abbvie

Protocol for Study M22-974

Subject Satisfaction and Natural Outcomes Following BOTOX® Cosmetic Treatment in Subjects with Upper Facial Lines

VERSION:	3.0	DATE:	14 December 2023
SPONSOR:	AbbVie	PLANNED NUMBER OF SITES:	Approximately 10
ABBVIE INVESTIGATIONAL PRODUCT:	BOTOX® Cosmetic (Botulinum Toxin Type A)	EudraCT:	Not applicable

FULL TITLE: A Prospective, Multi-center, Open-label Study to Evaluate Subject Satisfaction and Natural Outcomes Following Administration of BOTOX® Cosmetic (Botulinum Toxin Type A) Purified Neurotoxin Complex in Subjects with Upper Facial Lines (Glabellar Lines, Lateral Canthal Lines, and Forehead Lines)

Incorporating Versions 1.0, 2.0, and 3.0

PRINCIPAL INVESTIGATOR(S): Investigator information on file at AbbVie.

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Application with the Competent Authority. Additional study contact information can be found in the Operations Manual (Appendix F).

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1 SYNOPSIS

Title: A Prospective, Multi-center, Open-label Study to Evaluate Subject Satisfaction and Natural Outcomes Following Administration of BOTOX® Cosmetic (Botulinum Toxin Type A) Purified Neurotoxin Complex in Subjects with Upper Facial Lines (Glabellar Lines, Lateral Canthal Lines, and Forehead Lines)	
Background and Rationale:	BOTOX Cosmetic is an acetylcholine release inhibitor and a neuromuscular blocking agent approved for aesthetic treatment of glabellar lines (GL), lateral canthal lines (LCL), and forehead lines (FHL). It is typical for some clinicians to administer lower than labeled doses of botulinum toxin to avoid a "frozen" look. The intent of this study is to evaluate subject satisfaction and natural outcomes following administration of 64 Units (U) of BOTOX Cosmetic for multiple upper facial areas (GL, LCL, and FHL).
Objective and Primary Endpoint:	The objective of this study is to evaluate subject satisfaction and natural outcomes following simultaneous treatment of multiple upper facial lines (GL, LCL, and FHL) with 64 U of BOTOX Cosmetic. The primary endpoint is the responder status of *Mostly satisfied* or *Very satisfied* on the Facial Line Satisfaction Questionnaire (FLSQ) Follow-up Item 4 at Day 30.
Investigators:	Multi-center
Study Sites:	Approximately 10 sites
Study Population and Number of Subjects to be Enrolled:	Approximately 100 subjects in general good health with moderate to severe GL, LCL, and FHL.
Investigational Plan:	This is a prospective, multicenter, open-label study. Eligible subjects will receive a single fixed dose of 64 U of BOTOX Cosmetic on Day 1. Subjects will be followed monthly for up to 180 days after treatment.
Key Eligibility Criteria:	Adult male or female; ≥ 18 years of age; moderate to severe GL, LCL, and FHL, as determined by the investigator at maximum contraction at Day 1
Study Drug and Duration of Treatment:	Single treatment of BOTOX Cosmetic (64 U)
Date of Protocol Synopsis:	14 December 2023

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2 INTRODUCTION

2.1 Background and Rationale

Why Is This Study Being Conducted?

BOTOX Cosmetic (onabotulinumtoxinA/Botulinum Toxin Type A) is an acetylcholine release inhibitor and a neuromuscular blocking agent indicated in adults for the temporary improvement in the appearance of moderate to severe glabellar lines (GL) associated with corrugator and/or procerus muscle activity, moderate to severe lateral canthal lines (LCL) associated with orbicularis oculi activity, and moderate to severe forehead lines (FHL) associated with frontalis muscle activity.[1,2]

The contraction of these facial muscles serves a role in communicating an emotional state, which influences both how an individual presents themselves as well as how they are perceived by others.[3] Over time, the repetitive contraction of facial muscles, along with degenerative changes due to aging, can negatively affect social interactions, social perceptions and, ultimately, self-esteem.[4]

Facial rejuvenation has been rapidly gaining ground to improve subject satisfaction with facial appearances, which is often described as achieving a "natural and relaxed" look. It is typical for some clinicians to start with less than labeled doses of botulinum toxin to avoid a "frozen" look. As more experience has been gained, botulinum toxin dosing, precise placement, and injection techniques have become more fine-tuned. As a result of these advances, healthcare professionals have learned that proper botulinum toxin procedures can yield a natural look that drives subject satisfaction.[5]

Although limited, several studies have focused on patient outcomes associated with the improvement in signs of aging. The HARMONY study investigated the impact of fillers and onabotulinumtoxinA in a pan-facial approach and demonstrated that minimally invasive, multimodal treatment resulted in improvements in FACE-Q scores and perceived age, indicating a high degree of patient satisfaction and a younger facial appearance.[6] In addition, when independent observers were provided with enrolled subjects' paired before and after treatment images, the independent observers reported that subjects appeared to have a higher social status, look nearly 5 years younger, more healthy, approachable, more attractive, and more successful at attracting others after treatment.[7]

Significant improvements in patient-reported outcomes (PROs) have also been reported in a Phase 3 study assessing the effectiveness of onabotulinumtoxinA treatment of GL, LCL, and FHL.[8] Subjects were highly satisfied with onabotulinumtoxinA treatment and reported significant improvement in emotional and psychological well-being compared to placebo. Subject satisfaction remained high throughout the 6 -month double-blind period, and improvements were maintained with repeated onabotulinumtoxinA treatment during the following 6 -month open-label period.

The purpose of this study is to evaluate subject satisfaction and natural outcomes following BOTOX Cosmetic treatment of upper facial areas (GL, LCL, and FHL).

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2.2 Benefits and Risks to Subjects

The clinical efficacy and safety profile of BOTOX Cosmetic has been demonstrated in multiple clinical trials across several indications, with favorable benefit risk profiles. In general, adverse reactions occur within the first few days to weeks following injection of BOTOX Cosmetic and, while generally transient, may have a duration of several months or, in rare cases, longer.

While Allergan (an AbbVie company) does not consider Coronavirus disease 2019 (COVID-19) to be a safety concern for BOTOX Cosmetic due to its mechanism of action and route of administration, the sponsor is monitoring COVID-19 events during the pandemic closely. A review of COVID-19 events for the period of 01 January 2019 through 31 December 2021 did not identify any new or significant safety findings for the subjects receiving BOTOX Cosmetic treatment. Overall, the clinical course and presentation of patients with COVID-19 infection coincident with BOTOX Cosmetic is consistent with what has been described for the general population. Considering the COVID-19 pandemic and based on the limited information to date, no additional risk to study participants is anticipated with the use of BOTOX Cosmetic.

For further details, please see findings from completed studies, including safety data in the current BOTOX Cosmetic investigator's brochure.

3 OBJECTIVES AND ENDPOINTS

3.1 Objectives, Hypotheses, and Estimands

Objective

The objective of this study is to evaluate subject satisfaction and natural outcomes following the administration of 64 U of BOTOX Cosmetic in subjects with upper facial lines (GL, LCL, and FHL).

Clinical Hypothesis

Single treatment of upper facial lines with BOTOX Cosmetic at 64 U can lead to subject satisfaction and natural outcomes.

Estimands

The estimand corresponding to the primary endpoint is as follows:

- The proportion of subjects receiving treatment of BOTOX Cosmetic 64U who achieve the responder status of *Mostly satisfied* or *Very satisfied* on the Facial Line Satisfaction Questionnaire (FLSQ) Item 4 at the Day 30 assessment in the modified intention-to-treat (mITT) population. Subjects who have any intercurrent event resulting in not having a Day 30 assessment will not be included.

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The estimand corresponding to the secondary endpoint is as follows:

- The mean change from baseline in subject assessment based on Rasch-transformed score of FACE-Q Psychological Function at the Day 30 assessment for subjects who receive BOTOX Cosmetic 64 U in the mITT population. Subjects who have any intercurrent event resulting in not having a Day 30 assessment will not be included.

3.2 Primary Endpoint

The primary endpoint is the responder status of *Mostly satisfied* or *Very satisfied* on the Facial Line Satisfaction Questionnaire (FLSQ) Follow-up Item 4 at Day 30.

3.3 Secondary Endpoint

Secondary endpoint is

- Change from baseline in subject's assessment based on Rasch-transformed score of FACE-Q Psychological Function scale at Day 30

3.4 Additional Endpoints

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3.5 Safety Endpoints

The safety endpoint is the incidence of adverse events (AEs).

4 INVESTIGATIONAL PLAN

4.1 Overall Study Design and Plan

This is a 6-month, prospective, multicenter, open-label study to evaluate subject satisfaction and natural outcomes following the administration of BOTOX Cosmetic 64 U for the treatment of upper facial lines.

The study will enroll approximately 100 subjects with moderate to severe GL, LCL, and FHL as assessed by the investigator. Out of the approximately 100 enrolled subjects:

- approximately 20% of the study population will be treatment naïve to any botulinum toxin of any serotype for any indication,
- approximately 20% of the study population will be self-identified as male,

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- approximately 20% of the study population will be self-identified as Asian, and
- approximately 20% of the study population will have Fitzpatrick skin phototypes of IV, V, or VI.

A review of individual site data will be conducted once a sufficient number of subjects has been enrolled. The site will be permitted to enroll additional subjects upon sponsor approval. This process may be repeated as needed.

On Day 1, after subjects are verified to meet all eligibility criteria and have completed all baseline study procedures, they will receive 64 U of BOTOX Cosmetic. Each subject will receive a total of 16 injections (0.1 mL or 4 U of BOTOX Cosmetic per injection), with 5 injections in the glabellar complex, 3 injections in each of the lateral canthal area (6 total injections), and 5 injections in the frontalis muscle.

There are seven in-clinic visits: screening/baseline/treatment (Day 1), post-treatment follow-up visits (Days 30, 60, 90, 120, 150), and study exit (Day 180 or Early Exit). The study schema of the study is shown in Figure 1.

Further details on study procedures are located in the Operations Manual (Appendix E).

Figure 1. Study Schema

4.2 Discussion of Study Design

Choice of Control Group

This is an open-label study. There is no separate control group.

Appropriateness of Measurements

The primary efficacy measure used in this study (FLSQ) is a validated measure. Allergan has also developed and validated upper facial line severity scales (AGLSS, LCLSS, and FHLSS) in accordance with the United States Food and Drug Administration requirement. All efficacy-related measurements in this study are standard for assessing facial aesthetics correction (for GL, LCL, and FHL). All clinical procedures in this study are standard and generally accepted.

Suitability of Subject Population

The study population will include male and female adults with moderate to severe GL, LCL, and FHL at maximum contraction as assessed by investigators using the AGLSS, LCLSS, and FHLSS, respectively. To avoid confounding the study results, washout from prior facial aesthetic treatments is required as described in the eligibility criteria.

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Selection of Doses in the Study

BOTOX Cosmetic is currently approved for aesthetic treatment of GL, LCL and FHL. The total dose, dilution, injection pattern, and route of administration will follow the approved label, and each eligible subject will receive a fixed dose of 64 U of BOTOX Cosmetic on Day 1 (20 U to the glabellar complex, 24 U to the lateral canthal areas, and 20 U to the frontalis muscles).

5 STUDY ACTIVITIES

5.1 Eligibility Criteria

Subjects must meet all of the following criteria in order to be included in the study. Anything other than a positive response to the questions below will result in exclusion from study participation.

Rescreening is not allowed for individuals who do not meet Eligibility Criterion #8 (listed below). Any attempt to rescreen a subject must only occur after agreement with the sponsor. Rescreening can only occur once for any given potential subject.

Consent

1. Subjects must voluntarily sign and date an informed consent, approved by an independent ethics committee (IEC)/institutional review board (IRB), prior to the initiation of any screening or study-specific procedures.

2. Subjects are willing and able to comply with procedures required in this protocol.

3. Subjects must agree to have photos and videos taken during study visits. Subjects must consent to having photographs and videos taken for research/educational purposes but may still participate if he/she declines use of the photographs and videos for other purposes.

Demographic and Subject Characteristics

4. Adult male or female, at least 18 years old, at the time of signing the informed consent.

5. Subjects must have sufficient visual acuity without the use of eyeglasses (contact lens use acceptable) to accurately assess their facial wrinkles.

6. Subject must be able to follow study instructions and complete study assessment tools without any assistance or alterations to the assessment tools and complete all required study procedures.

7. Subject must be in good health as determined by medical history, vital signs, and investigator's judgement, including no known active pandemic infection.

Condition

8. Subject meets all of the following criteria prior to dosing on Day 1, as determined by the investigator:

- GL of Moderate (Grade 2) to Severe (Grade 3) on AGLSS at maximum contraction.

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- LCL of Moderate (Grade 2) to Severe (Grade 3) bilaterally (severity identical on both sides) on LCLSS at maximum contraction.
- FHL of Moderate (Grade 2) to Severe (Grade 3) on FHLSS at maximum contraction.

Subject History

9. No history of known immunization or hypersensitivity to any botulinum toxin serotype.

10. No history of an allergic reaction or significant sensitivity to constituents of the study drug (and its excipients) and/or other products in the same class.

11. No history of clinically significant (per investigator's judgment) drug or alcohol abuse within the last 6 months.

12. No presence of tattoos, jewelry, or clothing which obscures or interferes with the target area of interest and cannot be removed.

14. No history of clinically significant medical conditions or presence of current uncontrolled systemic disease or any other reasons, in the investigator's opinion, that may put the subject at significant risk, may confound the study results, or may interfere significantly with participation in the study.

15. Subjects cannot be directly or indirectly involved in the conduct and administration of this study as a principal investigator, sub-investigator, study coordinator, or other study staff member; or employee of the sponsor, or a first-degree family member, significant other, or relative residing with one of the above persons involved directly or indirectly in the study.

16. No known active severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. If a subject has signs/symptoms suggestive of SARS-CoV-2 infection, the subject must have a negative molecular (e.g., polymerase chain reaction [PCR] test result). Note: SARS-CoV-2 diagnostic tests should be applied following local requirements/recommendations.

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17. Subjects who do not meet SARS-CoV-2 infection eligibility criteria must be screen failed and may only rescreen after they meet the following SARS-CoV-2 infection viral clearance criteria:

- At least 10 days since first positive test result have passed in asymptomatic subjects or at least 10 days since recovery, defined as resolution of fever without use of antipyretics and improvement in symptoms

20. No history of any botulinum neurotoxin of any serotype for any indication within 6 months prior to Day 1.

21. No clinically significant abnormal vital signs at Day 1.

Contraception

22. Female subjects of childbearing potential must have a negative urine pregnancy test at Day 1 prior to study treatment.

23. Female subjects of childbearing potential must practice at least 1 protocol-specified method of birth control that is effective from study drug administration (Day 1) through a minimum of 60 days or until last study follow-up visit, whichever is longer. Female subjects of nonchildbearing potential do not need to use birth control.

24. Female subject who is not pregnant or breastfeeding and is not considering becoming pregnant or donating eggs from study drug administration (Day 1) through a minimum of 60 days after study drug administration or until last study follow-up visit, whichever is longer.

Concomitant Medications or Procedures

25. No anticipated need for treatment with botulinum toxin of any serotype for any indication during the study (other than study drug).

26. No anticipated need for surgery or overnight hospitalization during the study.

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27. No plans for an extended absence away from the immediate area of the study site that would preclude them from returning for all protocol-specified study visits.

28. In the investigator's opinion, subject is able and willing to maintain his or her standardized skin care regimen throughout the study period.

29. Subject must not have been treated with any investigational drug within 30 days or 5 half-lives of the drug (whichever is longer) prior to the first dose of study drug or is currently enrolled in another clinical study or was previously enrolled in this study.

5.2 Contraception Recommendations

Contraception Requirements for Females

Subjects must follow the following contraceptive guidelines as specified:

- Females, Non-Childbearing Potential

  Females do not need to use birth control during or following study drug treatment if considered of non-childbearing potential due to meeting any of the following criteria:

  1. Premenopausal female with permanent sterility or permanent infertility due to one of the following:
     - Permanent sterility due to a hysterectomy, bilateral salpingectomy, bilateral oophorectomy.
     - Non-surgical permanent infertility due to Mullerian agenesis, androgen insensitivity, or gonadal dysgenesis; investigator discretion should be applied to determining study entry for these individuals.
  2. Postmenopausal female
     - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
       - A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormone replacement therapy. However, in the absence of 12 months of amenorrhea, confirmation with more than 1 FSH measurement is required.
         - Females on hormone replacement therapy and whose menopausal status is in doubt, as determined by the investigator, will be required to use one of the non-hormonal (highly) effective contraception methods if they wish to continue their hormone replacement therapy during the study. Otherwise, they must discontinue hormone replacement therapy to allow confirmation of postmenopausal status before study enrollment.

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- Females, of Childbearing Potential
  - Females of childbearing potential must avoid pregnancy from study drug administration (Day 1) through a minimum of 60 days after the last dose or until last study follow-up visit, whichever is longer.
  - Females must commit to one of the following methods of birth control:
    - Combined (estrogen and progestogen containing) hormonal birth control (oral, intravaginal, transdermal, injectable) associated with inhibition of ovulation-initiated at least 30 days prior to Day 1.
    - Progestogen-only hormonal birth control (oral, injectable, implantable) associated with inhibition of ovulation initiated at least 30 days prior to Day 1.
    - Bilateral tubal occlusion/ligation (can be via hysteroscopy, provided a hysterosalpingogram confirms success of the procedure).
    - Intrauterine device (IUD).
    - Intrauterine hormone-releasing system.
    - Vasectomized partner (provided the partner has received medical confirmation of the surgical success of the vasectomy and is the sole sexual partner of the trial subject).
    - Practice true abstinence, defined as: Refraining from heterosexual intercourse when this is in line with the preferred and usual lifestyle of the subject (periodic abstinence [e.g., calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable).
    - Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action, initiated at least 30 days prior to Day 1.
    - Male or female condom with or without spermicide.
    - Cap, diaphragm, or sponge with spermicide.
    - A combination of male condom with cap, diaphragm, or sponge with spermicide (double barrier method).

Contraception recommendations related to use of concomitant therapies prescribed should be based on the local label.

5.3 Prohibited Medications and Procedures

The decision to administer a prohibited medication/treatment during the study period is done with the safety of the subject as the primary consideration. When possible, the sponsor is to be notified before the prohibited medication/treatment is administered.

In addition to the medications listed in the eligibility criteria, no other facial cosmetic procedures or treatments are to be performed throughout the duration of the study. Prohibited treatments and procedures include, but are not limited to:

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All other investigational drugs are prohibited.

5.4 Prior and Concomitant Procedures

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the subject is receiving at the time of enrollment or receives during the study must be recorded from 30 days prior to the study drug administration through the study exit. See below for details on special handling for the COVID-19 vaccine.

The use of any medication during the study (including prescription or over-the-counter medication, vitamins, and/or herbal supplements) is to be recorded on the subject's electronic case report form (eCRF) at each visit along with the reason the medication is taken, dates of use, and dosing regimen. Concomitant medications and concurrent procedures will also be collected at each visit.

Study site personnel should notify the sponsor immediately if a subject uses a concomitant medication or has a concurrent procedure that is prohibited per protocol (see Section 5.3). Subjects who use prohibited concomitant medications or have a prohibited concurrent procedure may be discontinued at the discretion of the investigator or sponsor. Concomitant medications and concurrent procedures will be tabulated and listed.

Non-live vaccines may be used during the study, if not contraindicated or medically inappropriate. When possible, study drug should be given at least ± 7 days from vaccine administration.

Co-administration of aminoglycosides or agents that could interfere with neuromuscular transmission (e.g., curare-like agents) or muscle relaxants are to be used with caution as the effects of the toxin, theoretically, could be potentiated.

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Systemic and topical hormones and their derivatives (e.g., sex steroids - androgens, estrogens, progesterone) should be maintained throughout the study period to avoid changes in skin, including but not limited to:

- Oral birth control
- IUDs/implants/injections
- Oral supplements including testosterone & estrogens and their derivatives, dehydroepiandrosterone (DHEA), etc.
- Topicals (anywhere on the body) including testosterone & estrogens and their derivatives, DHEA, etc.
- Androgel, Axiron, Testim, Fortesta, Vogelxo
- Emepelle (methyl estradiolpropanoate), Rejuvenate, All Natural Bioidentical Estradiol, Emerita Phytoestrogen

Subjects should maintain their skin care regimen throughout the study period.

Any questions regarding concomitant or prior procedures should be raised to the AbbVie non-emergency contact. Information regarding potential drug interactions with BOTOX Cosmetic can be located in the BOTOX Cosmetic Investigator's Brochure.

Subjects must be able to safely discontinue any prohibited medications as described in the eligibility criteria. Subjects must consent to the study prior to discontinuing any prohibited medications for the purpose of meeting study eligibility.

COVID-19 Pandemic-Related Vaccination Guidance

Select non-live vaccines (e.g., messenger ribonucleic acid, non-replicating viral vector, protein subunit, etc.) to prevent SARS-CoV-2 infection may be administered during the study, as long as components of the vaccine are not contraindicated.

The decision to receive a locally available vaccine should be based on local guidance and an individual discussion between the treating physician and the subject.

The potential impact of BOTOX Cosmetic on SARS-CoV-2 vaccination is unknown. Therefore, study drug should be administered as follows:

- Study drug is preferred to be administered, when possible, at least ± 14 days from the SARS-CoV-2 vaccine administration.

Note: The above guidance applies to all SARS-CoV-2 vaccine doses given as part of the complete vaccination course.

These recommendations may be subject to change based on the evolving knowledge around the use of SARS-CoV-2 vaccines and as more data are collected in real-world scenarios and clinical trials.

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Any SARS-CoV-2 vaccine information must be documented on the COVID-19 vaccine eCRF. Refer to the Operations Manual for instructions on reporting any AEs associated with the COVID-19 vaccine.

5.5 Withdrawal of Subjects and Discontinuation of Study

A subject may voluntarily withdraw or be withdrawn from the study at any time for reasons including, but not limited to, the following:

- The investigator believes it is in the best interest of the subject.
- The subject requests withdrawal from the study.
- Subject is significantly noncompliant with study procedures.

This is a single treatment study. Treatment will be administered on Day 1 only. In case of pregnancy or AE during the study after study treatment is provided, the subject should continue in the study for safety follow-up.

In case the subject has a desire to end his/her participation, or is discontinued for any reason, the Early Exit Visit procedures should be completed.

For subjects to be considered lost to follow-up, reasonable attempts must be made to obtain information on the subject's final status. At a minimum, 2 telephone calls must be made and 1 certified letter must be sent and documented in the subject's source documentation.

AbbVie may terminate this study prematurely, either in its entirety or at any site. The investigator may also stop the study at his/her site if he/she has safety concerns. If AbbVie terminates the study for safety reasons, AbbVie will promptly notify the investigator.

COVID-19 Pandemic-Related Acceptable Protocol Modification

During the COVID-19 pandemic, it has been necessary to employ mitigation strategies to enable the investigator to ensure subject safety and continuity of care. Acceptable mitigation strategies are identified and included in the Operations Manual (Appendix E).

The investigator should contact the sponsor's non-emergency medical contact before discontinuing a subject from the study for a reason other than described in the protocol to ensure all acceptable mitigation steps have been explored.

5.6 Follow-Up After Subject Discontinuation of Study Drug or from Study

To minimize missing data for efficacy and safety assessments, subjects should continue to be followed for all regularly scheduled visits, unless subjects have decided to discontinue the study participation entirely (withdrawal of informed consent). Subjects should be advised on the continued scientific importance of their data.

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If a subject prematurely discontinues study participation (withdrawal of informed consent), the procedures outlined for the Early Exit visit should be completed as soon as possible, preferably within 2 weeks. In addition, if subject is willing, a 30-day follow-up phone call after the last dose of study drug may be completed to ensure all treatment-emergent adverse events (TEAEs)/serious adverse events (SAEs) have been resolved.

5.7 Study Drug

Study drugs refer to drugs that are used (or can be used) in this study to assess the safety and the efficacy of the Investigational Product. Investigators will assess the relationship of adverse events to the use of study drugs.

Study drug will be provided by AbbVie and administered on Day 1, and subjects will not be retreated (Table 1).

Table 1. Study Drug Information

Product	Mode of Administration	Formulation	Total Treatment Dose	Manufacturer
BOTOX Cosmetic (100 U/vial)	Intramuscular Injection	Powder for solution	64 U	Allergan

Study drug provided by AbbVie should not be substituted or alternately sourced unless otherwise directed by AbbVie. Upon receipt, study drug should be stored as specified on the package insert and kept in a secure location. Study drug will only be used for the conduct of this study.

Additional information regarding the study drug and administration is available in the Operations Manual (Appendix E).

5.8 Randomization/Drug Assignment

All subjects who provide informed consent will be assigned a unique subject identification number at the Day 1 visit. For subjects who rescreen, the subject identification number assigned at the initial Day 1 visit should be used.

Randomization is not applicable since this is an open-label study.

5.9 Protocol Deviations

AbbVie does not allow intentional/prospective deviations from the protocol except when necessary to eliminate an immediate hazard to study subjects. The investigator is responsible for complying with all protocol requirements, written instructions, and applicable laws regarding protocol deviations. If a protocol deviation occurs (or is identified, including those that may be due to the COVID-19 pandemic), the investigator is responsible for notifying IEC/IRB, regulatory authorities (as applicable), and AbbVie.

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5.10 Data Monitoring Committee

A data monitoring committee is not planned for this study.

6 SAFETY CONSIDERATIONS

6.1 Complaints and Adverse Events

Complaints

A complaint is any written, electronic, or oral communication that alleges deficiencies related to the physical characteristics, identity, quality, purity, potency, durability, reliability, safety, effectiveness, or performance of a product/device. Complaints associated with any component of this investigational product must be reported to AbbVie.

Product Complaint

A product complaint is any complaint related to the biologic or drug component of the product or to the medical device component(s).

For a product this may include, but is not limited to, damaged/broken product or packaging, product appearance whose color/markings do not match the labeling, labeling discrepancies/inadequacies in the labeling/instructions (e.g., printing illegible), missing components/product, device damage or not working properly, or packaging issues.

Product complaints concerning the investigational product and/or device must be reported to AbbVie within 24 hours of the study site's knowledge of the event.

Reporting will be done via electronic data capture (EDC). The date the product complaint details are entered into EDC and the form is saved represents the date reported to AbbVie. A back-up paper form will be provided for reporting complaints related to unassigned product or in the event of an EDC system issue. If a back-up paper form is used, the date the form is emailed to RD_PQC_QA@abbvie.com represents the date reported to AbbVie.

All follow-up information is to be reported to the sponsor (or an authorized representative) and documented in source as required by the sponsor. Product complaints associated with AEs will be reported in the study summary. All other complaints will be monitored on an ongoing basis. Product complaints occurring during the study will be followed up to a satisfactory conclusion.

Medical Complaints/Adverse Events and Serious Adverse Events

An AE is defined as any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, regardless of whether the event is considered causally related to the use of the product.

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Such an event can result from use of the drug as stipulated in the protocol or labeling, as well as from "special situations" such as accidental or intentional overdose, medication error, occupational or accidental exposure, off-label use, drug abuse, drug misuse, or drug withdrawal, all which must be reported whether associated with an AE or not. Any worsening of a pre-existing condition or illness is considered an AE. Worsening in severity of a reported AE should be reported as a new AE. Laboratory abnormalities and changes in vital signs are considered to be AEs only if they result in discontinuation from the study, necessitate therapeutic medical intervention, and/or if the investigator considers them to be AEs.

The investigators will monitor each subject for clinical and laboratory evidence of AEs on a routine basis throughout the study. All AEs will be followed to a satisfactory conclusion.

An elective surgery/procedure scheduled to occur during a study will not be considered an AE if the surgery/procedure is being performed for a pre-existing condition and/or the surgery/procedure has been pre-planned prior to study entry. However, if the pre-existing condition deteriorates unexpectedly during the study (e.g., surgery performed earlier than planned), then the deterioration of the condition for which the elective surgery/procedure is being done will be considered an AE.

If an AE, whether associated with study drug or not, meets any of the following criteria, it is to be reported to AbbVie clinical pharmacovigilance as a SAE within 24 hours of the site being made aware of the SAE (refer to Section 4.2 of the Operations Manual for reporting details and contact information):

Death of Subject	An event that results in the death of a subject.
Life-Threatening	An event that, in the opinion of the investigator, would have resulted in immediate fatality if medical intervention had not been taken. This does not include an event that would have been fatal if it had occurred in a more severe form.
Hospitalization or Prolongation of Hospitalization	An event that results in an admission to the hospital for any length of time or prolongs the subject's hospital stay. This does not include an emergency room visit or admission to an outpatient facility.
Congenital Anomaly	An anomaly detected at or after birth, or any anomaly that results in fetal loss.
Persistent or Significant Disability/Incapacity	An event that results in a condition that substantially interferes with the activities of daily living of a study subject. Disability is not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle).

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Important Medical Event Requiring Medical or Surgical Intervention to Prevent Serious Outcome	An important medical event that may not be immediately life-threatening or result in death or hospitalization but based on medical judgment may jeopardize the subject and may require medical or surgical intervention to prevent any of the outcomes listed above (e.g., death of subject, life threatening, hospitalization, prolongation of hospitalization, congenital anomaly, or persistent or significant disability/incapacity). Additionally, any elective or spontaneous abortion or stillbirth is considered an important medical event along with any suspected transmission of an infectious agent via a medicinal product if no other serious criterion is applicable. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

All adverse events from the time of study drug administration will be collected for at least 30 days or until the last follow-up visit, whichever is longer, whether solicited or spontaneously reported by the subject. After 30 days following the last dose of study drug or last follow-up visit, whichever is longer, only spontaneously reported SAEs will be collected (nonserious AEs will not be collected). In addition, study procedure-related serious and nonserious adverse events will be collected from the time the subject signs the study-specific informed consent.

The following definitions will be used for Serious Adverse Reactions (SAR) and Suspected Unexpected Serious Adverse Reaction (SUSAR):

SAR	Defined as all noxious and unintended responses to an Investigational medicinal product (IMP) related to any dose administered that result in an SAE as defined above.
SUSAR	Refers to individual SAE case reports from clinical trials where a causal relationship between the SAE and the IMP was suspected by either the sponsor or the investigator, is unexpected (not listed in the applicable Reference Safety Information) and meets one of the above serious criteria.

AbbVie will be responsible for SUSAR reporting for the IMP in accordance with global and local requirements.

Adverse events will be monitored throughout the study to identify any of special interest that may indicate a trend or risk to subjects.

Adverse Event Severity and Relationship to Study Drug

The investigators will rate the severity of each AE as mild, moderate, or severe.

The investigator will use the following definitions to rate the severity of each AE:

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Mild	The adverse event is transient and easily tolerated by the subject.
Moderate	The adverse event causes the subject discomfort and interrupts the subject's usual activities.
Severe	The adverse event causes considerable interference with the subject's usual activities and may be incapacitating or life threatening.

The investigator will use the following definitions to assess the relationship of the AE to the use of study drug:

Reasonable Possibility	After consideration of factors including timing of the event, biologic plausibility, clinical judgment, and potential alternative causes, there is sufficient evidence (information) to suggest a causal relationship.
No Reasonable Possibility	After consideration of factors including timing of the event, biologic plausibility, clinical judgment, and potential alternative causes, there is insufficient evidence (information) to suggest a causal relationship.

Pregnancy

While not an AE, pregnancy in a study subject must be reported to AbbVie within 24 hours after the site becomes aware of the pregnancy. Subjects who become pregnant during the study will be encouraged to remain in the study for follow-up through study exit but will receive no further treatment with the study drug. If a pregnancy occurs in a study subject, information regarding the pregnancy and the outcome will be collected. Partner pregnancy information will not be collected.

The pregnancy outcome of an elective or spontaneous abortion, stillbirth or congenital anomaly is considered a SAE and must be reported to AbbVie within 24 hours after the site becomes aware of the event.

Possible Distant Spread of Toxin

Possible distant spread of toxin (PDSOT) is defined as a possible pharmacologic effect of botulinum toxin at sites noncontiguous and distant from the site of injection. Utilizing a standardized methodology to assess for PDSOT, MedDRA preferred terms (PTs) that may be associated with botulinum toxin effects have been prospectively identified (see the statistical analysis plan [SAP] for a complete list of these PTs). Adverse events reporting any of these terms will be medically reviewed on a regular basis throughout the study and will be summarized in the clinical study report.

7 STATISTICAL METHODS & DETERMINATION OF SAMPLE SIZE

7.1 Statistical and Analytical Plans

The statistical methods provided in this protocol will be focused on primary and secondary efficacy endpoints. Complete and specific details of the statistical analysis will be described in the SAP.

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7.2 Definition for Analysis Populations

The mITT population includes all enrolled subjects who receive the total dose of 64 U of BOTOX Cosmetic, as described in this study protocol.

The Safety Analysis Set consists of all subjects who receive at least 1 injection of study drug.

7.3 Handling Potential Intercurrent Events for the Primary and Secondary Efficacy Endpoints

Observed data will be used without imputation, so subjects who have an intercurrent event resulting in not having a Day 30 assessment for any reason will not be included. Intercurrent events include:

- Subjects who are enrolled but do not receive the total dose of 64 U of BOTOX Cosmetic, as described in this study protocol
- Subjects who are enrolled but prematurely discontinue the study before the Day 30 assessment
- Subjects who die before the Day 30 assessment
- Subjects who are lost to follow-up and are missing Day 30 data for the endpoint
- Subjects who continue in the study beyond Day 30, but are missing the Day 30 assessment for any reason

7.4 Statistical Analyses for Efficacy

Summary and Analysis of the Primary Endpoint

Analysis of the primary endpoint will be conducted based on mITT population. No formal statistical testing will be performed, and descriptive statistics will be tabulated. Observed data will be used without imputation.

Summary and Analysis of Secondary and Additional Endpoints

Analysis of the secondary and additional endpoints will be conducted based on mITT population. Descriptive statistics will be tabulated and observed data will be used without imputation.

Additional details will be provided in the SAP.

7.5 Statistical Analyses for Safety

The safety analyses will be performed using the safety population. For each safety endpoint evaluating change from baseline, the last non-missing safety assessment before study drug administration will be used as the baseline for all analyses of that endpoint.

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Treatment-emergent AEs (TEAEs) are defined as any AE with the onset that is after the first dose of study drug. Events in which the onset date is the same as the study drug start date are assumed to be treatment-emergent, unless known to have started prior to study drug administration.

An overview of AEs will be presented consisting of the number and percentage of subjects experiencing at least one event for each of the following AE categories:

- Any TEAE
- Any TEAE related to study treatment according to the investigator
  - Any TEAE related to study drug according to the investigator
  - Any TEAE related to study procedure according to the investigator
- Any mild TEAE
  - Any mild TEAE related to study treatment according to the investigator
- Any moderate TEAE
  - Any moderate TEAE related to study treatment according to the investigator
- Any severe TEAE
  - Any severe TEAE related to study treatment according to the investigator
- Any serious TEAE
  - Any serious TEAE related to study treatment according to the investigator
- Any TEAE leading to death
- Any PDSOT TEAE
- All deaths

Treatment-emergent adverse events will be summarized by system organ class (SOC) and PT; for TEAEs related with reasonable possibility to study treatment (including study drug related and study procedure related) as assessed by the investigator by SOC and PT; for maximum severity by SOC and PT; and for subject numbers by SOC and PT. Specific TEAEs will be counted once for each subject for calculating percentages, unless stated otherwise. In addition, if the same AE occurs multiple times within a subject, the highest severity and level of relationship to study treatment will be reported.

Treatment-emergent SAEs (including deaths) will be summarized by SOC and PT. All SAEs will be provided in listing format.

Possible distant spread of toxin TEAEs will be identified in the SAP and summarized by PT.

7.6 Interim Analysis

Not applicable for this study.

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7.7 Overall Type I Error Control

Not applicable for this study.

7.8 Sample Size Determination

No formal sample size calculation was performed.

For a conservative expected proportion of 75% for the primary endpoint (proportion of subjects reporting *Mostly satisfied* or *Very satisfied* on the FLSQ Follow-up Item 4 at Day 30), a sample size of 100 subjects in the study is required for an adjusted logit-based 95% binomial confidence interval to have a width of 16.8% (interval is 75% – 9.1% to 75% + 7.7% with recommended correction of – 1/2).[9]

8 ETHICS

8.1 Independent Ethics Committee/Institutional Review Board (IEC/IRB)

The protocol, informed consent form(s), recruitment materials, and all subject materials will be submitted to the IEC/IRB for review and approval. Approval of both the protocol and the informed consent form(s) must be obtained before any subject is enrolled. Any amendment to the protocol will require review and approval by the IEC/IRB before the changes are implemented to the study. In addition, all changes to the consent form(s) will be IEC/IRB approved.

8.2 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, Operations Manual, International Council for Harmonisation (ICH) guidelines, applicable regulations, and guidelines governing clinical study conduct and the ethical principles that have their origin in the Declaration of Helsinki. The responsibilities of the investigator are specified in Appendix B.

In the event a significant disaster/crisis (e.g., epidemic/pandemic, natural disaster, conflict/combat) occurs leading to difficulties in performing protocol-specified procedures, AbbVie may engage with study site personnel in efforts to ensure the safety of subjects, maintain protocol compliance, and minimize risks to the integrity of the study while trying to best manage subject continuity of care. This may include alternative methods for assessments (e.g., phone contacts or virtual site visits), and alternative locations for data collection (e.g., use of a local lab instead of a central lab). In all cases, these alternative measures must be allowed by local regulations and permitted by IRB/IEC. Investigators should notify AbbVie if any urgent safety measures are taken to protect the subjects against any immediate hazard.

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8.3 Subject Confidentiality

To protect subjects' confidentiality, all subjects and their associated samples will be assigned numerical study identifiers or "codes." No identifiable information will be provided to AbbVie.

9 SOURCE DOCUMENTS AND CASE REPORT FORM COMPLETION

The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be attributable, legible, contemporaneous, original, accurate, and complete to ensure accurate interpretation of data. Clinical site monitoring is conducted to ensure that the rights and well-being of human subjects are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol, ICH Good Clinical Practice (GCP), and applicable local regulatory requirement(s). During the COVID-19 pandemic, remote data review/verification may be employed if allowed by the local regulatory authority, IRB/IEC, and the study site.

10 DATA QUALITY ASSURANCE

AbbVie will ensure that the clinical trial is conducted with a quality management system that will define quality tolerance limits in order to ensure human subject protection and reliability of study results. Data will be generated, documented, and reported in compliance with the protocol, ICH GCP, and applicable regulatory requirements.

11 COMPLETION OF THE STUDY

The end-of-study is defined as the date of last visit of the last subject in the study.

12 REFERENCES

1. BOTOX® (onabotulinumtoxinA) Prescribing Information. (Revised May, 2018): Allergan, Inc; [Available from: http://www.allergan.com/assets/pdf/botox_pi.pdf.

2. BOTOX COSMETIC® Product Monograph. (Revised June, 2020): Allergan, Inc; [Available from: https://allergan-web-cdn-prod.azureedge.net/allergancanadaspecialty/allergancanadaspecialty/media/actavis-canada-specialty/en/products/pms/2020-06-29-botox-cosmetic-product-monograph.pdf.

3. Martinez L, Falvello VB, Aviezer H, et al. Contributions of facial expressions and body language to the rapid perception of dynamic emotions. Cogn Emot. 2016;30(5):939-52.

4. Bale C, Archer J. Self-perceived attractiveness, romantic desirability and self-esteem: a mating sociometer perspective. Evol Psychol. 2013;11(1):68-84.

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5. Molina B, David M, Jain R, et al. Patient Satisfaction and Efficacy of Full-Facial Rejuvenation Using a Combination of Botulinum Toxin Type A and Hyaluronic Acid Filler. Dermatol Surg. 2015;41 Suppl 1:S325-32.

6. Weinkle SH, Werschler WP, Teller CF, et al. Impact of Comprehensive, Minimally Invasive, Multimodal Aesthetic Treatment on Satisfaction With Facial Appearance: The HARMONY Study. Aesthet Surg J. 2018;38(5):540-56.

7. Dayan S, Rivkin A, Sykes JM, et al. Aesthetic Treatment Positively Impacts Social Perception: Analysis of Subjects From the HARMONY Study. Aesthet Surg J. 2019;39(12):1380-9.

8. De Boulle K, Werschler WP, Gold MH, et al. Phase 3 Study of OnabotulinumtoxinA Distributed Between Frontalis, Glabellar Complex, and Lateral Canthal Areas for Treatment of Upper Facial Lines. Dermatol Surg. 2018;44(11):1437-48.

9. Edwardes M. The evaluation of confidence sets with application to binomial intervals. Stat Sin. 1998;8(2):393-409.

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APPENDIX A. STUDY-SPECIFIC ABBREVIATIONS AND TERMS

Abbreviation	Definition
AE	adverse event
AGLSS	Allergan Glabellar Line Severity Scale
COVID-19	coronavirus disease 2019
DHEA	dehydroepiandrosterone
eCRF	electronic case report form
EDC	electronic data capture
FDA	Food and Drug Administration
FHL	forehead lines
FHLSS	Forehead Line Severity Scale
FLSQ	Facial Line Satisfaction Questionnaire
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GL	glabellar lines
ICH	International Council for Harmonisation
IEC	independent ethics committee
IMP	investigational medicinal product
IRB	institutional review board
IUD	intrauterine device
LCL	lateral canthal lines
LCLSS	Lateral Canthal Line Severity Scale
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intention-to-treat
N/A	not applicable
NTEA	Neurotoxin Treatment Experience Assessment
PCR	polymerase chain reaction
PDSOT	possible distant spread of toxin
PRO	patient-reported outcome
PT	preferred term
RSI	reference safety information
SAE	serious adverse event
SAP	statistical analysis plan

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SAR	serious adverse reaction
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SOC	system organ class
SUSAR	suspected unexpected serious adverse reaction
TEAEs	treatment-emergent adverse events
U	units
UFL	upper facial lines
VDS	verbal descriptor scale
WOCBP	women of childbearing potential

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APPENDIX B. RESPONSIBILITIES OF THE INVESTIGATOR

Protocol M22-974: A Prospective, Multi-center, Open-label Study to Evaluate Subject Satisfaction and Natural Outcomes Following Administration of BOTOX® Cosmetic (Botulinum Toxin Type A) Purified Neurotoxin Complex in Subjects with Upper Facial Lines (Glabellar Lines, Lateral Canthal Lines, and Forehead Lines)

Protocol Date: 14 December 2023

Clinical research studies sponsored by AbbVie are subject to the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practices (GCP) and local laws and regulations and guidelines governing the study at the site location. In signing the Investigator Agreement, the investigator is agreeing to the following:

1. Conducting the study in accordance with ICH GCP, the applicable regulatory requirements, current protocol and operations manual, and making changes to a protocol only after notifying AbbVie and the appropriate Institutional Review Board (IRB)/Independent Ethics Committee (IEC), except when necessary to protect the subject from immediate harm.
2. Personally conducting or supervising the described investigation(s).
3. Informing all subjects, or persons used as controls, that the drugs are being used for investigational purposes and complying with the requirements relating to informed consent and ethics committees (e.g., IEC or IRB) review and approval of the protocol and its amendments.
4. Reporting complaints that occur in the course of the investigation(s) to AbbVie.
5. Reading the information in the Investigator's Brochure/safety material provided, including the instructions for use and the potential risks and side effects of the investigational product(s).
6. Informing all associates, colleagues, and employees assisting in the conduct of the study about their obligations in meeting the above commitments.
7. Maintaining adequate and accurate records of the conduct of the study, making those records available for inspection by representatives of AbbVie and/or the appropriate regulatory agency, and retaining all study-related documents until notification from AbbVie.
8. Maintaining records demonstrating that an ethics committee reviewed and approved the initial clinical protocol and all of its amendments.
9. Reporting promptly to AbbVie, the ethics committee/institutional review boards (as required) and other appropriate individuals (e.g., coordinating investigator, institution director):
    - All changes in the research activity and all unanticipated problems involving risks to human subjects or others
    - Any departure from relevant clinical trial law or regulation, GCP, or the trial protocol that has the potential to affect the following:
        - Rights, safety, physical or mental integrity of the subjects in the clinical trial
        - Scientific value of the clinical trial, reliability or robustness of data generated
10. Providing direct access to source data documents for study-related monitoring, audits, IEC/IRB review, and regulatory inspection(s).

Signature of Principal Investigator	Date
Name of Principal Investigator (printed or typed)	

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APPENDIX C. LIST OF PROTOCOL SIGNATORIES

Name	Title	Functional Area
[redacted]		Clinical Development Medical Affairs Statistics

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APPENDIX D. ACTIVITY SCHEDULE

The following tables show the required activities across the study. The individual activities are described in detail in the **Operations Manual** (Appendix E). Allowed modifications due to COVID-19 are detailed in the Operations Manual.

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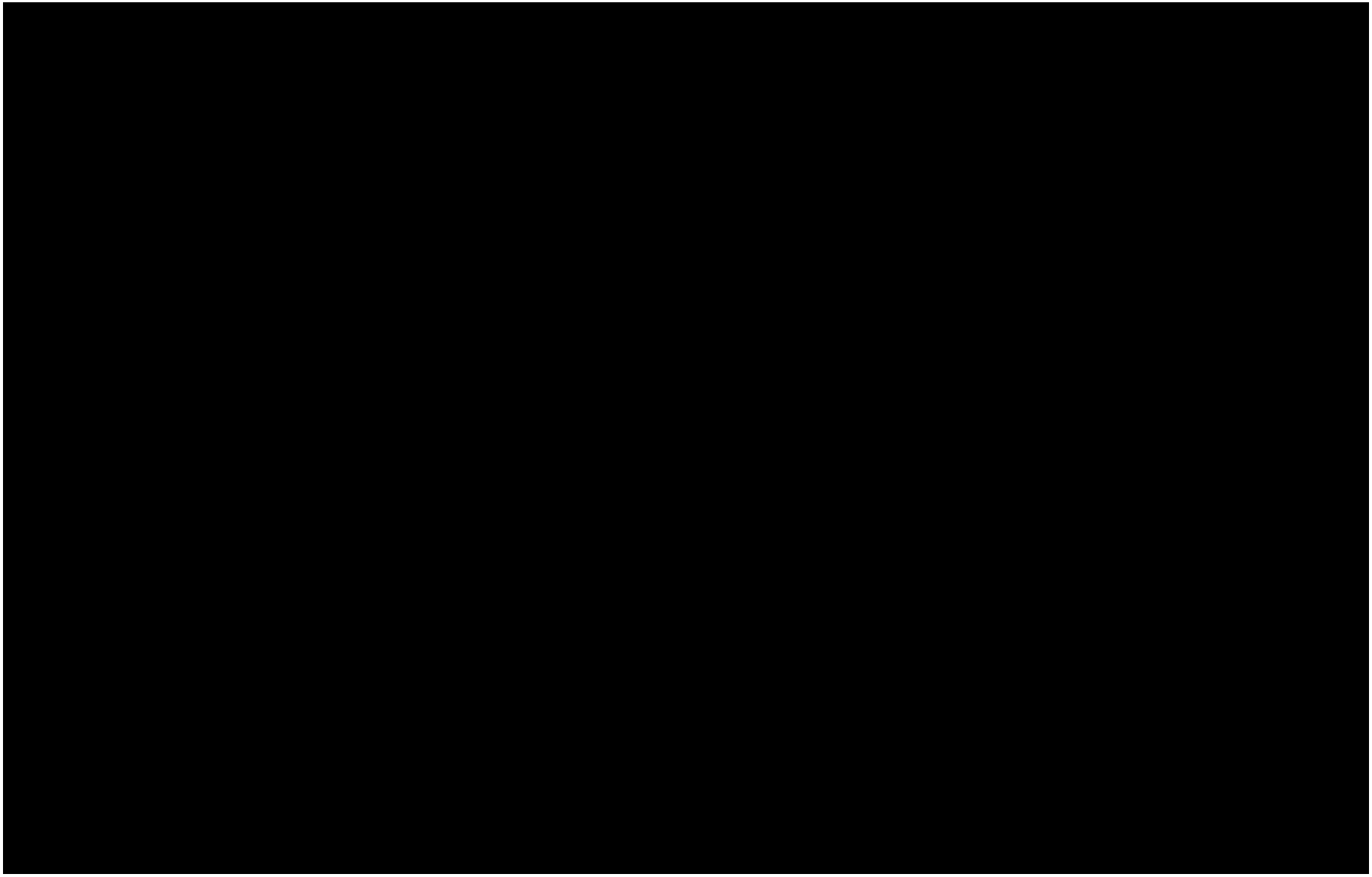

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APPENDIX E. PROTOCOL SUMMARY OF CHANGES

Previous Protocol Versions

Protocol	Date
Version 1.0	03 June 2022
Version 2.0	26 June 2023

The purpose of this version is to correct minor clerical errors for consistency throughout the protocol in addition to the following:

1. Protocol (Title Page) and Operations Manual (Appendix F, Section 1 and Section 4.2) were updated to reflect the current Sponsor/emergency medical and non-emergency contacts.
2. Protocol (Section 3.4) and Operations Manual (Appendix F, Section 3.6) were updated to correct measurement of efficacy onset from "Day 1 up to Day 14" to "Day 2 to Day 15."
3. Protocol (Section 4.1) was updated to allow more flexibility in enrollment and to reflect review of site data.
4. Protocol (Section 5.1, eligibility criterion #3) was updated for consistency with the Operations Manual (Appendix F, Section 3.1). Eligibility criterion #8 was updated for clarity.
5. Protocol (Section 5.2) was updated to provide additional language for females on hormone replacement therapy whose menopausal status is in doubt.
6. Protocol (Section 5.7) and Operations Manual (Appendix F, Section 6.2, Section 6.3, and Section 6.6) were updated, as the study drug will be sourced commercially.
7. Protocol (Section 6.1) was updated to clarify that partner pregnancy information will not be collected.
8. Operations Manual (Appendix F, Section 3.11) was updated to remove a sentence regarding images captured on Day 1. A sentence was added to allow for image collection to be repeated within 7 days as needed.

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