not respond to these measures may require endotracheal intubation and mechanical ventilation. Opiate reversal agents may be used in subjects who received opioid rescue medications.

In addition, systemic toxicity of EB-001 may be treated with a multi-valent anti-toxin.

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) will 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

The primary efficacy objective is to estimate the reduction of pain with EB-001, assessed as the difference in AUC for the NPRS pain scores over the 12-96 hours postsurgical period.

The null hypothesis is that the AUC for the EB-001 arm is greater than or equal to that of the placebo arm. The alternative hypothesis is that the AUC for EB-001 is smaller (indicating less pain) than that for placebo.

H_0: $AUC_{EB\text{-}001} \geq AUC_{Placebo}$

H_A: $AUC_{EB\text{-}001} < AUC_{Placebo}$

While not a formally powered study, a one sided hypothesis that the AUC for NPRS and NPRS-A will be used to inform the primary clinical hypothesis and support this objective.

10.3 Analysis 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.

Analyses of using the PP and Safety populations will analyze subjects according to the treatment received. In the event that the subject receives the wrong treatment, they will be excluded from the per protocol population.

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 including oxygen saturation level documented every 2 hours 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. The 95% confidence intervals may be shown as appropriate.

Statistical hypothesis testing will be performed, and one-sided p-values will be provided.

10.4.2 Analysis of the Primary Efficacy Endpoint(s)

The primary endpoint is the area under the curve (AUC) of subject's assessment of pain at rest using the Numeric Pain Rating Scale (NPRS) between 12 and 96-hour post-surgery ($AUC_{12\text{-}96}$).

The primary endpoint will be analyzed using Analysis of variance (ANOVA) techniques with Treatment as the independent variable. Comparisons of the treatment arms to placebo will be performed using Dunnet's test. Additional covariates may be included in the model as exploratory analyses. Specifics of the analysis methodology and exploratory analyses will be defined in the SAP.

10.4.3 Analysis of the Secondary Endpoint(s)

Continuous secondary endpoints will be analyzed using similar methods as specified for the primary endpoint. Categorical endpoints (such as PGA) will be summarized and treatments compared using Fishers Exact, Chi-Square, or Cochran-Mantel- Haenszel techniques as appropriate. All secondary analyses will be specified in the detailed Statistical Analysis Plan (SAP).

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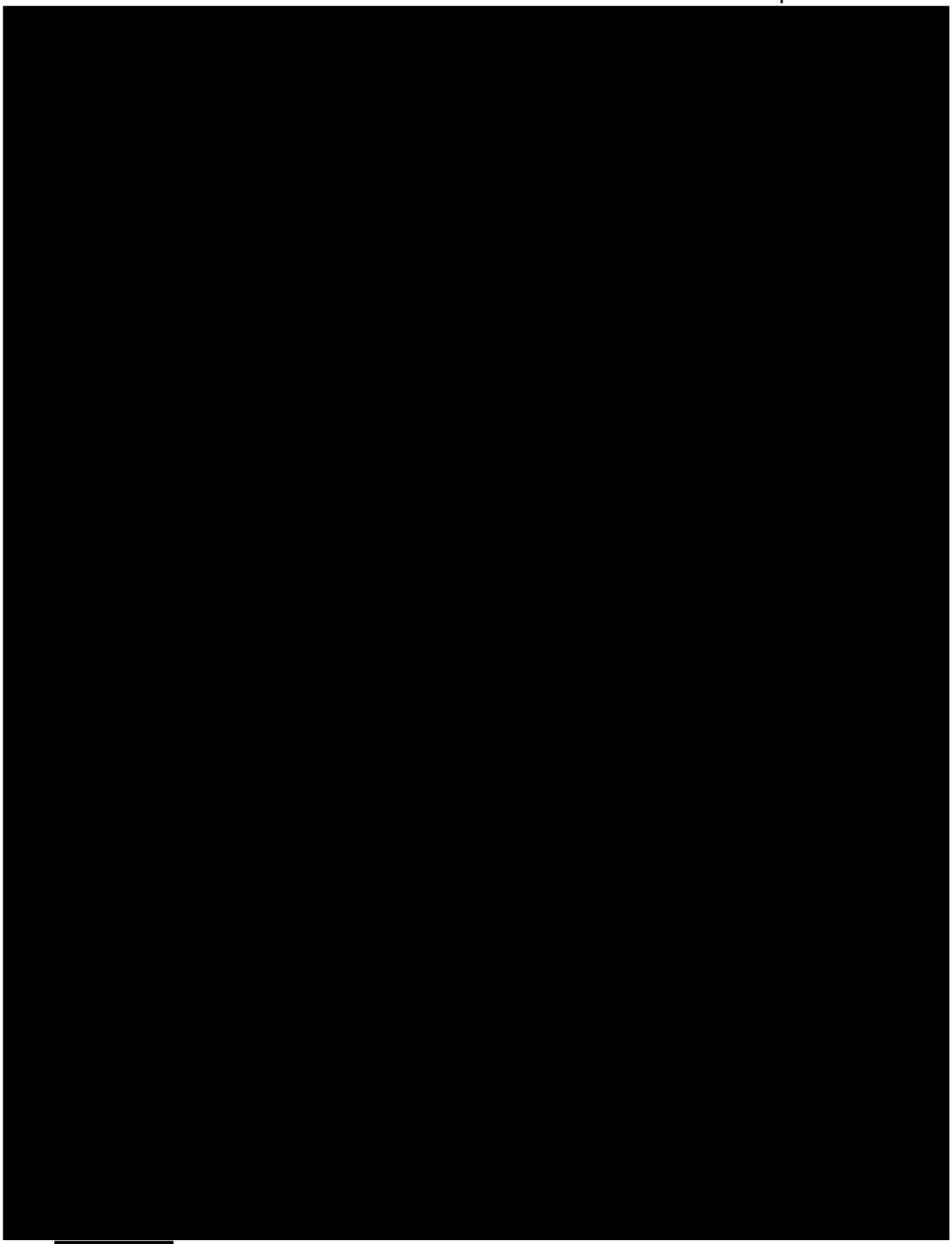

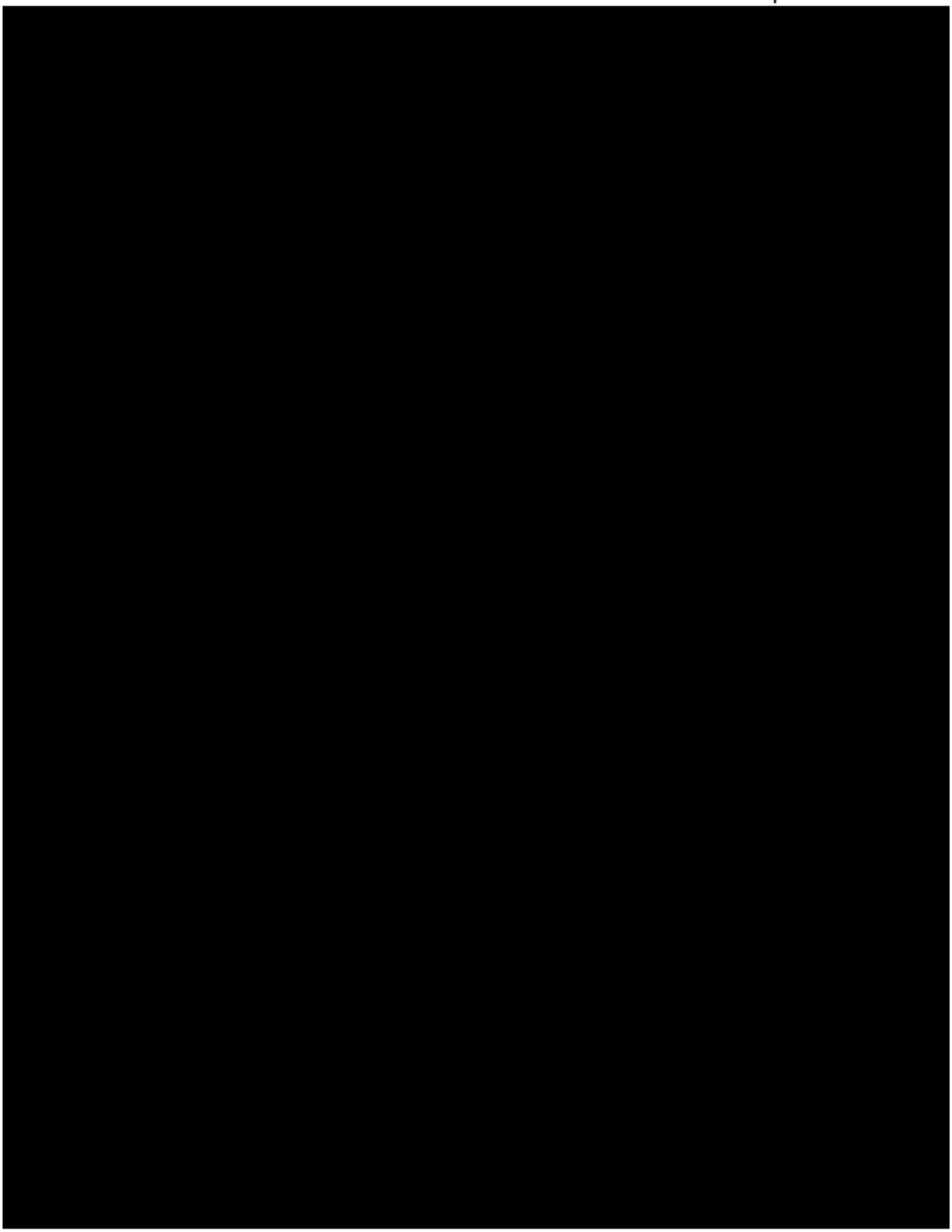

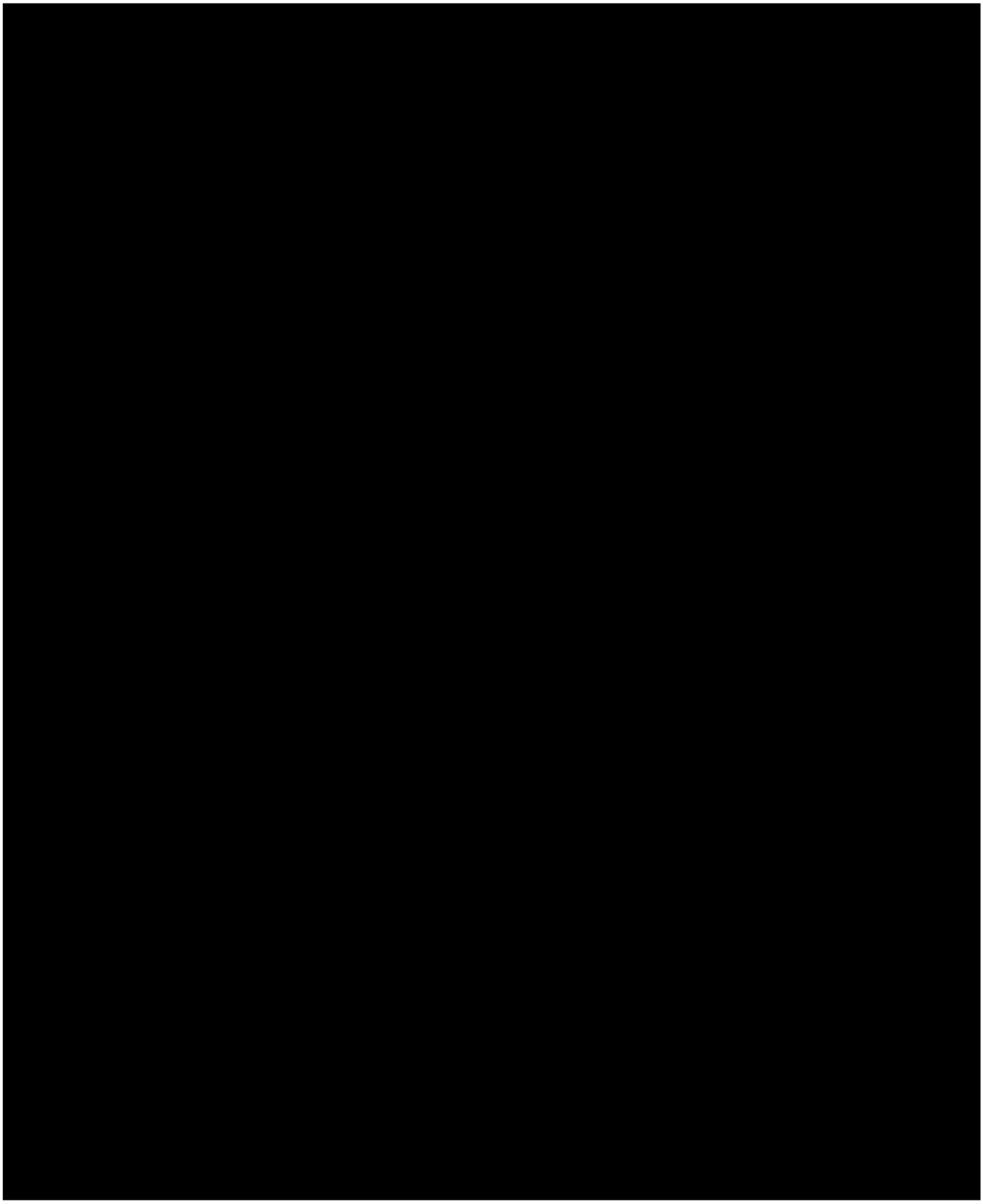

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10.5 Sample Size

Subjects will be allocated to receive either EB-001 or placebo in a 1:1 ratio in Cohorts 1-3, a 4:1 ratio in Cohort 4, a 2:1 ratio in Cohort 5, a 3:1 Ratio in Cohort 6, and a 5:1 ratio in Optional Cohort 7 in Stage 1 stratified by ethnicity (Hispanic and non-Hispanic) starting from Cohort 2. The planned total sample size in Stage 1 will be up to 40-58 subjects (up to 24-39 for EB-001 and up to 16-19 for placebo) (Figure 1). Optional Cohort 7 will be considered after dosing of subjects in Cohorts 1-6.

Subjects in each arm of Stage 2 will be randomly allocated to receive either EB-001 or placebo. The planned total sample size will be 66 subjects (44 for EB-001 and 22 for placebo) in Stage 2 stratified by ethnicity (Hispanic and non-Hispanic) (Figure 1).

Sample size of this study is not based on formal computations. However, 22 for active and 22 for placebo provide ~67% power. This power is based on one-sided alpha of 0.05, a mean baseline maximum pain score of 7.5, AUC12-96 ~440 with no drug effect, the delta AUC of 110 (drug and placebo difference), and SD of 170 AUC12-96.

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 in Stage 1 or various arms in Stage 2. Subjects are considered to be randomly assigned to the study when they are assigned to receive either EB-001 or placebo. Subjects will be randomly allocated to receive either EB-001 or placebo stratified by ethnicity (Hispanic and non-Hispanic) starting from Cohort 2. In Stage 1, subjects in cohorts 1, 2, and 3 will receive active or placebo drug in a 1:1 ratio, in which subjects in the sentinel groups of these cohorts will receive active or placebo drug in a 1:2 ratio. Subjects in cohort 4 will receive active or placebo drug in a 4:1 ratio. Subjects in cohort 5 will receive active or placebo drug in a 2:1 ratio. Subjects in cohort 6 will receive active or placebo drug in a 3:1 ratio, in which subjects in the sentinel group will receive active or placebo drug in a 1:1 ratio. In the optional Cohort 7 of Stage 1, subjects will receive active or placebo drug in a 5:1 ratio.

In Stage 2, there will be 2 doses of EB-001 (to be determined by the SRC after last dosing of last subject of Stage 1) and placebo in a 1:1:1 ratio for a total of 66 subjects.

Each cohort will have a fixed dose of EB-001. The study in both stages will be conducted in a blinded manner (single-blind in Stage 1, double-blind in Stage 2). 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, unless otherwise specified, 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.

In the 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 unblinded CRA 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/Unblinding of Sponsor Personnel

During this study, staff of Bonti and designee will be unblinded to treatment allocation in Stage 1, and blinded to treatment allocation in Stage 2, except as described in this section and in the Site Blinding Plan. The periodic SRC 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. Upon notification of an unblinding event, the Sponsor will assess the need for potentially removing the unblinded personnel from the trial.

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. Upon notification of an unblinding event, the Sponsor will assess the need for potentially removing the unblinded personnel from the trial. 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 randomization list. Details of the process to be followed are provided in the study manual(s) provided to the site. In the event that the treatment assignment is unblinded, Bonti or designee will be notified immediately that the blind has been broken, but will not be informed of the actual treatment assignment of the subject unless required for SAE reporting or other specific reason. Other study team personnel will remain blinded unless unblinding is necessary for the safety of the subject.

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 on subject blood samples to better understand or develop treatments for pectoral muscle pain, 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 or blue 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.

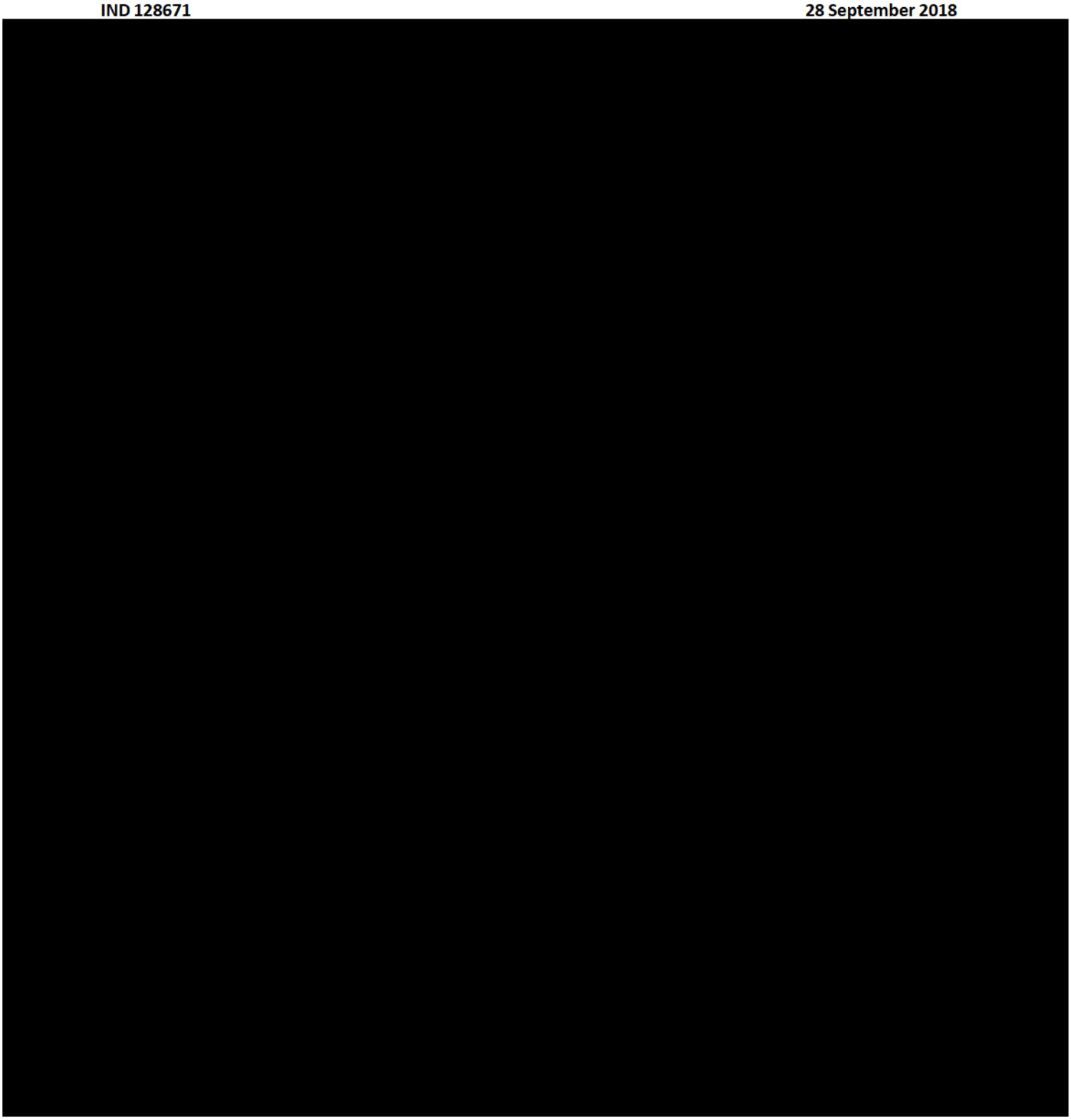
These practices are consistent with ICH E6:

- 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.



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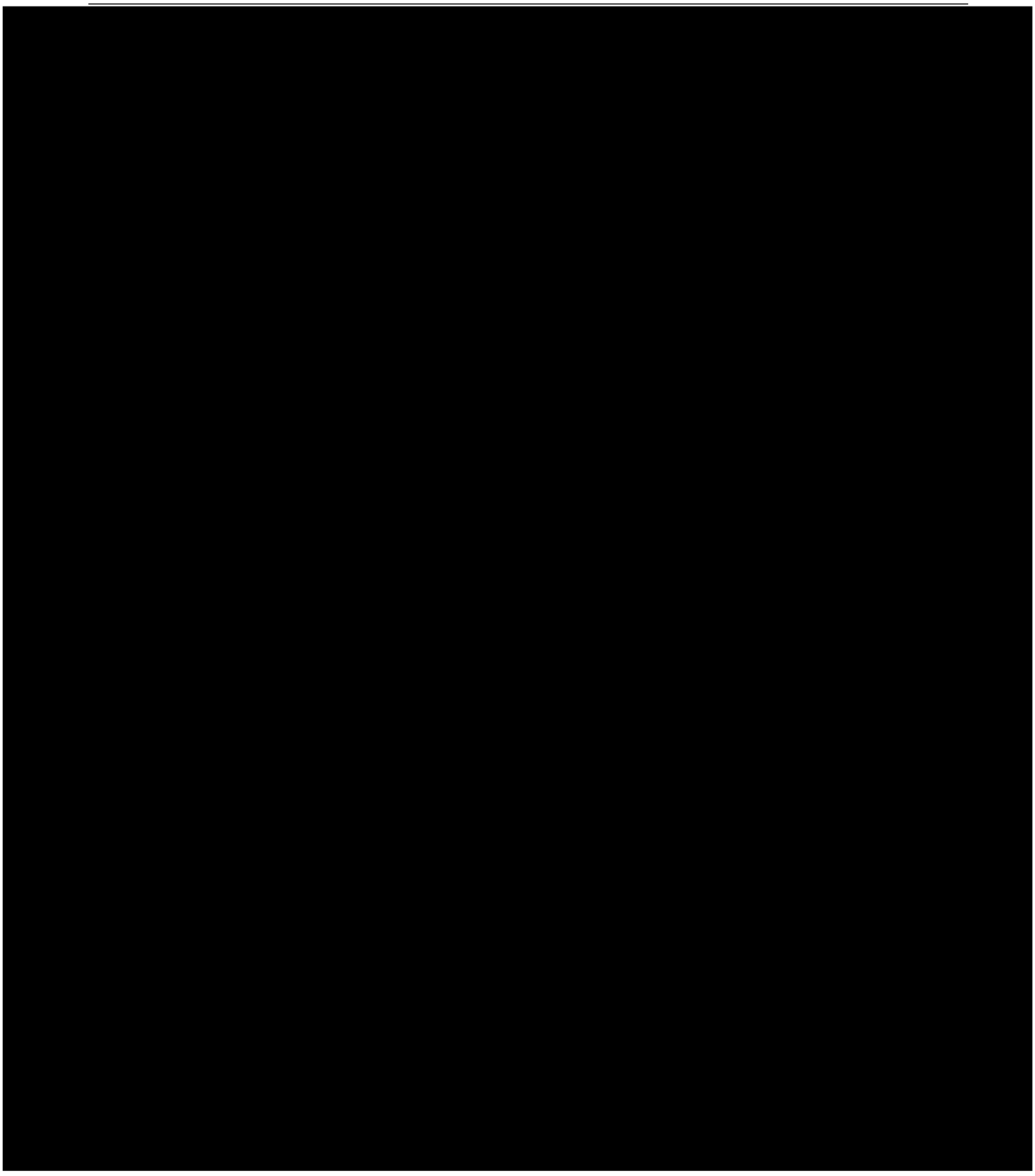

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