

**NCT01917006**

**Study ID: 191622-133**

**Title:** An Exploratory Study of the Safety and Efficacy of BOTOX® for the Treatment of Premature Ejaculation

**Protocol Amendment 2 Date:** 15 Jul 2016

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## An Exploratory Study of the Safety and Efficacy of BOTOX® for the Treatment of Premature Ejaculation

Protocol Number: 191622-133 Amendment 2

EudraCT Number (if applicable): 2013-001650-94

Phase: 2a

Name of Investigational Product: BOTOX®

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Approval Date: 15-Jul-2016

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Refer to the final page of this protocol for electronic signature and date of approval.

The following information can be found on FDA Form 1572 and/or study contacts page and/or trial master file: Name and contact information of Allergan study personnel; name, address, and statement of qualifications of each investigator; name of each subinvestigator working under the supervision of the investigator; name and address of the research facilities to be used; name and address of each reviewing IRB; 21 CFR 312.23 section 6(iii)b.

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**INVESTIGATOR SIGNATURE PAGE**

INVESTIGATOR:

I agree to:

- Implement and conduct this study diligently and in strict compliance with the protocol, good clinical practices and all applicable laws and regulations.
- Maintain all information supplied by Allergan in confidence and, when this information is submitted to an Institutional Review Board (IRB), Independent Ethics Committee (IEC) or another group, it will be submitted with a designation that the material is confidential.
- Ensure that all persons assisting with the trial are adequately informed about the protocol, the investigational product(s), and their trial-related duties and functions.

I have read this protocol in its entirety and I agree to all aspects.

\_\_\_\_\_  
Investigator Printed Name


\_\_\_\_\_  
Signature

\_\_\_\_\_  
Date

Approval Date: 15-Jul-2016

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## Protocol Summary

**Study Compound(s):** BOTOX® (Botulinum Toxin Type A) Purified Neurotoxin Complex (United States Adopted Name is OnabotulinumtoxinA)

**Phase:** 2a

**Study Objective(s):** To explore the safety and efficacy of a range of doses of BOTOX for the treatment of premature ejaculation (PE) in male patients

**Clinical Hypotheses:** BOTOX injected bilaterally into the bulbospongiosus muscle has an acceptable safety profile and shows an efficacy signal in comparison to placebo, as demonstrated by an increased intravaginal ejaculatory latency time (IELT).

### Study Design

**Structure:** Multicenter, randomized, double-blind, placebo-controlled pilot study, followed by an open-label observation period

**Duration:** Up to 24 weeks following randomization

**Study Treatment Groups:** BOTOX

**Controls:** Placebo (saline)

**Dosage/Dose Regimen:** Patients will receive a single treatment of either BOTOX or placebo delivered bilaterally to the bulbospongiosus muscle. The initial BOTOX total dose will be [REDACTED] and the maximum BOTOX total dose will be [REDACTED]

For Cohort 6, patients may participate in two periods: randomization and open-label. During the randomization period, patients will receive a single treatment of either BOTOX [REDACTED] or placebo delivered bilaterally to the bulbospongiosus muscle. All patients continuing into the open-label period will receive an additional treatment of BOTOX [REDACTED] delivered bilaterally to the bulbospongiosus muscle.

The table below shows the planned dose escalation scheme.

Cohort	Total Dose	Sample Size	Total Patients in Cohort
1	[REDACTED]	N = 8	10
	Placebo	N = 2	
2	[REDACTED]	N = 8	10
	Placebo	N = 2	
3	[REDACTED]	N = 8	10
	Placebo	N = 2	
4	[REDACTED]	N = 8	10
	Placebo	N = 2	
5	[REDACTED]	N = 8	10
	Placebo	N = 2	
6	[REDACTED]	N = 12	24
	Placebo	N = 12	

\* Based on DRC recommendations Cohort 6 is to be performed with [REDACTED] of BOTOX and a randomization ratio of 1:1 for the first 12 weeks with 24 patients

**Randomization/Stratification:** For Cohorts 1-5, patients will be enrolled in cohorts consisting of 10 patients. Within each cohort, 8 patients will receive BOTOX and 2 patients will receive placebo (see table above). Sentinel dosing of the first 2 patients (1 BOTOX, 1 placebo) will occur at the commencement of Cohort 1 and also for any subsequent cohort that escalates the dose. Following a 1-week observation period providing there are no safety concerns with the sentinel patients, the remainder of the cohort will be enrolled.

Dose escalation will be based on the independent Data Review Committee (DRC) recommendation, following review of 4 weeks of safety and efficacy data from the preceding cohort. The DRC may also recommend to repeat cohorts, de-escalate the dose, assess alternative doses, or stop the study.

Based on the DRC recommendation for Cohort 6, patients will be enrolled in a 1:1 ratio of BOTOX [REDACTED] to placebo in the randomized period of the study and may elect to continue into the open-label period as described below. No stratification will be implemented.

*Visit Schedule:*

Cohorts 1 to 5:

- Screening period (washout if required will occur during the screening period)
- Day 1: Treatment visit
- Day 2: Follow-up telephone visit
- Week 1: Follow-up visit (telephone visit for nonsentinel patients, clinic visit for sentinel patients)
- Weeks 2, 4, and 8: Follow-up clinic visits
- Week 12: Clinic visit/study exit visit

Cohort 6 (Randomized Period):

- Screening period (washout if required will occur during the screening period)
- Day 1: Treatment visit
- Day 2: Follow-up telephone visit
- Week 1: Follow-up telephone visit
- Weeks 2, 4, and 8: Follow-up clinic visits
- Week 12: Clinic visit/study exit visit

Cohort 6 (Open-Label Period):

- Day 1: Treatment visit (may occur on the same day as the week 12 visit of the randomization period)
- Day 2: Follow-up telephone visit
- Week 2 and 8: Telephone follow-up visit
- Weeks 4 and 12: Follow-up clinic visit/study exit visit

---

### Study Population Characteristics

*Number of Patients:* Based on the proposed doses it is anticipated that approximately 74 patients will be enrolled in the 6 planned cohorts. The actual number of patients entering the study will be determined by the number of cohorts (eg, escalations, repeat doses, de-escalations, or when the study is stopped). No more than 80 patients will be enrolled in the study.

*Condition/Disease:* premature ejaculation (PE)

*Key Inclusion Criteria:*

- written informed consent has been obtained from both the patient and his female partner
- male aged 18 to 60 years
- in a stable monogamous sexual relationship with a female partner for at least 6 months (with the intention to continue with the same partner for the duration of the study)
- diagnosed with lifelong PE (defined as symptoms starting at the time the patient became sexually active)

- [REDACTED]
  - [REDACTED]
  - [REDACTED]
  - [REDACTED]
- [REDACTED]
  - [REDACTED]
  - [REDACTED]
  - [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]

*Key Exclusion Criteria:*

- any medical or surgical condition that could be associated with secondary (acquired) PE or patient has PE which is situational or attributable to relationship issues
- [REDACTED]
- [REDACTED]
  - [REDACTED]
  - [REDACTED]
  - [REDACTED]
  - [REDACTED]
  - [REDACTED]
  - [REDACTED]
- [REDACTED]
- patient has had prior genital, prostatic or lower urinary tract surgery (other than vasectomy or circumcision)
- [REDACTED]

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- [REDACTED]
- [REDACTED]
- history of any neurologic condition that may affect sexual function or findings at study entry which may be consistent with a neurological condition that may affect sexual function
- [REDACTED]
- [REDACTED]
- botulinum toxin therapy of any serotype for any non-urological condition or usage (eg, cosmetic or chronic migraine) during the 12 weeks prior to screening, or planned usage during the course of this study

---

**Response Measures**

*Efficacy:*

- IELT (measured by stopwatch and captured on the SID)

[REDACTED]

- [REDACTED]
- [REDACTED]

[REDACTED]

- [REDACTED]
- [REDACTED]

[REDACTED]

- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]

---

**General Statistical Methods and Types of Analyses:**

The final analysis will be performed when all patients have completed or exited the study. The modified intent-to-treat (mITT) population, defined as all randomized patients that have received study medication and have postbaseline IELT data available, will be used to analyze all efficacy variables. Analyses on the mITT population will be based on the dose actually received by the patient. The per protocol (PP) population, defined as patients in the mITT population without significant protocol deviations, will also be used for efficacy analysis. The primary efficacy variable (change from baseline in logarithm value of the patient’s geometric mean IELT) in relation to dose levels will be analyzed by using an analysis of covariance (ANCOVA) model with treatment as the fixed effect and baseline IELT as the covariate to assess the relationship of response

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across the BOTOX dose levels. Geometric mean IELT data up to week 12 will be log-transformed prior to analysis. Analysis of the primary efficacy variable using the PP population will also be performed.

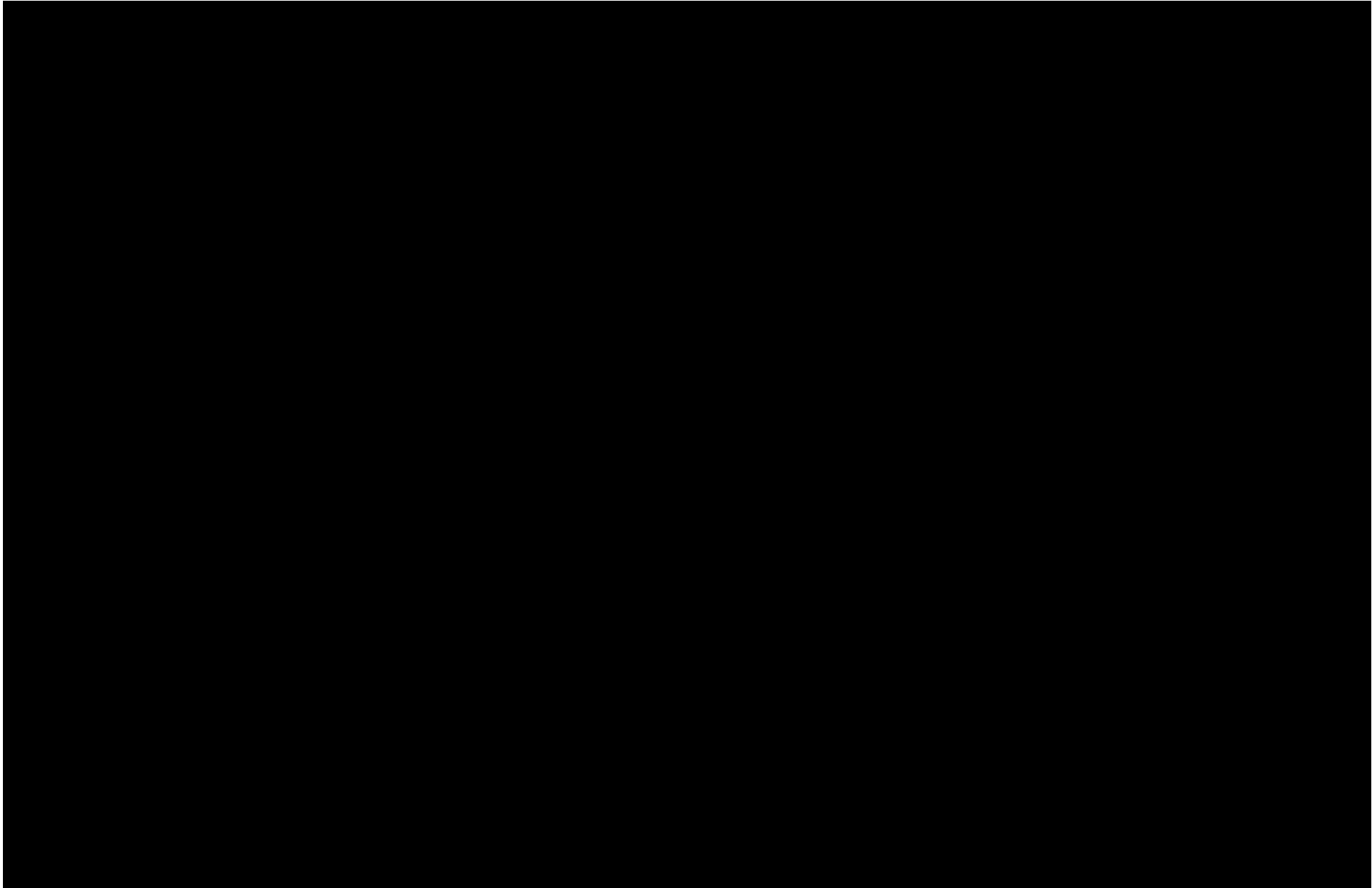
A pairwise comparison of each BOTOX dose group versus placebo will be made for percent responders for the patient-reported outcomes of [REDACTED]

All safety analyses will be performed on the safety population (ie, all patients who receive study medication). The incidence of adverse events will be presented. Mean change from baseline will be compared for each BOTOX dose group versus placebo for the [REDACTED] questionnaires.

Data will be summarized with descriptive statistics, frequency tables, and data listings. Categorical variables will be analyzed using Fisher's exact test, Pearson's chi-square test, or Cochran-Mantel-Haenszel methods, as appropriate. Continuous variables will be analyzed using either ANCOVA or corresponding nonparametric methods.

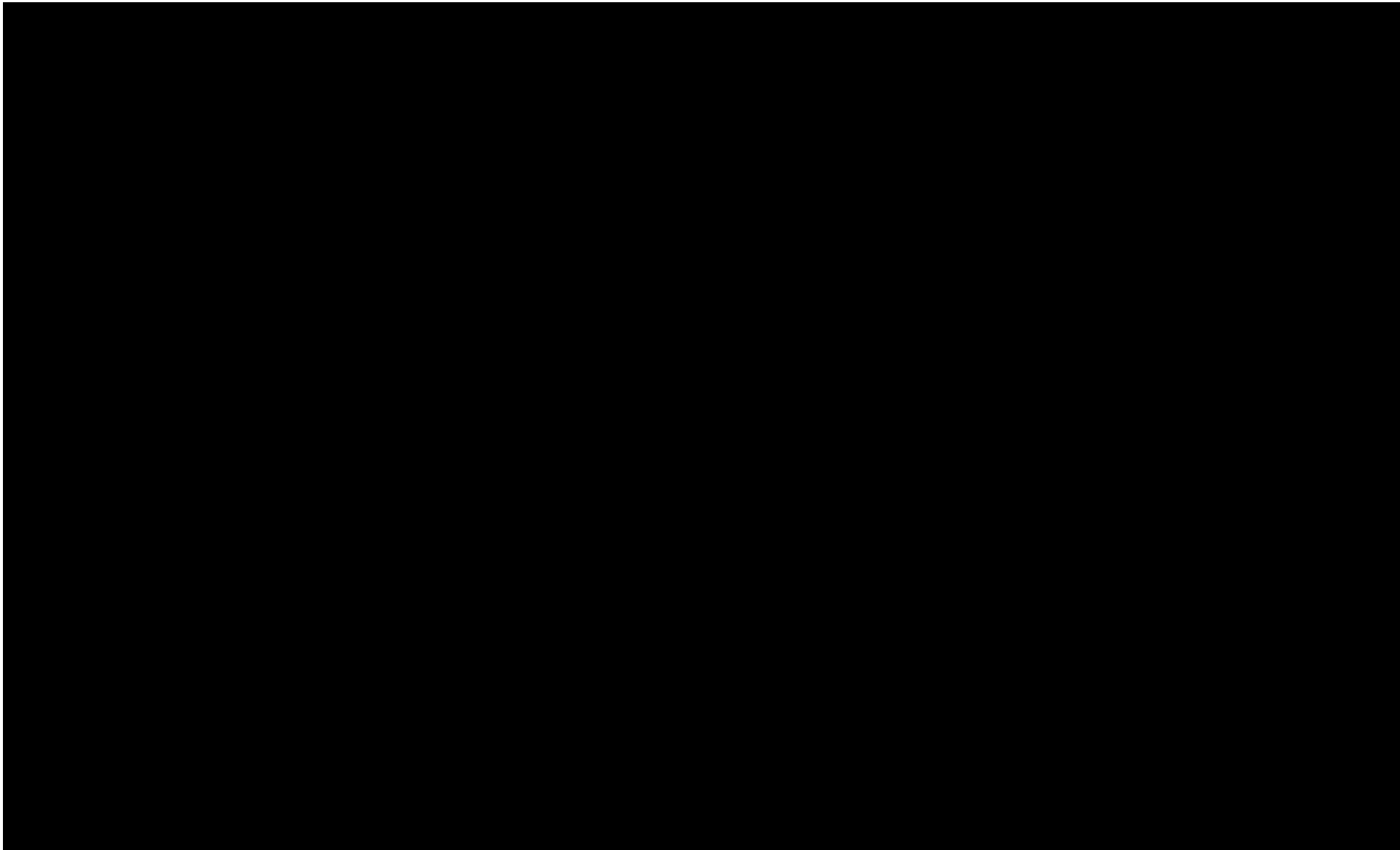
*Sample Size Calculation:* For this exploratory study, an empirical sample size is used. For Cohorts 1-5, 8 patients will be randomized to receive BOTOX and 2 patients to placebo. In Cohort 6, 24 patients will be randomized in a 1:1 ratio of BOTOX to placebo.

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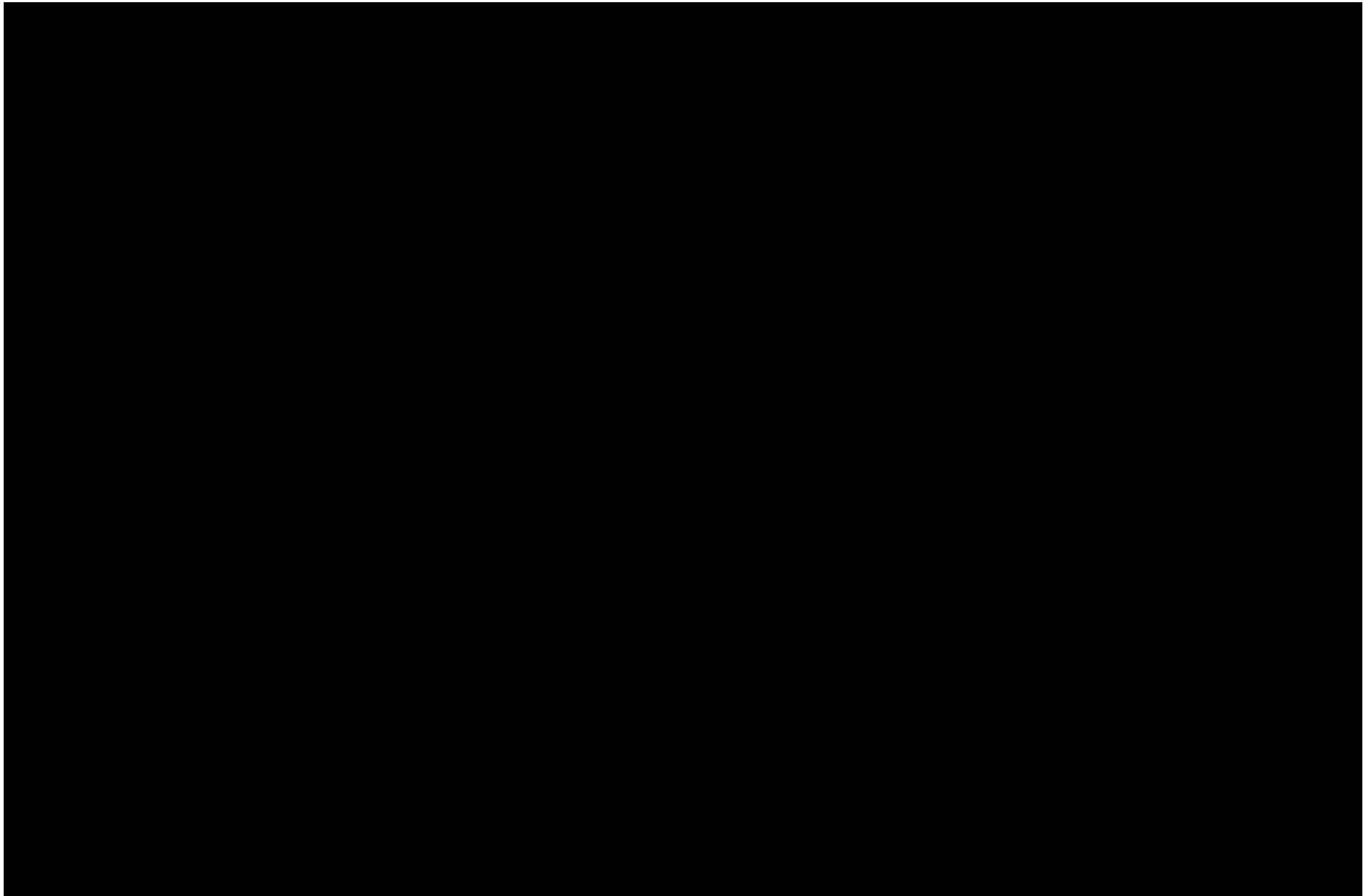


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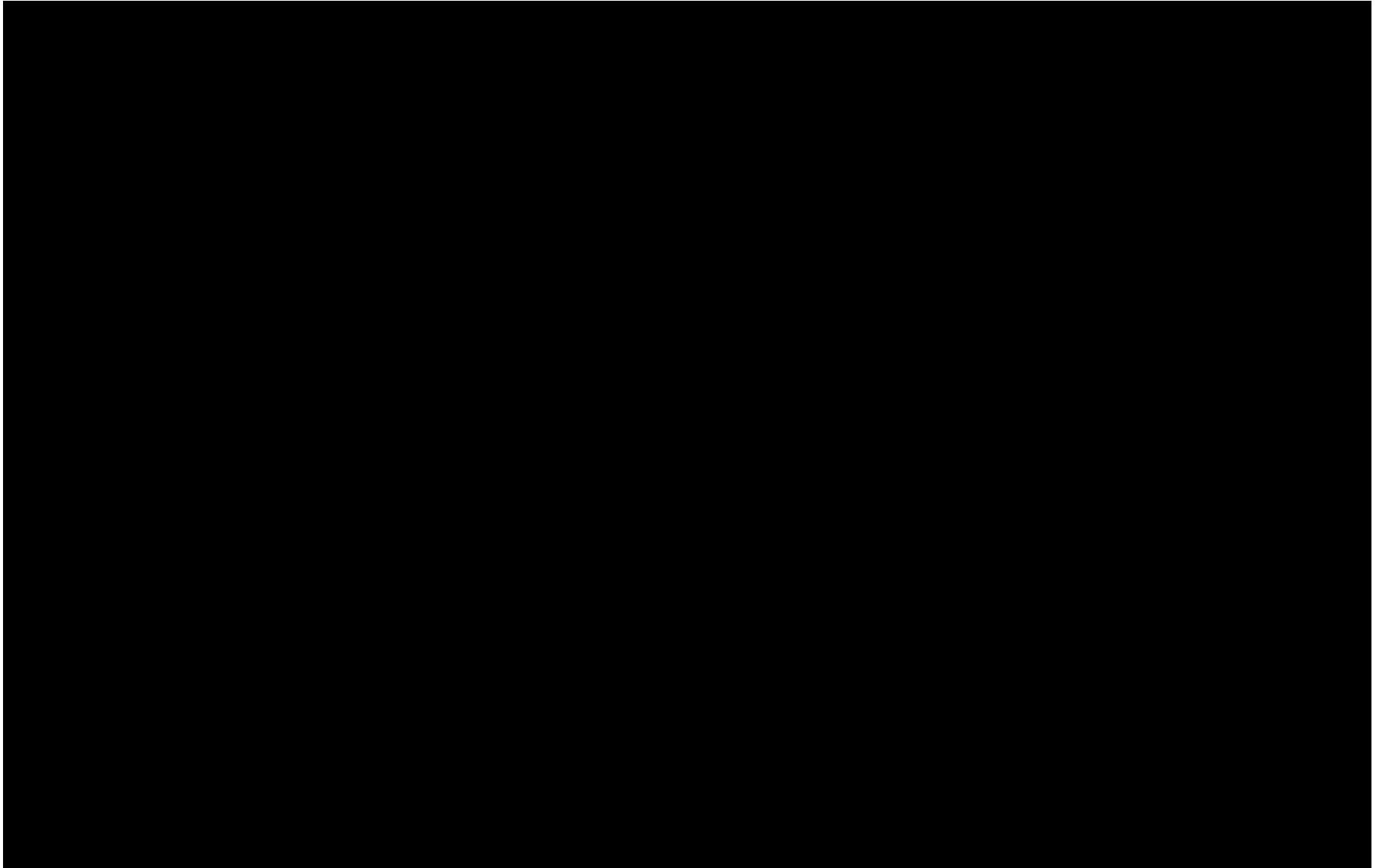




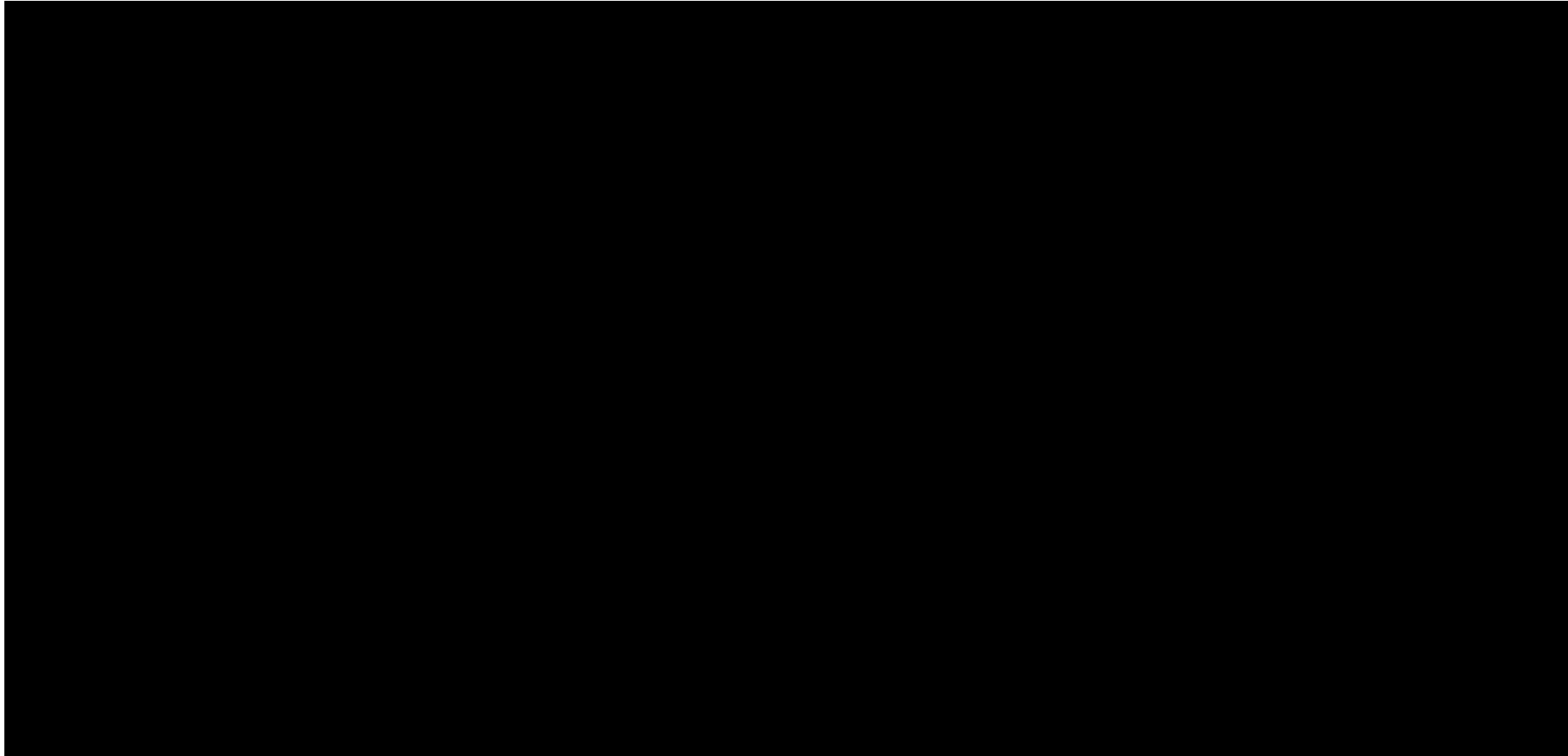
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## 1. Background and Clinical Rationale

### 1.1 Epidemiology, Definition, and Assessment

Premature ejaculation (PE) is one of the most common forms of male sexual dysfunction, affecting approximately 13% to 30% of adult men (depending on the definition used) (Laumann et al, 2005; Patrick et al, 2005), although this is likely an underestimate due to a reluctance to report the condition (Symonds et al, 2003). Unlike erectile dysfunction (ED), PE does not appear to be associated with increasing age (Althof, 2006; Porst et al, 2007).

Studies of men with PE have consistently shown high levels of personal distress and reductions in levels of sexual functioning, self-esteem, satisfaction, overall quality of life, as well as interpersonal difficulty (Rowland et al, 2007; Rosen and Althof, 2008). The condition for many men serves as a barrier to seeking and becoming involved in relationships (Symonds et al, 2003). Studies in the female partner also consistently show greater sexual problems, reduced satisfaction, distress, interpersonal difficulty, and decreased sexual pleasure (Rowland et al, 2007; Althof, 2006). PE thereby causes emotional and physical dissatisfaction for both the man and also for the couple as a whole (Graziottin and Althof, 2011).

PE has been defined by the International Society of Sexual Medicine (ISSM) as “a male sexual dysfunction characterized by ejaculation which always or nearly always occurs prior to or within about 1 minute of vaginal penetration, and the inability to delay ejaculation on all or nearly all vaginal penetrations, and negative personal consequences, such as distress, bother, frustration, and/or the avoidance of sexual intimacy” (McMahon et al, 2008).

PE can be classified into 2 main subtypes (Godpodinoff, 1989; Waldinger, 2008):

- life-long (primary), which is present from the time a male begins puberty and continues throughout life
- acquired (secondary), which develops later in life and may be due to other causes

Stopwatch assessment of the intravaginal ejaculatory latency time (IELT) is widely used in clinical trials as an objective assessment of the condition. Multinational normative data from an unselected population of approximately 500 men demonstrated a median IELT of 5.4 minutes (range 0.55 to 44.1 minutes) (Waldinger, 2005a). Using 0.5 and 2.5 percentiles as disease cutoffs, this equated to IELTs of 0.9 and 1.3 minutes, respectively. Therefore, an

IELT of < 1 minute is regarded as an acceptable limit for disease definition (Waldinger et al, 2005b).

## 1.2 Etiology of Premature Ejaculation

Previously PE was assumed to be due to psychological or interpersonal issues. However, recent animal and human sexual psychopharmacological studies have attributed a neurobiological basis, and possible genetic etiology to primary PE (Waldinger, 2002). Neurobiological factors include glans penis hypersensitivity, hypersensitive ejaculatory reflex, increased cortical representation of the pudendal nerve, and disturbances in central serotonergic neurotransmission (McMahon et al, 2008). Genetic factors include a possible association between a 5-HT transporter (5-HTT) promoter gene polymorphism and short IELTs in men with lifelong PE (Janssen et al, 2009).

## 1.3 Physiology of Ejaculation

Ejaculation is the culmination of male sexual behavior and is intimately associated with orgasm. It is composed of 2 distinct phases:

- Emission is the ejection of semen into the posterior urethra via epithelial secretion and smooth muscle contraction within the accessory sex glands.
- Expulsion is the intense rhythmic contractions of the pelvic floor muscles that propels the semen distally through the bulbar and penile urethra and empties the semen out of the urethral meatus. The bulbospongiosus muscle (BSM) is the principal muscle involved in expulsion although other muscles such as the ischiocavernosus muscles are also involved to a much lesser extent.

The process is triggered by a complex spinal reflex which originates within the spinal generator for ejaculation (SGE) in the thoracolumbar region of the spinal cord. Ejaculation is an autonomic mediated event and tight coordination of the sympathetic, parasympathetic, and somatic divisions of the nervous system are necessary for normal ejaculation to occur (Giuliano and Clément, 2012).

## 1.4 Treatment of Premature Ejaculation

There are a limited number of treatment options currently available for the treatment of PE. Treatments currently being used for PE include behavioral techniques, topical therapies, and oral medications.

First-line therapy for PE tends to include behavioral techniques such as the 'stop-start' and 'squeeze' techniques (Semans, 1956; Masters and Johnson, 1970), and precoitus masturbation (Sadeghi-Nejad and Watson, 2008). These techniques are only moderately successful and can be intrusive during sexual intercourse for the patient and female partner, and time-consuming to learn. Although short-term benefits have been reported, long-term response rates fall to 25% at 3 years for behavioral therapy (Hawton et al, 1986).

Topical therapies tend to be local anesthetics or herbal-based creams, gels, ointments, or spray formulations and are applied shortly prior to intercourse (Morales, 2012), eg, Promescent<sup>®</sup> (United States [US]) and STUD 100/Premjact desensitizing spray (United Kingdom [UK]) which have local anesthetics (such as lidocaine) as the active ingredient. These topical therapies have limited clinical evidence to support their effective use in patients with PE. In addition, topical therapies are only moderately effective and have been associated with penile hypoesthesia and vaginal numbness, which in some cases results in female anorgasmia (McMahon et al, 2008). Topical therapies also affect spontaneity of sexual intercourse as patients need to allow sufficient time for the treatment to take effect.

Several oral pharmacological agents have been used for the treatment of PE including centrally acting agents such as selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants, and tramadol; however, these classes of medications may require daily dosing and are associated with neurocognitive and systemic adverse effects. Many men are reluctant to use these medications because of these adverse effects. Locally acting medications such as phosphodiesterase type-5 inhibitors (PDE5i) and alpha antagonists have also been used; however, there is limited robust evidence to support their usage in the treatment of PE. In addition, the majority of these pharmacological treatments require on-demand dosing which hinders the spontaneity of intercourse (McMahon et al, 2008).

No oral treatment has been specifically approved for the treatment of PE by the US Food and Drug Administration (US FDA), and the only oral medication specifically approved by European regulators for this indication is the short-acting SSRI, dapoxetine; which can be used as an “on demand” therapy. Dapoxetine is associated with vasovagal-mediated syncope and there is little data on the long-term adverse effects of its usage (Hutchinson et al, 2012).

Therefore, there is a significant unmet need for an effective and safe long-acting PE treatment that does not have systemic side effects.

## 1.5 Rationale for BOTOX

BOTOX<sup>®</sup> is licensed globally in over 80 countries for a wide range of indications characterized by muscle hyperactivity. Approved therapeutic indications targeting skeletal muscle include blepharospasm, hemifacial spasm, strabismus, cervical dystonia, and focal spasticity. BOTOX is also approved in over 30 countries for cosmetic indications targeting skeletal muscle, including upper facial rhytides (forehead, lateral canthus, and glabellar lines).

In addition, urological indications targeting the smooth muscle have recently received regulatory approval in the US, many of the European Union countries, Australia, New Zealand, and Canada for the use of BOTOX in the treatment of neurogenic detrusor overactivity, as well as for the treatment of overactive bladder.

It is proposed that a pharmacologic decrease in muscle contractility, as might be achieved with targeted BOTOX injections, could be an effective treatment for PE. BOTOX has a well-described mode of action, with presynaptic blockade of acetylcholine release at the neuromuscular junction leading to a decrease in neuromuscular transmission and long-term relaxation of an injected muscle. If injected into the skeletal muscles of the pelvic floor, such as the bulbospongiosus, which are involved in the rhythmic contractions during ejaculation, it can be hypothesized that a delay in the initiation of rhythmic pelvic floor contractions and a resultant delay in ejaculation will occur.

A nonclinical study in 33 male Long-Evans rats demonstrated that bilateral injections of BOTOX of either 0.5 U or 1 U in the bulbospongiosus muscle resulted in a significant increase in ejaculatory latency when compared to pretreatment levels. Rats injected with saline did not show a significant increase in ejaculatory latency. There were no safety issues identified and BOTOX treatment did not impact the ability to achieve mount or intromission ([Serefoglu et al, 2012](#)).

Based on previous experience with BOTOX in a wide variety of neuromuscular conditions (both skeletal and smooth muscle), it would be expected that a single treatment administration will provide a sustained effect lasting several months.

The purpose of this study is to explore several doses of BOTOX to assess if BOTOX may have utility in the treatment of PE.

The safety of BOTOX has been widely studied and found to be safe across a wide range of indications. In 3 completed phase 2 studies, the safety of BOTOX has also been evaluated after a single injection into the male reproductive system (ie, the prostate) in 468 men with



benign prostatic hyperplasia (Studies 191622-091, -100, and -517). The 191622-091 spermatogenesis and semen quality study demonstrated that following injections of 200 U BOTOX directly into the prostate, there was no impact on any semen parameters compared to placebo (including sperm count, semen volume, sperm concentration, sperm motility, and sperm morphology). Also, in Studies 191622-100 and 191622-517, where BOTOX doses up to 300 U were injected into the prostate gland, there was no effect on erectile function. Therefore, it is expected that injection into muscles that are involved in sexual function (ie, bulbospongiosus muscle) at the proposed doses will be safe and will have no impact on semen parameters or erectile function.

The safety of bulbospongiosus injections with BOTOX is further supported by a randomized, placebo-controlled, pilot study (Gottsche et al, 2011). In the study, 100 U BOTOX was injected into the bulbospongiosus muscle of 23 male patients with chronic pelvic pain syndrome to assess relief of pain symptoms. There were no complications in any patient related to the injection procedure, and no analgesics were required during or following the injections. Over the 3 months of follow up, no adverse events or systemic side effects were reported.

The data from this study will be used to assist in the design of future clinical trials for PE, and the study data may also help develop a better understanding of diseases capable of being treated with BOTOX.

## 1.6 Nonclinical Toxicology

BOTOX has been studied in rodents and primates in over 300 nonclinical studies since 1991. Single- and repeat-dose nonclinical safety studies, including reproductive toxicity, and genotoxicity of BOTOX in various animal species have shown no noteworthy adverse local or systemic effects following intramuscular administration at clinically relevant dose levels.

Rats had no noteworthy adverse local or systemic effects following single dose injections in skeletal muscle up to 10 U/kg and in monthly doses (7 repeated injections) up to 16 U/kg. The lowest observable adverse effect level (LOAEL) for systemic toxicity occurred following single doses at 50 U/kg and at 24 U/kg with repeated administration. When BOTOX was given intravenously (IV) to rats, no adverse effects were observed up to 10 U/kg, while doses of  $\geq 25$  U/kg were associated with similar decreases in body weight as those observed following intramuscular (IM) administration. Deaths were observed occasionally at 50 U/kg and frequently at  $\geq 100$  U/kg. The IV single dose LOAEL for systemic toxicity was approximately 50 U/kg. In monkeys, single IM administrations of  $\leq 16$  U/kg did not produce evidence of systemic toxicity while doses of 24 U/kg or greater

produced multiple clinical signs and occasional mortality. In repeat dose studies, increased tolerance was associated with the dispersion of the total BOTOX dose over multiple injection sites. Bimonthly or trimonthly injections of 16 U/kg divided into 2 injection sites produced clinical signs of systemic toxicity and mortality; however, when divided over 6 sites, no systemic toxicity was observed. The no observed adverse effect level (NOAEL) in monkeys was 8, 12, or 16 U/kg for 2, 4, or 6 injection sites, respectively.

Reproductive toxicity studies were conducted in mice, rats, and rabbits. BOTOX was not found to be selectively toxic to reproduction in rats. Adverse effects on male fertility and female estrous cycling and fertility occurred only at dosages that induced exaggerated pharmacological effects. Embryo-fetal toxic and teratogenic effect evaluations did not show any selective fetal toxicity and maternal effects were due to the anticipated pharmacological actions of BOTOX. Maternal and developmental NOAEL values determined for rats in peri- and postnatal studies were the same as those established in other reproductive studies and no effects of BOTOX were observed on the behavior or reproductive performance of filial 1 animals.

The mutagenic potential for BOTOX has been determined in a battery of evaluations including the Ames assay, AS52/XPRT mammalian cell forward gene study, in vitro chromosomal aberration in Chinese Hamster Ovary cells, and an in vivo mouse micronucleus assay. No mutagenic or genotoxic potential of BOTOX was demonstrated.

BOTOX is not structurally related to any known carcinogens and has been shown to be nongenotoxic and nonmutagenic. There is no evidence of any cumulative effects due to toxin. Thus, long-term studies to evaluate the carcinogenic potential of BOTOX in animals are not deemed necessary and have not been performed. This is consistent with the International Council on Harmonisation (ICH) Guideline on the Need for Carcinogenicity Studies of Pharmaceuticals ([ICH Topic S1A, CPMP/ICH/140/95](#)).

The antigenic potential of BOTOX was evaluated in a comprehensive battery of tests that included studies for indirect hemagglutinin reactions, passive cutaneous anaphylaxis in rats and guinea pigs, and antigenicity in guinea pigs. Results of these studies indicate that BOTOX, which contains human serum albumin (HSA), and its placebo, are antigenic in animal models. This is an expected response to the administration of a foreign protein, HSA, in a nonhomologous test system. HSA is found in the BOTOX formulation far in excess of the toxin protein (0.5 mg HSA versus approximately 4 to 5 nanograms of toxin). Antibodies were not identified in the animal models used, thus it is not possible to comment on the relative occurrence of antibodies to HSA and to the toxin.

The hemolytic potential of BOTOX was evaluated in vitro in human whole blood and was found not to cause hemolysis up to 100 U/mL.

Additionally, to examine the effects of potential inadvertent injection, monkeys have been given a single injection of 3.4 U/kg/site BOTOX into the prostatic urethra and proximal rectum (6.8 U/kg total) or 3.4 U/kg/site BOTOX into the urinary bladder wall (base) and left seminal vesicle (6.8 U/kg total). No drug-related effects on clinical observations, physical examination, rectal temperature, clinical pathology, or histology were observed. There was no evidence of local toxicity in any tissue and no signs of systemic toxicity. Bladder stones were observed in one animal dosed into the prostatic urethra and proximal rectum. Bladder stones are an uncommon finding in nonhuman primates. Further studies were conducted as part of the Allergan's benign prostatic hyperplasia program, and concluded that these findings were considered species specific and not relevant to human administration.

BOTOX is approved in skeletal muscle indications for doses up to 360 U. Based on the nonclinical toxicology, the IM (skeletal) repeat dose NOAEL of 8 to 16 U/kg in monkeys provides a safety margin of 96- to 193-fold over the planned starting BOTOX total dose of 5 U (0.083 U/kg). In rats, the IM (skeletal) repeat dose NOAEL of 16 U/kg is 193-fold the starting dose of 5 U. The highest BOTOX total dose proposed for the study is 100 U (2.5 U/kg). The safety margins in monkeys are 3.2 to 6.4 fold, and in rats 6.4-fold the maximum intended human dose for this indication.

Further details regarding the nonclinical toxicology of BOTOX are contained in the Investigator's Brochure.

## **2. Study Objectives and Clinical Hypotheses**

### **2.1 Study Objectives**

To explore the safety and efficacy of a range of doses of BOTOX for the treatment of PE in male patients.

### **2.2 Clinical Hypotheses**

BOTOX injected bilaterally into the bulbospongiosus muscle has an acceptable safety profile and shows an efficacy signal in comparison to placebo, as demonstrated by an increased IELT.

### 3. Study Design

This is a phase 2a, multicenter, randomized, double-blind, placebo-controlled, single treatment, pilot study followed by an open-label observation period, to assess a range of BOTOX doses for the treatment of male patients with PE. Patients will attend a minimum of 6 or 7 clinic visits and also have 1 or 2 telephone visits in the randomized period: screening, day 1 (treatment), day 2 (telephone visit for non-sentinel patients, clinic visit for sentinel patients, week 1 (telephone visit, and weeks 2, 4, 8, and 12/study exit). Partners will need to either attend a clinic visit or participate on a video conference during the screening period to provide informed consent and to receive training on measurement and recording of the IELT. For the open-label period, patients will have 2 clinic visits (weeks 4 and 12/study exit), along with 3 telephone visits (day 2, weeks 2, and 8).

For Cohorts 1-5, patients will be enrolled in cohorts of 10 patients. Within each cohort, 8 patients will receive BOTOX and 2 patients will receive placebo. For Cohort 6, patients will be enrolled into the randomized period in a 1:1 ratio, with 12 patients receiving BOTOX [REDACTED] and 12 patients receiving placebo. Cohort 6 patients may choose to participate in the open-label period where they will receive BOTOX [REDACTED]. For each treatment, patients will receive one injection of study medication delivered by ultrasound guidance bilaterally to the bulbospongiosus muscle.

Table 3–1 shows the planned dose escalation scheme; although, other interim doses may be recommended for investigation by the independent Data Review Committee (DRC) following data review.

**Table 3–1 Planned Dose Escalation Scheme**

Cohort	Total Dose	Sample Size	Total Patients in Cohort
1	██████████	N = 8	10
	Placebo	N = 2	
2	██████████	N = 8	10
	Placebo	N = 2	
3	██████████	N = 8	10
	Placebo	N = 2	
4	██████████	N = 8	10
	Placebo	N = 2	
5	██████████	N = 8	10
	Placebo	N = 2	
6	██████████	N = 12	24
	Placebo	N = 12	

Sentinel dosing will occur during Cohorts 1-5 (see Section 3.1). When the full complement of 10 patients for the cohort has been enrolled, randomization will be halted to allow for observation of the cohort and DRC evaluation. When all remaining patients from a cohort have week 4 data available, the DRC will evaluate the unblinded safety and efficacy data to provide study recommendations (see Section 3.2). Cohort 6 will enroll 24 patients, based on the DRC recommendation of data analysis from Cohorts 1-5.

### 3.1 Sentinel Dosing (Cohorts 1-5 only)

Two sentinel patients will be enrolled at the commencement of Cohort 1 and also for any subsequent cohort that escalates the dose. The sentinel patients will receive double-blind study treatment administration with either BOTOX or placebo in a 1:1 ratio. Prior to selection as a sentinel patient, the investigator must ensure the patient agrees to attempt masturbations (see Section 6.3.5) during the first week following study treatment as a safety assessment of ejaculation, and to record the outcome of each masturbation attempt on the masturbatory ejaculation record (██████████). Sentinel patients are to be instructed to commence masturbations after 48 hours following study treatment and to attempt at least 2 masturbations before the week 1 visit.

At the week 1 visit, each sentinel patient will attend a clinic visit and will provide the completed ██████████ for review and discussion with the investigator to assess ejaculations and to determine if the patient has experienced any adverse events after study treatment. Vital signs and concurrent medications/procedures will also be recorded. This information will be provided to the DRC. If the DRC is satisfied that there are no significant safety concerns,

then the remainder of the cohort will be opened for enrollment. If the DRC determine that there are safety concerns then the sentinel patients will be unblinded to the DRC. The DRC may recommend opening of enrollment of the cohort, stopping further enrollment of the cohort, or enrolling additional sentinel patients within the cohort (maximum of 2 further sentinel patients) treated with BOTOX, prior to making a DRC recommendation to proceed.

### **3.2 Data Review Committee (Cohorts 1-5 only)**

In addition to reviewing safety data from the sentinel patients (see Section 3.1); the independent DRC will review cumulative unblinded safety and efficacy data when at least 4 weeks of data are available for all patients remaining in a cohort. The DRC will make recommendations for dose escalations, dose de-escalations, assessing alternative doses from the planned dose escalation scheme, repeating cohorts, and stopping the study.

The review of safety data will be to ensure that it is appropriate to escalate to the subsequent dose. Based on the risk/benefit profile, the DRC may also recommend stopping the study, based either on the safety data or on the efficacy data (if a signal of efficacy is achieved).

The independent DRC will be composed of an external urologist and internal Allergan members who are independent of the study team. Details of the DRC membership, data review procedures, frequency of review, stopping criteria, and communication between the DRC and other parties are detailed in the DRC charter.

For Cohort 6, no data review will be conducted by the DRC as this will be the final cohort of the study.

### **3.3 Open Label Period (Cohort 6)**

At week 12, during the randomized period exit visit, patients who complete the double-blind period of the study will be eligible to enroll into the open-label period of the study.

The patient must complete the double-blind portion of the study and have received the first injection at least 12 weeks prior before receiving the second injection in the open-label period. Day 1 of the open-label period may occur on the same day as the week-12 visit of the randomized period (provided the 1st injection occurred at least 12 weeks prior) and may occur up to 4 weeks following the week-12 visit of the randomized period, provided all inclusion/exclusion criteria are met on the day of treatment.

If the Week 12 exit visit of the randomization period and the Day 1 treatment visit of the open-label period do not occur on the same day, the assessments of the Week 12 exit visit of

the randomization period should not be repeated at the Day 1 treatment visit of the open-label period, with the exception of recording AEs, concomitant medications/procedures, and vital signs.

### **3.3.1 Qualification for Open-Label Period**

To be able to enroll into the open-label period, the patient must meet these qualification criteria:

1. The patient must request to continue his participation and inclusion into the open-label period
2. The patient must complete the double-blind portion of the study and have received the first injection at least 12 weeks prior before receiving the second injection in the open-label period
3. The patient must be free of ejaculatory adverse events
4. The investigator deems that the open-label period treatment is medically appropriate and no condition or situation exists which, in the investigator's opinion, puts the patient at significant risk from receiving a second treatment

### **3.3.2 Day 1 of Open-Label Period Injection**

Day 1 of the open-label period may occur on the same day as the week-12 visit of the randomized period (provided the 1<sup>st</sup> injection occurred at least 12 weeks prior) and may occur up to 4 weeks following the week-12 visit of the randomized period, provided all inclusion/exclusion criteria continue to be met on the day of treatment. Week 12 exit assessments of the randomization period should not be repeated at the Day 1 treatment visit of the open-label period, with the exception of recording AEs, concomitant medications/procedures, and vital signs.

## **4. Study Population and Entry Criteria**

### **4.1 Number of Patients**

Approximately 74 patients will be enrolled in the study.

For Cohort 6, approximately 24 patients will be enrolled at approximately 15 sites in the US and UK.

## 4.2 Study Population Characteristics

Men aged between 18 and 60 years in a stable monogamous sexual relationship with a female partner, who have PE as defined by the 2008 ISSM guidelines and who meet the eligibility criteria for this protocol as specified in Sections 4.3 and 4.4.

## 4.3 Inclusion Criteria

The following are requirements for entry into the study:

- [REDACTED]
- [REDACTED]
- 3. male aged 18 to 60 years
- 4. in a stable monogamous sexual relationship with a female partner for at least 6 months (with the intention to continue with the same partner for the duration of the study)
- 5. diagnosed with lifelong PE (defined as symptoms starting at the time the patient became sexually active)
- [REDACTED]
  - [REDACTED]
  - [REDACTED]
  - [REDACTED]
- [REDACTED]
  - [REDACTED]
  - [REDACTED]
  - [REDACTED]

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[REDACTED]

9. the patient has the ability to follow study instructions and complete study assessment tools, (eg, questionnaires) without any assistance or alteration to the assessment tools, except for the stopwatch and SID which may be completed with assistance from the female partner

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

#### 4.4 Exclusion Criteria

The following are criteria for exclusion from participating in the study:

##### *Premature Ejaculation Exclusion Criteria*

1. any medical or surgical condition that could be associated with secondary (acquired) PE or patient has PE which is situational or attributable to relationship issues

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█ [REDACTED]

█ [REDACTED]

4. patient reports pain on ejaculation

█ [REDACTED]

█ [REDACTED]

█ [REDACTED]

*Previous Medications/Treatments/Techniques Exclusion Criteria*

█ [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

█ [REDACTED]

10. patient has had prior genital, prostatic or lower urinary tract surgery (other than vasectomy or circumcision)

11. circumcision within 6 months of screening

12. current enrollment in an investigational drug or experimental medical device study; or use of an investigational drug or experimental medical device within 1 month of screening

*Partner Exclusion Criteria*

[Redacted]

[Redacted]

[Redacted]

*General Medical/Surgical Exclusion Criteria*

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

22. [Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

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[REDACTED]

***BOTOX-specific Exclusion Criteria***

- 30. any previous or current usage of botulinum toxin therapy of any serotype for any urological condition (eg, prostatic, detrusor, urethral, sphincteric, or pelvic floor injection therapy)
- 31. botulinum toxin therapy of any serotype for any nonurological condition or usage (eg, cosmetic, chronic migraine) during the 12 weeks prior to screening, or planned usage during the course of this study

[REDACTED]

- 34. any medical condition that may put the patient at increased risk with exposure to BOTOX including diagnosed myasthenia gravis, Eaton-Lambert syndrome, amyotrophic lateral sclerosis, or any other condition that might interfere with neuromuscular function

**4.5 Permissible and Prohibited Medications/Treatments**

**4.5.1 Permissible Medications/Treatments**

Patients must continue stable usage of concomitant therapies (except for prohibited medications/treatments; see Section 4.5.2) for the duration of the study.

As needed sleeping medications may be used, but should be avoided in the 12 hours prior to intended vaginal intercourse with their female partner (if a patient does use a sleeping medication within 12 hours of vaginal intercourse, this will not be considered a deviation to the protocol).

Medications/treatments considered necessary for the patient’s welfare may be given at the discretion of the investigator. If the permissibility of a specific medication/treatment is in question, please contact Allergan.

### 4.5.1.1 Acceptable Contraceptive Methods

If the female partner is of childbearing potential then a reliable method of contraception must be used.

[REDACTED]

The following methods of contraception, if properly used, are generally considered reliable for the female partner: oral contraceptives, patch contraceptives, injection contraceptives, diaphragm or cervical cap with spermicide, vaginal contraceptive ring, intrauterine device, surgical sterilization (bilateral tubal ligation or hysterectomy), or male patient has had a vasectomy.

The investigator will discuss contraception methods with each couple and each couple will determine the appropriate method of contraception to be used during their participation in the study.

If a study patient’s female partner becomes pregnant during the study, the investigator will notify the sponsor immediately after the pregnancy is confirmed. The investigator will (1) notify the female partner’s physician that the patient was being treated with an investigational drug, and (2) follow the progress of the pregnancy. The investigator must document the outcome of the pregnancy and provide a copy of the documentation to Allergan.

### 4.5.2 Prohibited Medications/Treatments/Techniques

No new medications or therapies (including behavioral therapy) for PE may be commenced during the study.

The decision to administer a prohibited medication/treatment is done with the safety of the study participant as the primary consideration. When possible, Allergan are to be notified before a prohibited medication/treatment is administered.

[REDACTED]

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[REDACTED]

Botulinum toxin therapy of any serotype for any indication is prohibited during the study. Patients who have used a botulinum toxin for any (nonurological) indication prior to study entry must not undergo screening until 12 weeks have elapsed since their previous botulinum toxin administration.

### 4.5.3 Anticoagulant and Antiplatelet Medications

The following classes of medications are prohibited at least 3 days immediately preceding the treatment visit:

- Anticoagulants, antiplatelet medications, or medications with anticoagulative effects which include the following:
  - warfarin and other coumadin derivatives

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Note: if the couple are not able to provide at least 4 evaluable events per month; if they alter their sexual practices; if they alter any behavioral techniques for PE; or if the patient alters alcohol consumption, these will not be considered deviations from the protocol.

## **5. Study Treatments**

### **5.1 Study Treatments and Formulations**

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

### **5.2 Control Treatment**

Each vial of placebo (formulation number: [REDACTED] contains 0.9 mg sodium chloride in a sterile, vacuum-dried form without preservatives. The diluent will be 0.9% sterile saline (without preservatives) for injection of placebo.

### **5.3 Methods for Blinding**

To maintain the double blind, the BOTOX and placebo vials and kits will be identically labeled.

### **5.4 Treatment Allocation Ratio and Stratification**

Patients will be randomly allocated (based on a randomization schedule, prepared by Allergan biostatistics) to BOTOX or placebo.

Study medication allocation will be performed using the interactive voice response system (IVRS) or the interactive web response system (IWRS).

For Cohorts 1-5, the allocation ratio for sentinel patients will be 1:1 BOTOX to placebo. The allocation ratio for subsequent patients will be 7:1 BOTOX to placebo. Two additional sentinel patients can be enrolled if requested by the DRC; further sentinel patients will be treated with BOTOX and will be in addition to the 10 planned patients within a cohort.



For Cohort 6, no sentinel dosing will occur. Twenty-four patients will be randomized at a ratio of 1:1 to receive either BOTOX [REDACTED] or placebo. Patients who choose to participate in the open-label period will receive treatment with [REDACTED] BOTOX.

There will be no stratification performed in the study.

### **5.5 Method for Assignment to Treatment Groups/Randomization**

Prior to initiation of study treatment, each patient who provides informed consent will be assigned a screening number that will serve as the patient number on all study documents.

Randomization will occur on the same day as, and prior to study treatment reconstitution/administration. At the time of randomization, eligible patients will be randomly assigned to receive BOTOX or placebo as described in Section 5.4.

In Cohorts 1-5, the dose of BOTOX received will be determined by the dose being assessed in the cohort in which the patient is enrolled; see Table 3-1 showing the planned dose escalations.

Randomized patients who exit the study prior to receiving study treatment may be replaced to ensure that the expected number of patients within a cohort receive treatment.

An automated IVRS/IWRS will be used to assign patient numbers, patient initials, and randomize patients. Treatment assignment is based on a randomization scheme prepared by Allergan biostatistics. Central randomization will occur.

Study medication will be labeled with medication kit numbers. The IVRS/IWRS system will provide the site with the specific medication kit number(s) for each randomized patient at the time of randomization. Sites will dispense study medication according to the IVRS/IWRS instructions. Sites will receive IVRS/IWRS confirmation notifications for each transaction. All notifications are to be maintained with the study source documents.

### **5.6 Treatment Regimen and Dosing**

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

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[REDACTED]

### **5.6.1 Treatment Regimen/Dosage Adjustments (Cohorts 1-5 only)**

Following unblinded evaluation by the DRC of at least 4 weeks of data from all remaining patients in the preceding cohort along with cumulative data from earlier cohorts, the DRC will recommend the appropriate dose for investigation in the subsequent cohort, or to stop the study. The planned dose escalation scheme is provided in Table 3–1, although the DRC may recommend alterations to the scheme including repeating cohorts, de-escalating or assessing alternative doses.

### **5.7 Storage of Study Medications/Treatments**

The study medication must be stored in a secure area and administered only to patients entered into the clinical study, at no cost to the patient, in accordance with the conditions specified in this protocol.

[REDACTED]

[REDACTED] Refer to the Pharmacy Manual for guidelines on acceptable variances and instructions for reporting to Allergan.

[REDACTED]

Storage conditions of vacuum-dried and reconstituted study medication will be documented.

Used investigational product vials may be stored at room temperature in a secure designated area until shipped for destruction by the site monitor.

### **5.8 Preparation of Study Medications/Treatments**

Training and instructions for reconstitution of the study drug will be provided to study sites and detailed in the Pharmacy Manual.

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[REDACTED]  
[REDACTED] The following must be completed prior to reconstitution of study medication and treatment administration:

- Final eligibility must be fully satisfied, including satisfying all inclusion and exclusion criteria (see Sections 4.3 and 4.4)
- The IVRS/IWRS will be used for randomization to allocate a drug kit number(s) associated with a box(es) of study medication. Each box will contain labeled vial of study medication. Study medication must be prepared by the DR from the specific kit(s) corresponding to the number assigned by IVRS/IWRS.
- The DR must review the relevant reconstitution instructions
- Study site personnel must notify Allergan or its designee immediately to advise of any situation in which the study medication vials are defective or diluted improperly (refer to the Pharmacy Manual)

The DR will prepare 1 mL of study medication to be provided to the investigator in 2 syringes of 0.5mL each.

## 5.9 Treatment Administration

Treatment administration must be performed by a urologist or other appropriately qualified physician who has received study-specific training on how to perform the [REDACTED]  
[REDACTED]  
[REDACTED]

### 5.9.1 Anesthesia and Sedation

The following options are permitted either alone or in combination before treatment administration:

- no anesthesia
- topical local anesthesia

- sterile local anesthetic topical preparation (eg, lidocaine cream) may be applied to the skin around the injection site
- local anesthetic injections to skin
  - sterile local anesthetic solution (eg, lidocaine solution) may be injected to the skin overlying the injection site
- Sedation
  - if it is clinically indicated, may be administered to the patient at the investigator's discretion

The type of anesthesia/sedation used and the administration method must be recorded. All local anesthesia and sedation must be administered according to local site practice and it must be confirmed prior to administration that the patient is not allergic to the anesthetic/sedative drug(s) (see study manual for additional details regarding anesthesia and sedation usage).

### **5.9.2 Bulbospongiosus Injection Technique**

Step-by-step details of the bulbospongiosus injection technique (including diagrams of the appropriate injection site) are provided in the study manual.

A diagram of the location of the bulbospongiosus muscle is provided in Attachment 12.4.

### **5.9.3 Posttreatment Observation Period**

The patient must be observed for at least 30 minutes post injection, and allowed to leave the clinic at the discretion of the investigator.

During the posttreatment observation period:

- vital signs must be collected prior to patient leaving the clinic
- any adverse events must be recorded
- any concomitant procedures/treatments performed post-injection must be recorded

## 5.9.4 Posttreatment Instructions for Patients

### *Instructions For All Patients*

Prior to leaving the site, all patients will be instructed to:

- refrain from having intercourse with their female partner for at least 48 hours
- aim for a minimum of 4 evaluable sexual events per month for the remainder of the randomized period of the study
- record all sexual events in the SID. Patients will be reminded what constitutes an evaluable event, how to measure the IELT and how to record the information in the SID (see Section 6.3.4 and Attachment 12.2)
- not alter their usual sexual practices (see Section 4.6)
- bring the SID to all study visits
- report any posttreatment adverse events including ejaculation adverse events
- seek immediate medical care and to contact the investigative site immediately if they develop priapism, significant bleeding, or signs of infection around the injection site
- contact the study site (or have a family member or friend contact the study site) to report any hospitalizations
- maintain the dose of any concomitant medication. If there are any changes to medications, dosages, or frequency, the changes must be reported to the investigator at the next study visit
- maintain the frequency of any concomitant procedure
- refrain from commencing any new medication or therapies (including behavioral therapy) for PE during the study (see Section 4.5.2)
- contact the site if they are having any difficulty with following and/or conducting study procedures (eg, the stopwatch assessment and SID completion)
- contact the study site as soon as possible if they cannot make their next scheduled study visit in order to reschedule

- receive a telephone call from the site the day after treatment

**Instructions For Sentinel Patients Only (Cohorts 1-5)**

Prior to leaving the site, sentinel patients will also be instructed to:

█ [REDACTED]

█ [REDACTED]

- attend a clinic visit 1 week following treatment

█ [REDACTED] and SID to the week 1 clinic visit

**6. Response Measures and Summary of Data Collection Methods**

**6.1 Efficacy Measures**

**6.1.1 Primary Efficacy Measure**

The primary efficacy measure is IELT as measured by stopwatch.

The IELT is captured on the SID and provides an objective assessment of the pharmacologic effects of study treatment on PE.

The primary efficacy variable will be change from baseline in the logarithm value of individual patient’s geometric mean IELT across all the evaluable ejaculatory attempts recorded in the SIDs at the end of the randomized 12 week follow-up period.

█ [REDACTED]

█ [REDACTED]

█ [REDACTED]

█ [REDACTED]

█ [REDACTED]

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[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

**6.3 Examination Procedures, Tests, Equipment, and Techniques**

Study evaluations and treatments must be performed by the same investigator/sub-investigator throughout the study whenever possible (see Table 1 and Table 2). If it is not possible for the same individual to follow the patient, then an attempt should be made to have visits overlap (examine the patient together and discuss findings) for at least one visit.

**6.3.1 Medical History, Physical Examination, and Vital Signs**

**6.3.1.1 Medical History**

A standard medical history (including all relevant conditions that the patient has had in the past or currently has) must be obtained at screening and before randomization at the treatment visit (day 1).

A sexual history must also be obtained including usage and duration of usage of all previous self-initiated or health-care-professional prescribed treatments/therapies/techniques for PE (may include, but not limited to behavioral therapies, distraction techniques, topical or oral therapies, use of condoms, etc).

All medical and surgical procedures must have an associated medical history entry.

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### 6.3.1.2 Physical Examination

A physical examination will be performed at screening and at week 12 (exit visit) of the randomized period and at week 12 of the open-label period of Cohort 6 (study exit for open label). The investigator will examine the patient for any physical abnormality of the following systems: general appearance; head, eyes, ears, nose, and throat; heart/cardiovascular; lungs; abdomen; neurologic; extremities; back; musculoskeletal; lymphatic; skin; genitourinary; and rectal. The patient's weight will also be measured. The patient's height will only be measured at the screening visit.

### 6.3.1.3 Vital Signs

Vital signs will be measured at screening, treatment/day 1 (prior to injection and prior to leaving the clinic), and all follow-up clinic visits. The following vital signs will be measured:

- pulse rate (beats per minute): the patient should be resting in a seated position for a minimum of 5 minutes prior to measurement. Pulse rate is then counted over 30 seconds ( $\times 2$ ).
- blood pressure (mm Hg): the patient must be resting in a seated position for a minimum of 5 minutes prior to measurement. Systolic/diastolic blood pressure will be measured with a sphygmomanometer.
- temperature ( $^{\circ}\text{C}/^{\circ}\text{F}$ ): temperature assessment method must be performed consistently throughout the study.

### 6.3.2 Blood Specimen Procedures

Blood samples will be obtained for the analyses of hematology and non-fasting serum chemistry.

A central laboratory will be used to analyze all blood specimens, including any repeat laboratory tests. Instructions for the collection, processing, shipment, and storage of blood samples are provided in the central laboratory manual.

All hematology and serum chemistry laboratory test results will be:

- forwarded from the central laboratory to the study site and to Allergan or its designee



- reviewed by the investigator for the clinical significance of any abnormalities
- evaluated and managed, if the laboratory result is abnormal, and conducted according to local site practice
- recorded on an adverse event electronic case report form (eCRF) page, for any clinically significant abnormalities

The laboratory results from the screening period must be reviewed prior to randomization (including the most recent results if any investigations were repeated), and randomization/treatment administration must only be performed if the investigator deems the results to be acceptable.

### **6.3.2.1 Hematology**

Hematology blood samples are to be collected at screening, week 4, and week 12 of both the randomized period and the open-label period.

Hematology measures are as follows: hematocrit, hemoglobin, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, mean corpuscular volume (MCV), platelets, red blood cell (RBC) count, RBC morphology, total white blood cell (WBC) count and differential (eg, neutrophils, bands, lymphocytes, monocytes, basophils, and eosinophils).

### **6.3.2.2 Serum Chemistry**

Nonfasting serum chemistry blood samples are to be collected at screening, and weeks 4 and 12 of both the randomized period and the open-label period.

Serum chemistry measures are as follows: albumin, alkaline phosphatase, alanine transaminase, aspartate transaminase, bicarbonate, calcium, chloride, creatinine, creatine kinase, direct bilirubin, non-fasting glucose, indirect bilirubin, magnesium, phosphorous, potassium, sodium, total bilirubin, total cholesterol, total protein, urea nitrogen, and uric acid.

### **6.3.3 Urine Specimen Procedures**

Urine samples will be obtained for central laboratory urine analysis and for urine culture and sensitivity.

A central laboratory will be used to analyze all urine specimens, including any repeat laboratory tests. Instructions for the collection, processing, shipment, and storage of urine samples are provided in the central laboratory manual.

All urine laboratory test results will be:

- forwarded from the central laboratory to the study site and to Allergan or its designee
- reviewed by the investigator for the clinical significance of any abnormalities
- evaluated and managed, if the laboratory result is abnormal, and conducted according to local site practice
- recorded on an adverse event eCRF page, for any clinically significant abnormalities

The laboratory results from the screening period must be reviewed prior to randomization (including the most recent results if any investigations were repeated), and randomization/treatment administration must only be performed if the investigator deems the results to be acceptable.

### **6.3.3.1 Central Laboratory Urine Analysis**

Urine samples are to be collected at screening, and weeks 4 and 12 of both the randomized period and the open-label period.

The urine will be analyzed for clarity, color, bilirubin, blood, glucose, ketones, leukocyte esterase, nitrite, pH, protein, specific gravity, urobilinogen, microscopic sediment (WBCs, RBCs, casts, bacteria, crystals, and epithelial cells).

### **6.3.3.2 Urine Culture and Sensitivity**

The urine culture and sensitivity sample will be analyzed as a reflex (automatic) test by the central laboratory when the central laboratory urine analysis results are suggestive of a urinary tract infection (eg, positive leukocyte esterase, nitrites, blood, or microscopic sediments such as WBCs, RBCs, and/or bacteria).

### **6.3.4 Intravaginal Ejaculatory Latency Time**

Patients will document sexual activities in the SID during screening and for 12 weeks following treatment to provide baseline and posttreatment IELT data.

Either the patient or female partner may operate the stopwatch, although the preference is for the female partner to operate the stopwatch. The stopwatch operator must be consistent throughout screening and the posttreatment period.

In the SID, patients will be asked to record the date and start time of each sexual encounter, the duration of intercourse (ie, the time from vaginal penetration until ejaculation, measured with a stopwatch), and a description of when the ejaculation occurred (ie, prior to penetration, intravaginal, did not occur, or after withdrawal) for all sexual intercourse attempts.

Patients must be instructed:

- that any behavioral techniques that were performed prior to screening should also be continued consistently for the duration of the study
- that the patient and female partner must not significantly alter their normal sexual practices during the course of the study (eg, amount of foreplay, use of lubrication, or position).
- that condoms must not be used during the study
- not to withdraw the penis from the vagina during intercourse as this would make the event nonevaluable
- to record all sexual intercourse events that constitute an attempt at penile penetration of the vagina, including any ejaculation that occurs before, during, or after the act of vaginal penetration
- that if ejaculation does not occur during intercourse and a new vaginal penetration is attempted, these separate vaginal penetrations must be recorded on the SID as 2 separate events

Additional study site instructions regarding the SID are provided in Attachment 12.2.

Sexual events recorded on the SID will be reviewed by the site and/or Allergan (or designee) to determine if the events are evaluable.

### 6.3.4.1 Definition of Evaluable Intravaginal Ejaculatory Latency Time Events

An evaluable event is defined as:

- an event in which the patient and his female partner had vaginal intercourse, and the couple have recorded that the ejaculation occurred ‘intravaginally’ and duration of time from penetration to ejaculation has been recorded

OR

- an event in which the patient and his female partner attempted to have vaginal intercourse. However, the couple have recorded that ejaculation occurred “prior to vaginal penetration”. In this scenario, the duration of time will be recorded as zero for the purpose of calculating the average IELT.

Any other scenarios will not be considered as evaluable and must not be included in the screening average IELT calculation.

### 6.3.4.2 Screening Intravaginal Ejaculatory Latency Time Collection

The patient will receive a stopwatch, the SID and written instructions during screening. The site will also provide training on the usage of the stopwatch and SID to the patient and female partner.

Patients who are taking medications that require a washout must be instructed not to commence IELT data collection until the day after the washout period has completed.

[REDACTED]

The couple must be instructed to record at least 4 evaluable attempts at vaginal sexual intercourse during a maximum of 28 days. Patients who do not record 4 evaluable events in a period of 28 days will not be eligible for study entry. Sites may contact the patient via telephone (at the sites discretion) to determine if the patient has achieved 4 evaluable events prior to the patient returning to the site for review of the SID and determination of eligibility. There is no minimum time period to collect the 4 evaluable events (more than 4 evaluable can be collected).

Eligibility will be determined from the 4 most recent evaluable events recorded on the SID during the screening period (see Section 4.3).

- The mean (average) IELT of these 4 most recent evaluable events must be  $\leq 1$  minute.
- None of these 4 most recent evaluable events can have an IELT  $\geq 2$  minutes. If any one of the 4 most recent evaluable events is  $\geq 2$  minutes, the patient is ineligible for study participation.

The site should determine which events are evaluable using the definitions in Section 6.3.4.1. If there is any ambiguity regarding if an event is evaluable the site should contact Allergan for clarification. Allergan will confirm the average IELT prior to patient randomization.

Note: if  $> 4$  events have been recorded during screening then all events must be reported on the eCRF whether or not the event is evaluable; although, only the 4 most recent evaluable events will be used to determine eligibility as described above.

### **6.3.4.3 Posttreatment Intravaginal Ejaculatory Latency Time Collection**

Patients will be instructed to refrain from having intercourse for at least 48 hours posttreatment. Patients will be reminded of the correct collection of IELT data and completion of the SID.

The couple will be instructed to record all posttreatment sexual intercourse events in the same manner as for the screening assessment, until they exit the study.

The couple will be instructed to aim for a minimum of 4 evaluable events per month and their sexual practices must remain consistent with their practices prior to study entry and during the screening period (see Section 4.6).

Patients are to be reminded to bring the SID to all study clinic visits. The site must record all available events (evaluable and not evaluable) in the eCRF.

### **6.3.5 Masturbatory Events**

*Sentinel Patients (Cohorts 1-5)* must attempt at least 2 masturbations (starting 48 hours after treatment) prior to the week 1 visit. These masturbations are to be [REDACTED], so that any safety issues related to ejaculation can be identified early and reported to the DRC prior to opening the remainder of the cohort for enrollment (see Section 3.1).

***Nonsentinel Patients (Cohorts 1-6)*** are not required to perform masturbation nor complete the [REDACTED] unless they complain of difficulty or an adverse event related to ejaculation (see Section 6.3.5.2).

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

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### 6.3.5.2 Ejaculation Adverse Events

Adverse events related to ejaculation are whenever possible to be based on findings during masturbation. If the patient complains of an ejaculation issue during nonmasturbatory situations (eg, vaginal intercourse), the site must ask the patient to confirm the findings during masturbation (if possible) and to record the finding on the [REDACTED], prior to reporting the finding as an adverse event. If the patient declines to perform a masturbation and/or completion of the [REDACTED], this should be recorded in the source documentation.

If the patient was unable to ejaculate despite sufficient manual stimulation and sufficient sexual arousal (in the patient's opinion) and the patient did not feel that with continued stimulation that ejaculation could be achieved then this must be recorded as:

- an adverse event of “delayed ejaculation” if the period of manual stimulation was < 30 minutes
- an adverse event of “anejaculation” if the period of manual stimulation was  $\geq$  30 minutes

For other ejaculation difficulties during masturbation this must be recorded as:

- an adverse event of “retrograde ejaculation”, if the patient felt that ejaculation/orgasm occurred but no semen was expelled during or immediately following ejaculation
- an adverse event of “weak ejaculation”, if ejaculation/orgasm occurred but the perceived force/strength of the ejaculation was noticeably reduced
- an adverse event of “dribbling ejaculation”, if ejaculation occurred but the semen only dribbled out during the ejaculation or shortly after the ejaculation
- an adverse event of “painful ejaculation”, if ejaculation occurred and was associated with pain for the patient

If the patient is unable or unwilling to attempt masturbations (due to religious or other reasons) then the investigator must attempt to determine the character of the ejaculatory abnormality by taking a detailed history from the patient (eg, regarding ejaculation during vaginal intercourse). In such situations, the investigator will categorize the adverse event based on their best judgment.

### 6.3.6 Questionnaire Assessments

The versions of the questionnaires provided in Attachment 12.1 of this protocol are examples and in practice will be replaced with the appropriate versions for the country where the questionnaire will be administered.

Questionnaires must be administered prior to the patient undergoing any procedures at the study visit.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

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[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]

[REDACTED]

#### **6.4 Other Study Supplies**

The following will be provided by Allergan:

- all supplies needed for blood and urine sampling (except syringes and needles)
- needles for injection of study medication

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- materials for shipment of laboratory samples to central laboratory
- stopwatches
- paper data collection materials (eg, questionnaires, SID, [REDACTED] etc)

The following will be provided by the investigator:

- syringes and needles (for reconstitution of study medication, blood sampling, and local anesthetic administration, if applicable)
- equipment for ultrasound guided treatment administration (eg, ultrasound machine, suitable ultrasound probe, ultrasound gel, and if applicable needle guides);  
Note: ultrasound equipment may be provided by Allergan if requested by the site
- sterile pads
- antiseptic solution/wipes for cleaning treatment injection area
- local anesthetic medication and sedation (if applicable)

[REDACTED]

- sterile saline (0.9% without preservative) as diluents
- appropriate electronic connections to access study-related systems (eg, high-speed internet, telephone)

## 6.5 Summary of Methods of Data Collection

An IVRS/IWRS will be used to assign patient identification numbers, patient initials, randomize patients, and manage study medication inventory.

Data for this study will be collected using eCRFs via an electronic data capture system.

Source documents will be used at the sites and may include, but are not limited to, a patient's medical record, hospital charts, clinic charts, the investigator's patient study files, still capture images and video recordings as well as the results of diagnostic tests such as laboratory tests.

A qualified central laboratory will be used for the analysis of all blood and urine samples. Laboratory data will be transferred to Allergan on a periodic basis throughout the study.

## 7. Statistical Procedures

The final analysis will be performed when all patients have completed or exited the study. A detailed analysis plan will be finalized prior to the study database lock.

### 7.1 Analysis Populations

There are 3 analysis populations: modified intent-to-treat (mITT), per protocol (PP) and safety:

- The mITT population will be used to analyze all efficacy variables; the mITT population is defined as all randomized patients that have received study medication and have postbaseline IELT data available. Analyses on the mITT population will be based on the dose actually received by the patient.
- The PP population includes patients in the mITT population who have had no significant protocol deviations and will also be used for analyzing the primary efficacy variable and summarizing baseline characteristics.
- The safety population includes all treated patients and will be used in the analysis of all safety data.

### 7.2 Collection and Derivation of Primary and Secondary Efficacy Assessments

#### 7.2.1 Primary Efficacy Variable

The primary variable for assessing the efficacy of BOTOX versus placebo will be the change from baseline in logarithm value of the individual patient's geometric mean IELT for the entire 12 weeks of the randomized period of the study. Only evaluable events on the logs will be used to calculate the geometric mean IELT. Nonevaluable events will not form part of the calculation. Data handling conventions including missing data imputation will be discussed in detail in the statistical analysis plan.

#### 7.2.2 Secondary Efficacy Variables

- geometric mean IELT up to week 2, 4, 6, 8, and 10, respectively
- average IELT up to week 2, 4, 6, 8, 10, and 12, respectively

## 7.3 Hypothesis and Methods of Analysis

### 7.3.1 Primary Efficacy Analyses

The primary timepoint for analysis is week 12.

**The primary null hypothesis:** At the primary efficacy timepoint the difference in mean change from baseline in logarithm value of the geometric mean IELT between placebo and BOTOX is at zero; and there is no dose response shown in the change from baseline in logarithm value of the geometric mean IELT.

**The primary alternative hypothesis:** At the primary efficacy timepoint the difference in mean change from baseline in logarithm value of the geometric mean IELT between placebo and BOTOX is not equal to zero; or there is a dose-response in the change from baseline in logarithm value of the geometric mean IELT.

The primary efficacy variable (change from baseline in the logarithm value of individual patient's geometric mean IELT) in relation to dose levels will be analyzed using an analysis of covariance (ANCOVA) model with treatment as the fixed effect and baseline logarithm value in geometric mean IELT as the covariate to assess the relationship of response across the BOTOX dose levels. Geometric means of the IELT up to week 12 will be log-transformed prior to analysis.

No multiplicity adjustment will be taken.

Analysis of the primary efficacy variable using a PP population will also be performed.

The log-transformed primary efficacy variable will also be analyzed with a linear regression model to assess the dose-response of the active treatments.

Details will be specified in the statistical analysis plan.

### 7.3.2 Secondary Efficacy Analyses

The following key secondary efficacy variables will be analyzed using ANCOVA, with the treatment as factor and with baseline value as a covariate:

- log-transformed geometric mean IELT up to week 2, 4, 6, 8, and 10, respectively
- average IELT up to week 2, 4, 6, 8, 10, and 12, respectively

- interval-based geometric mean IELT and average IELT for week 4, 8, and 12 (ie, events between baseline and week 4, between week 4 and week 8, and between week 8 and week 12)

Responder analyses using the fold-change threshold of 3, 4, 5, 6, 7, and 8 in the geometric mean IELT will also be conducted.

In addition, geometric mean IELT at visits will be analyzed using a likelihood-based Z-score, as well as a bootstrap test for pair-wise comparisons between each active treatment group and the placebo (Zhou et al, 1997). Nonparametric analysis including, but not limited to the Wilcoxon rank-sum test will also be performed on the geometric mean IELT. Details will be provided in the statistical analysis plan.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

- [REDACTED]
- [REDACTED]

[REDACTED]

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- [REDACTED]
- [REDACTED]

Approval Date: 15-Jul-2016

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[REDACTED]

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[REDACTED]

#### 7.4 Subgroup Analyses

No subgroup analysis is planned, but may be included in the final statistical analysis plan if deemed necessary.

#### 7.5 Sample Size Calculation

For this exploratory study, an empirical sample size is used. For Cohorts 1-5, 8 patients will be randomized to receive BOTOX and 2 patients to placebo. In Cohort 6, 24 patients will be randomized in a 1:1 ratio. The power for detecting 2, 3 and 4-fold change (the ratio between groups) with differing values for the coefficient of variation (CV) assuming the IELT is log-normally distributed, using a 2-group t-test with a 1-sided 0.10 significance level are presented in Table 7-1. The CV assumption is estimated from the pooled analysis of week 12 data from Priligy (dapoxetine hydrochloride) film-coated tablets, 30 and 60 mg ([Public Assessment Report Scientific Discussion of Priligy, 2008](#)) (Table 7-2). The CV in the pivotal studies at week 12 ranges from 0.85 to 1.64. The commercial [REDACTED] Guide 5.1 (procedure [REDACTED]) was used for the power calculation.

**Table 7–1 Power Calculation with Different Expected Fold-change Comparison Ratio and Coefficient of Variations**

Expected Fold-change	BOTOX versus Placebo	Coefficient of Variation	Power
2	8 versus 2	1	38%
		1.5	30%
		2	26%
2	8 versus 8	1	63%
		1.5	48%
		2	41%
3	8 versus 2	1	61%
		1.5	47%
		2	40%
3	8 versus 8	1	89%
		1.5	75%
		2	65%
4	8 versus 2	1	76%
		1.5	59%
		2	51%
4	8 versus 8	1	97%
		1.5	88%
		2	79%
2	12 versus 12	1	76%
		1.5	60%
		2	51%
3	12 versus 12	1	97%
		1.5	88%
		2	79%
4	12 versus 12	1	>99%
		1.5	96%
		2	91%

**Table 7–2 Coefficient of Variation at Week 12 in Priligy Pivotal Studies**

Study	Treatment Group	Mean (SD)	Coefficient of Variation
C-20052-012	Placebo	1.7 (2.09)	1.23
	DPX 30 mg PRN	2.9 (3.59)	1.24
	DPX 60mg PRN	3.4 (3.97)	1.17
C-2002-013	Placebo	1.8 (2.33)	1.29
	DPX 30 mg PRN	2.7 (3.39)	1.26
	DPX 60mg PRN	3.3 (3.40)	1.03
PRE-3001	Placebo	1.9 (3.11)	1.64
	DPX 30 mg PRN	3.2 (4.61)	1.44
	DPX 60mg PRN	3.5 (4.04)	1.15
PRE-3003	Placebo	2.4 (2.05)	0.85
	DPX 30 mg PRN	3.9 (3.95)	1.01
	DPX 60mg PRN	4.2 (3.97)	0.95
Pooled	Placebo	1.9 (2.43)	1.28
	DPX 30 mg PRN	3.1 (3.91)	1.26
	DPX 60mg PRN	3.6 (3.85)	1.07

DPX = dapoxetine hydrochloride; PRN = as needed; SD = standard deviation



## **7.6 Interim Analyses**

No interim analysis is planned for this study.

## **8. Study Visit Schedule and Procedures**

Please see Table 1 and Table 2 for the schedules of visits and procedures and Section 6.3 for detailed information on study procedures, tests, equipment, and techniques.

### **8.1 Patient Entry Procedures**

#### **8.1.1 Overview of Entry Procedures**

Prospective patients as defined by the criteria in Sections 4.3 and 4.4 (inclusion/exclusion criteria) will be considered for entry into this study.

#### **8.1.2 Informed Consent and Patient Privacy**

The study will be discussed with the patient and their female partner and both must be willing to participate and give informed consent. The patient must give informed consent prior to any study-related procedures or change in treatment. The patient and their female partner must also give authorization (US only), data protection consent (UK only), and other written documentation in accordance with the relevant country and local privacy requirements (where applicable). The patient must give patient privacy authorization prior to any study-related procedures or change in treatment.

Each patient that provides informed consent will be assigned a patient number that will be used on patient documentation throughout the study.

If the female partner does not provide consent or privacy authorization, the patient will be considered a screen failure. The female partner will not be assigned a separate screening number as no data will be collected from/about the partner.

### **8.2 Washout of Prohibited Medications**

If washout is required for the purposes of this study then the patient must sign the informed consent before the washout is commenced.

Patients taking prohibited medications must undergo a washout of the medications for at least 28 days prior to performing screening efficacy assessments (eg, stopwatch IELT measurements, SID, and health outcomes questionnaires). Any screening IELT data collected

prior to washout completion will not be considered as evaluable. The screening period may occur over several visits if needed.

A full list of prohibited medications requiring washout is provided in Section 4.5.2.

### **8.3 Procedures for Final Study Entry**

A patient is considered to have enrolled in the study upon randomization after the investigator re-verifies the patient has met all the inclusion/exclusion criteria for study entry. The investigator should also confirm that blood and urine results are acceptable prior to randomization. The treatment visit (day 1) can occur on the same day as the final screening visit if all eligibility criteria are met, depending on site and patient preference.

See Section 5.5 for the method for assignment to treatment groups/randomization.

#### **8.3.1 Extended Screening Period**

In some instances, a patient may remain in the screening period beyond 70 days (10 weeks) (maximum of 42 days of screening plus 28 days for washout, if applicable). Examples may include a randomization halt in support of DRC data review or other reason as approved by Allergan.

With the approval of the Allergan study manager, the screening period may be extended and the following procedures repeated to confirm the patient's continued eligibility for participation in the study (information may be collected by telephone):

- inclusion/exclusion criteria
- medical history
- concomitant medications/procedures
- adverse events

At the investigator's discretion or on request by Allergan, other assessments (eg, blood tests, urine tests, vital signs, IELT assessment, or questionnaires) may also be repeated to ensure the patient's continued eligibility in the study.

## 8.4 Visits and Associated Procedures

For summaries of the procedures to be performed, see Table 1 and Table 2 (Schedules of Visits and Procedures). A description of individual procedures is provided in Section 6.3. Evaluations should be performed by the same evaluator throughout the study whenever possible. During the study, every effort should be made to perform the study procedures as described in Table 1 and Table 2.

## 8.5 Instructions for the Patients

All patients and their female partners will be instructed to:

- attempt vaginal intercourse at a minimum of 4 times per month and to use the stopwatch and complete the SID as instructed
- not to change their usual sexual practices (see Section 4.6)
- refrain from condom use (see Section 4.5.1.1)
- refrain from use of prohibited medications (see Section 4.5.2)
- continue use of any ongoing medications or therapies. Any changes in dose or frequency or stoppage should be reported during a scheduled clinic visit.
- bring the SID and [REDACTED] to the study site at each scheduled clinic visit
- call the study site if any of the following occur
  - the patient experiences any difficulties following the study treatment administration or study procedures
  - the patient has any questions on completion of the SID or [REDACTED]
  - the patient is hospitalized
  - the patient's female partner becomes pregnant
  - the patient and their female partner are no longer in a stable monogamous sexual relationship

- the patient is unable to attend a scheduled clinic visit in order to reschedule the visit

For sentinel patients in Cohorts 1-5 only, the patient will be instructed to attempt and record a minimum of 2 masturbations (starting 48 hours after study treatment administration) on the [REDACTED] prior to attending the week 1 clinic visit.

## **8.6 Unscheduled Visits**

Unscheduled visits can be performed if safety concerns arise and at the discretion of the investigator. Additional examinations may be performed as necessary to ensure the safety and wellbeing of patients during the study.

## **8.7 Compliance with Protocol**

Participating patients should be able to attend all clinic visits and to adhere to the SID completion, appropriate stopwatch use, and testing parameters (patient only) as described in this protocol.

Data will be recorded on the appropriate eCRF supported by appropriate source documentation. At each visit, patients should be asked if any concomitant medications had been used, if they had undergone any concurrent procedures (nonstudy procedures), and their compliance with the protocol since the previous visit.

## **8.8 Early Discontinuation of Patients**

Patients may voluntarily withdraw from the study at any time.

Notification of early patient discontinuation from the study and the reason for discontinuation will be made to Allergan and will be clearly documented on the appropriate eCRF. If a patient exits the study prior to completion, whenever possible all week 12 exit visit assessments should be performed at the time of exit.

## **8.9 Withdrawal Criteria**

Patients have the right to withdraw from the study at any time and for any reason without prejudice to his future medical care by the physician or institution. The investigator and Allergan also have the right to withdraw a patient from the study at any time for any reason.

Where possible, the decision to withdraw a patient from the study should be discussed with Allergan.

Patients should be discontinued from the study if any of the following criteria are met.

- patient develops (or has an exacerbation of) any medical condition that, in the opinion of the investigator, would put the patient at an unacceptable medical risk or compromises the patient's ability to participate in the study
- patient or their female partner is unwilling or unable to continue to comply with the study procedures

## **8.10 Study Termination**

The study may be stopped at his/her study site at any time by the site investigator. Allergan may stop the study (and/or the study site) for any reason with appropriate notification.

## **8.11 Definition of Study End**

The end of the study is defined as the date of the last visit of the last patient participating in the study.

## **9. Adverse Events**

Adverse events occurring during the study will be recorded on an adverse event case report form including seriousness, severity, action taken, and relationship to study medication or injection procedure. If adverse events occur, the first concern will be the safety of the study participants.

### **9.1 Definitions**

#### **9.1.1 Adverse Event**

An adverse event is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An adverse event 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, whether or not related to the medicinal (investigational) product. In addition, during the screening period, adverse events will be assessed regardless of the administration of a pharmaceutical product.

Note: Adverse events must be collected once informed consent has been obtained, regardless of whether or not the patient has been administered study drug.

Adverse events will be assessed, documented, and recorded in the eCRF throughout the study (ie, after informed consent has been obtained). At each visit, the investigator will begin by querying for adverse events by asking each patient a general, nondirected question such as “How have you been feeling since the last visit?” Directed questioning and examination will then be done as appropriate. All reported adverse events will be documented on the appropriate eCRF.

### **9.1.2 Definition of Ejaculation Adverse Events**

Study-specific definitions for ejaculation adverse events are provided in Section 6.3.5.2.

In addition, all patients who report an ejaculatory adverse event should be encouraged by the site to attempt a masturbation and record the results on the [REDACTED] (both sentinel and nonsentinel patients) to help the investigator accurately characterize the event.

### **9.1.3 Serious Adverse Event**

A serious adverse event is any adverse event occurring at any dose that results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (see Section 9.3 for procedures for reporting a serious adverse event.)

Allergan considers all cancer adverse events as serious adverse events. In addition, Allergan considers any abortion (spontaneous or nonspontaneous) as a serious adverse event.

Preplanned surgeries or procedures for pre-existing, known medical conditions for which a patient requires hospitalization is not reportable as a serious adverse event.

Any preplanned surgery or procedure should be clearly documented in the site source documents by the medically qualified investigator at the time of the patient’s entry into the study. If it has not been documented at the time of the patient’s entry into the study, then it should be documented as a serious adverse event and reported to Allergan.

### 9.1.4 Severity

A clinical determination will be made of the intensity of an adverse event. The severity assessment for a clinical adverse event must be completed using the following definitions as guidelines:

Mild	Awareness of sign or symptom, but easily tolerated.
Moderate	Discomfort enough to cause interference with usual activity.
Severe	Incapacitating with inability to work or do usual activity.
Not applicable	In some cases, an adverse event may be an ‘all or nothing’ finding which cannot be graded.

### 9.1.5 Relationship to Study Medication or Study Procedure

A determination will be made of the relationship (if any) between an adverse event and the study medication or study procedure, as applicable. A causal relationship is present if a determination is made that there is a reasonable possibility that the adverse event may have been caused by the study medication or study procedure.

## 9.2 Procedures for Reporting Adverse Events

Any adverse event must be recorded on the appropriate eCRF.

All adverse events that are drug-related and unexpected (not listed as treatment-related in the current Investigator's Brochure) must be reported to the governing Institutional Review Board/Independent Ethics Committee (IRB/IEC) as required by the IRB/IEC, local regulations, and the governing health authorities. Any adverse event that is marked ‘ongoing’ at the exit visit must be followed-up as appropriate.

## 9.3 Procedures for Reporting a Serious Adverse Event

Any serious adverse event occurring during the study period (beginning with informed consent) and for at least 28 days after the last dose of study medication must be immediately reported but no later than 24 hours after learning of a serious adverse event. Serious adverse events must be reported to Allergan (or Agent of Allergan) as listed on the Allergan Study Contacts Sheet and recorded on the serious adverse event form. All patients with a serious adverse event must be followed up and the outcomes reported. The investigator must supply

Allergan and the IRB/IEC with any additional requested information (eg, autopsy reports and discharge summaries).

In the event of a serious adverse event, the investigator must:

1. notify Allergan immediately by fax or email using the serious adverse event form (contact details can be found on page 1 of the serious adverse event form, phone numbers and relevant Allergan personnel contacts are also on the front page of protocol and Study Contacts Page.
2. obtain and maintain in his/her files all pertinent medical records, information, and medical judgments from colleagues who assisted in the treatment and follow-up of the patient.
3. provide Allergan with a complete, written description of the adverse event(s) on the serious adverse event form describing the event chronologically, including any treatment given (eg, medications administered, procedures performed) for the adverse event(s). Summarize relevant clinical information about the event: signs, symptoms, diagnosis, clinical course and relevant clinical laboratory tests, etc. Include any additional or alternative explanation(s) for the causality which includes a statement as to whether the event was or was not related to the use of the investigational drug.
4. promptly inform the governing IRB/IEC of the serious adverse event as required by the IRB/IEC, local regulations, and the governing health authorities.

#### **9.4 Procedures for Unblinding of Study Medication**

When necessary for the safety and proper treatment of the patient, the investigator can unblind the patient's treatment assignment to determine which treatment has been assigned and institute appropriate follow-up care. When possible, the sponsor (Allergan Medical Safety Physician) should be notified prior to unblinding study medication. The investigator must inform the sponsor (Allergan Medical Safety Physician) of the unblinding if there is no notification prior to the unblinding.

The treatment assignment for the patient can be determined by designated site personnel calling into the IVRS or IWRS system via password protected access. The reason for breaking the code must be recorded in the patient's source documents.



## **10. Administrative Items**

This protocol is to be conducted in accordance with the applicable Good Clinical Practice (GCP) regulations and guidelines, eg, the ICH Guideline on GCP.

### **10.1 Protection of Human Patients**

#### **10.1.1 Compliance with Informed Consent Regulations (US 21 CFR Part 50) and Relevant Country Regulations**

Written informed consent is to be obtained from each patient prior to any study-related activities or procedures in the study.

#### **10.1.2 Compliance With IRB or IEC Regulations**

This study is to be conducted in accordance with IRB regulations (US 21 CFR Part 56.103) or applicable IEC regulations. The investigator must obtain approval from a properly constituted IRB/IEC prior to initiating the study and re-approval or review at least annually. Allergan is to be notified immediately if the responsible IRB/IEC has been disqualified or if proceedings leading to disqualification have begun. Copies of all IRB/IEC correspondence with the investigator should be provided to Allergan.

#### **10.1.3 Compliance With Good Clinical Practice**

This protocol is to be conducted in accordance with the applicable GCP regulations and guidelines.

#### **10.1.4 Compliance With Electronic Records; Electronic Signatures Regulations (US 21 CFR Part 11)**

This study is to be conducted in compliance with the regulations on electronic records and electronic signature.

### **10.2 Changes to the Protocol**

The investigator must not implement any deviation from or changes of the protocol without approval by Allergan and prior review and documented approval/favorable opinion from the IRB/IEC of a protocol amendment, except where necessary to eliminate immediate hazards to study patients, or when the changes involve only logistical or administrative aspects of the study (eg, change in monitors, change of telephone numbers).

### **10.3 Patient Confidentiality**

A report of the results of this study may be published or sent to the appropriate health authorities in any country in which the study drug may ultimately be marketed, but the patient's name will not be disclosed in these documents. The patient's name may be disclosed to the Sponsor of the study, Allergan, or the governing health authorities or the US FDA if they inspect the study records. Appropriate precautions will be taken to maintain confidentiality of medical records and personal information.

#### **10.3.1 Patient Privacy**

Written authorization (US sites only), data protection consent (UK sites only), and other documentation in accordance with the relevant country and local privacy requirements (where applicable) is to be obtained from each patient prior to enrollment into the study, in accordance with the applicable privacy requirements (eg, the Health Insurance Portability and Accountability Act Standards for Privacy of Individually Identifiable Health Information ("HIPAA"), European Union Data Protection Directive 95/46/EC ["EU Directive"]).

In accordance with HIPAA requirements, additional purposes of this study include the following:

- to publish anonymous patient data from the study; and
- to create and maintain a data repository

### **10.4 Documentation**

#### **10.4.1 Source Documents**

Source documents may include, but is not limited to, a patient's medical records, hospital charts, clinic charts, the investigator's patient study files, as well as the results of diagnostic tests such as ultrasound visualizations, x-rays, laboratory tests, and electrocardiograms. Any document, paper or electronic, that contains patient related information, whether the information is transcribed into the eCRF or not, is considered source documentation. The investigator's copy of the eCRFs serves as part of the investigator's record of a patient's study-related data.

At a minimum the following information should be entered into the patient's medical record:

- patient's name

- patient's contact information
- date that the patient entered the study, patient number, and patient randomization number along with anonymous patient identification and date of birth used in the eCRF
- study title and/or the protocol number of the study and the name of Allergan
- a statement that informed consent was obtained (including the date), treatment risk/benefits discussed, study related questions answered, and a copy provided to the patient
- a statement that informed consent was obtained from the female partner, study related question answered, and a copy provided to the patient/female partner
- a statement that written authorization (US sites only), data protection consent (UK sites only), or other country and local patient privacy required documentation for this study has been obtained (including the date) for both the patient and the female partner
- dates of all patient visits
- progress notes summarizing all patient visits
- medical and surgical history (including sexual history and all prior therapies and medications for treatment of PE or other previous sexual conditions)
- injection procedure with details on dosage and time of injection, and any local anesthesia or sedation used and route of administration of the anesthetic
- all concurrent medications, concurrent procedures, and behavioral therapies and other PE interventions (list all prescription and nonprescription medications/techniques being taken/done at the time of enrollment. At each subsequent visit, changes to the list of medications should be recorded).
- occurrence and status of any adverse events (including any procedure-related adverse events)
- date the patient exited the study, and a notation as to whether the patient completed the study or reason for discontinuation
- the results of laboratory tests performed by the central laboratory

- results of laboratory tests performed by the site (eg, urine pregnancy test [female partner])
- concurrent procedures performed during the study
- vital signs and physical examination findings
- height and weight
- key study variables
- details of training including topic (eg, IELT/SID or [REDACTED]), trainer (eg, investigator), trainee (eg, patient and/or female partner), and date conducted

The responses to the following questionnaires/assessments entered directly onto the appropriate form will be considered source data:

[REDACTED]

- SID

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

In addition, study drug accountability and reconstitution records will be retained as source documentation.

#### **10.4.2 Case Report Form Completion**

The investigator is responsible for ensuring that data are properly recorded on each patient's eCRF and related documents. An investigator who has signed the protocol signature page will electronically sign the Data Review Form in the eCRF to indicate the observations and findings are recorded on the eCRFs correctly and completely. The eCRFs are to be submitted to Allergan in a timely manner at the completion of the study, or as otherwise specified by Allergan.

### **10.4.3 Study Summary**

An investigator's summary will be provided to Allergan within a short time after the completion of the study, or as designated by Allergan. A summary is also to be provided to the responsible IRB/IEC.

### **10.4.4 Retention of Documentation**

All study related correspondence, patient records (ie, source documents listed in Section 10.4.1), consent forms, patient privacy documentation, records of the distribution and use of all investigational products, questionnaires, SIDs, [REDACTED], correspondence with the IRB/IEC, copies of eCRFs, and other essential documents should be maintained on file.

For countries falling within the scope of the ICH guidelines, Allergan-specific essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirement(s) or if needed by the sponsor.

In addition, for countries not falling within the scope of the ICH guidelines, local regulatory requirements should be followed regarding the retention of clinical study documentation.

Allergan requires that it be notified in writing if the investigator wishes to relinquish ownership of the data so that mutually agreed-upon arrangements can be made for transfer of ownership to a suitably qualified, responsible person.

## **10.5 Labeling, Packaging, and Return or Disposal of Study Medications/Treatments**

### **10.5.1 Labeling/Packaging**

The investigational materials will be packaged and labeled in identically appearing vials. The study treatment will be identified as an investigational compound. The study number and kit number will be identified on the unit label.

### **10.5.2 Clinical Supply Inventory**

The investigator must keep an accurate accounting of the number of investigational units received from Allergan, dispensed to the patients, the number of units returned to the investigator by the patient, and the number of units returned to Allergan during and at the completion of the study. A detailed inventory must be completed for the study medication. The study medication must be dispensed only by an appropriately qualified person to patients in the study. The medication is to be used in accordance with the protocol by patients who are under the direct supervision of an investigator.

### **10.5.3 Return or Disposal of Study Medications/Treatments and/or Supplies**

All clinical study medications/treatments will be returned to Allergan or Allergan designee for destruction.

### **10.6 Monitoring by the Sponsor**

A representative of Allergan will monitor the study on a periodic basis. The determination of the extent and nature of monitoring will be based on considerations such as the objective, purpose, design, complexity, blinding, size, and endpoints of the study.

Authorized representatives of Allergan or regulatory authority representatives will conduct on-site visits to review, audit and copy study-related documents. These representatives will meet with the investigator(s) and appropriate staff at mutually convenient times to discuss study-related data and questions.

### **10.7 Handling of Biological Specimens**

Samples of blood and urine for evaluation of hematology, chemistries, and urinalysis will be analyzed at a centralized clinical laboratory with certification from a recognized accreditation agency (eg, College of American Pathology [CAP] or Clinical Laboratory Improvement Amendments [CLIA] certification).

The central laboratory manual provides details regarding the laboratory collection and shipment procedures for blood and urine samples in this study.

## **10.8 Publications**

Allergan as the sponsor, has proprietary interest in this study. Authorship and manuscript composition will reflect joint cooperation between multiple investigators and sites and Allergan personnel. Authorship will be established prior to the writing of the manuscript. As this study involves multiple centers, no individual publications will be allowed prior to completion of the final report of the multicenter study except as agreed with Allergan.

## **10.9 Coordinating Investigator**

A signatory coordinating investigator will be designated prior to the writing of the clinical study report.

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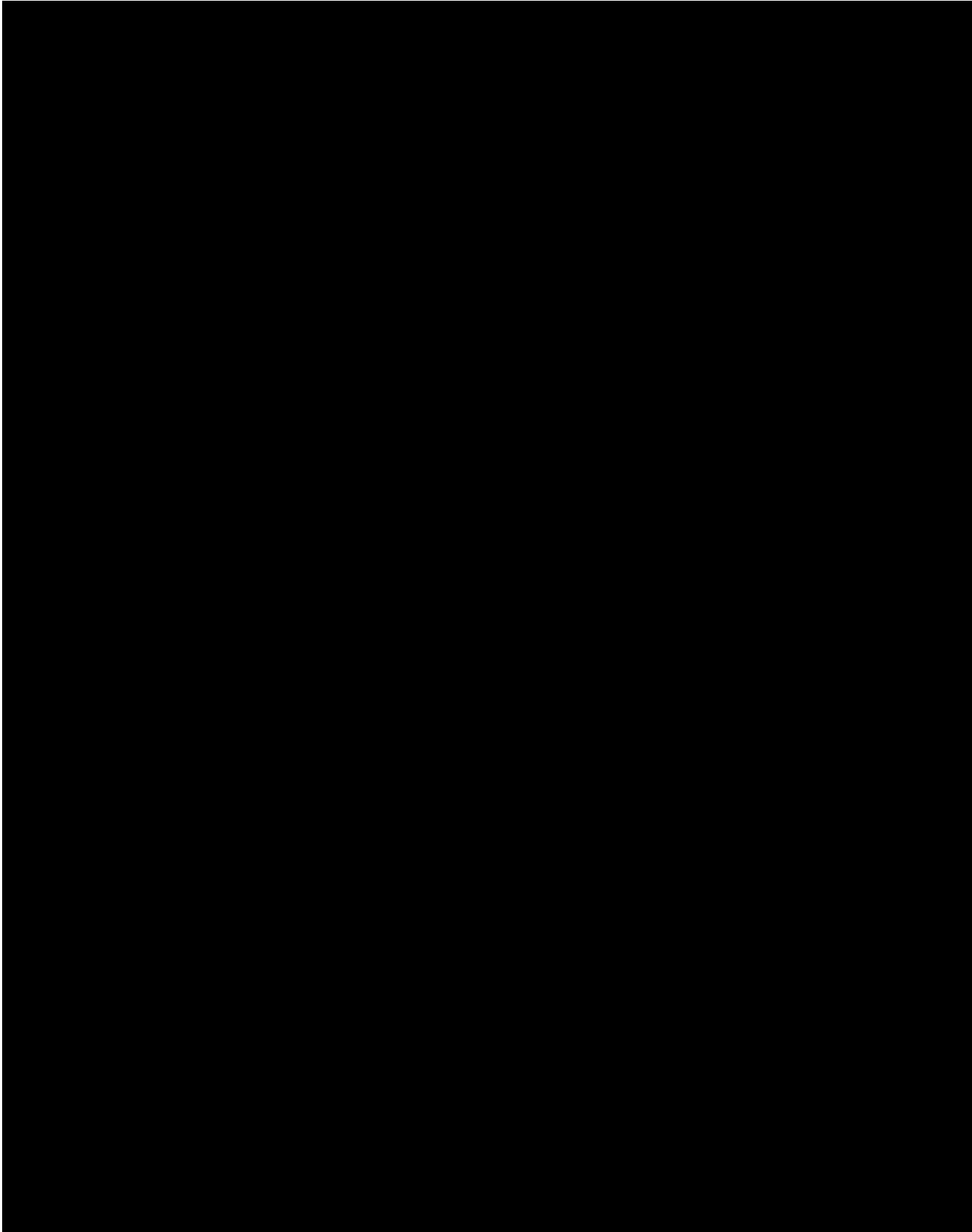
## **12. Attachments**

### **12.1 Patient Questionnaires and Instructions for Administration**

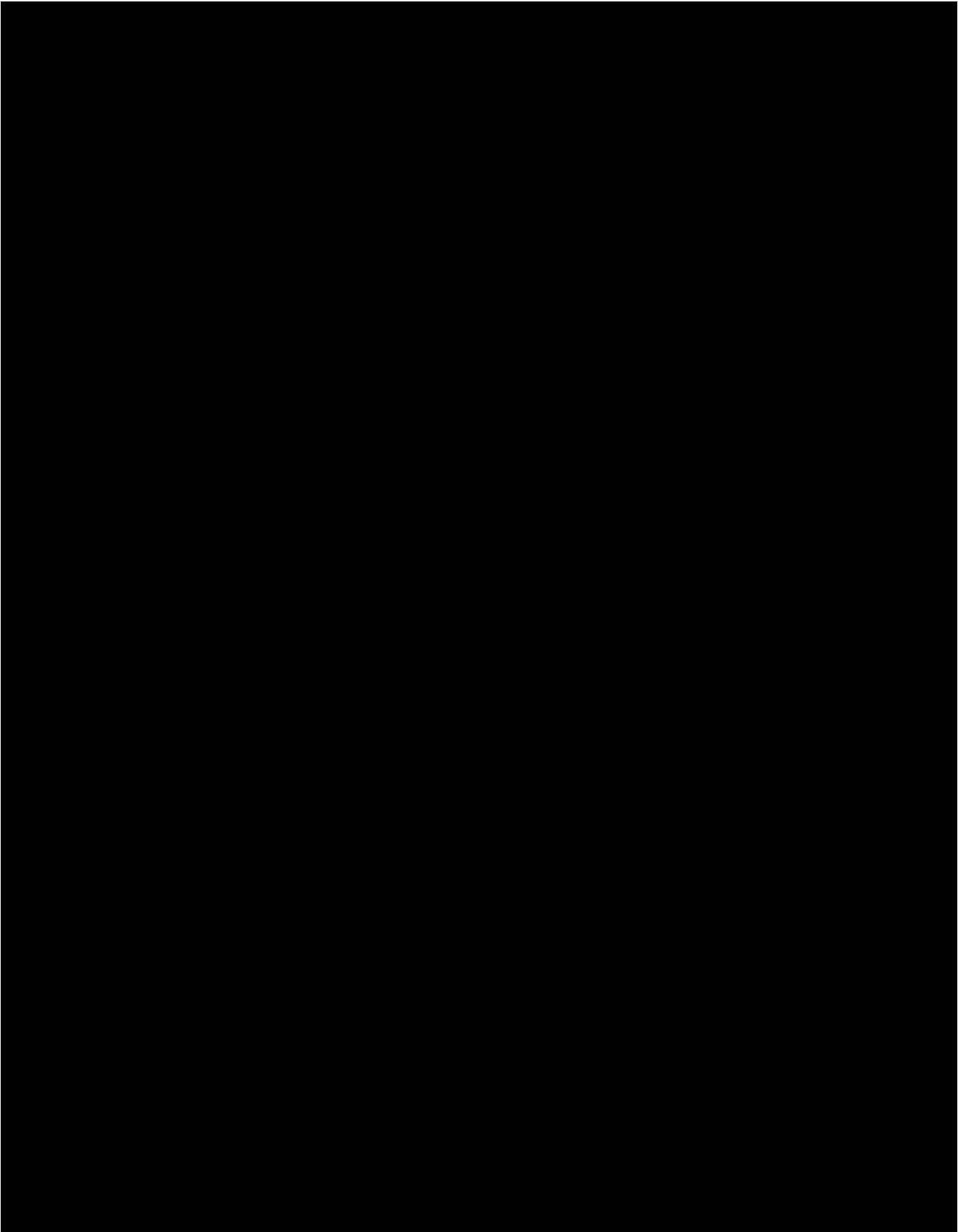
Study sites should adhere to the following instructions for all patient questionnaires:

- administered to patients prior to having any other study procedure performed at the study visit (including prior to interview procedures, such as concurrent medications, concurrent procedures, adverse event review, etc)
- completed only by the patient (no outside influences such as family/female partner or study personnel) using a black, ball point pen on a firm writing surface
- administered in a quiet place with ample time for the patient to complete the questionnaire
- filled out completely by the patient (every question must be answered)
- initialed and dated on the last page by the patient completing the questionnaire
- completed only at the protocol-specific study visits (no attempt should be made at any subsequent visit to administer missed questionnaires)
- Photocopies or protocol attachment examples of blank questionnaires must not be used by patients (only originals provided by Allergan are to be provided to the patient).
- checked for completeness, and not content, by the study site personnel in the patient's presence. Study site personnel will verify that all corrections made by the patient are initialed/dated by the patient. Study site personnel should not change responses on the questionnaires.

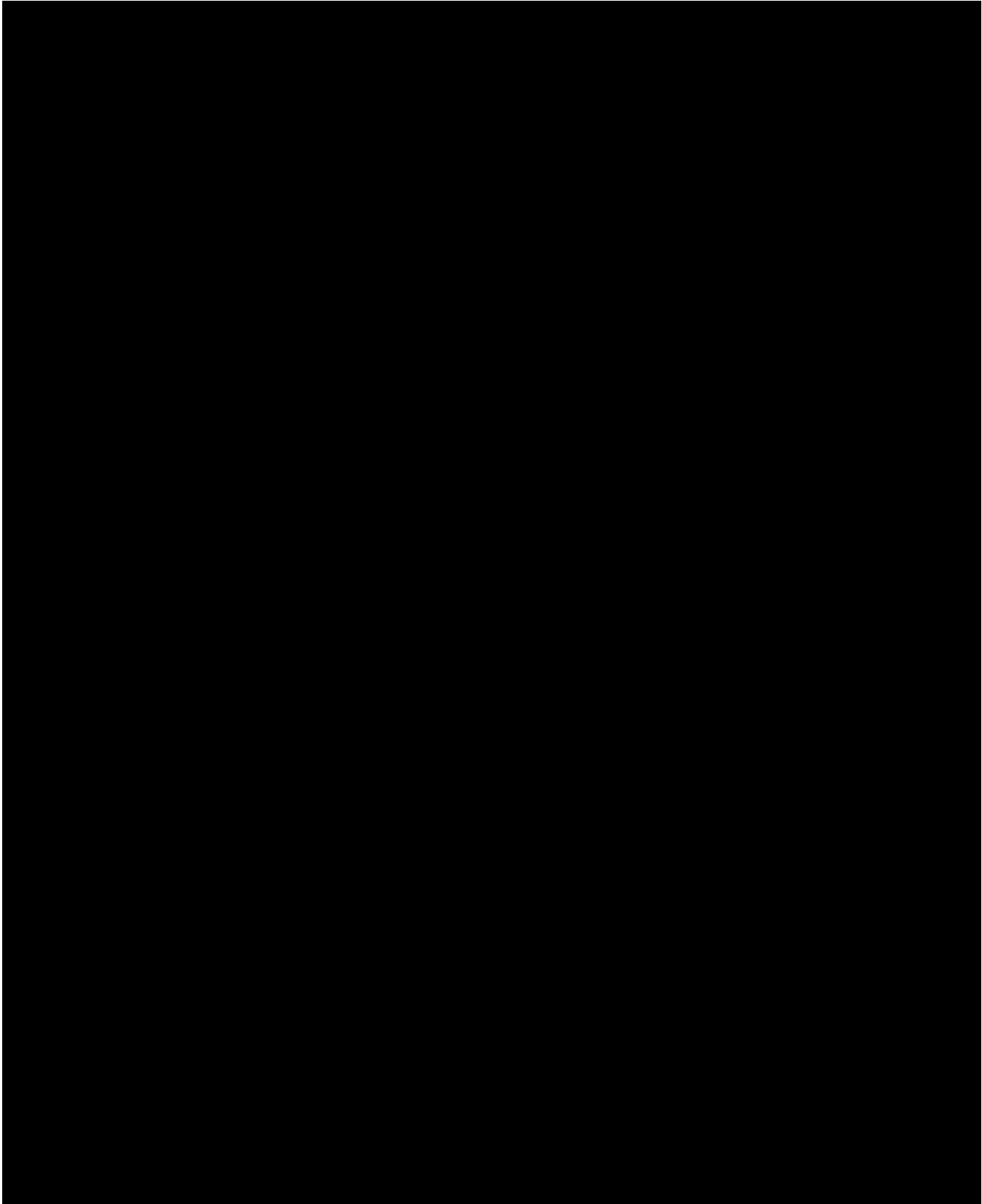
Examples of each patient questionnaire to be used during this study are provided in the sections below.



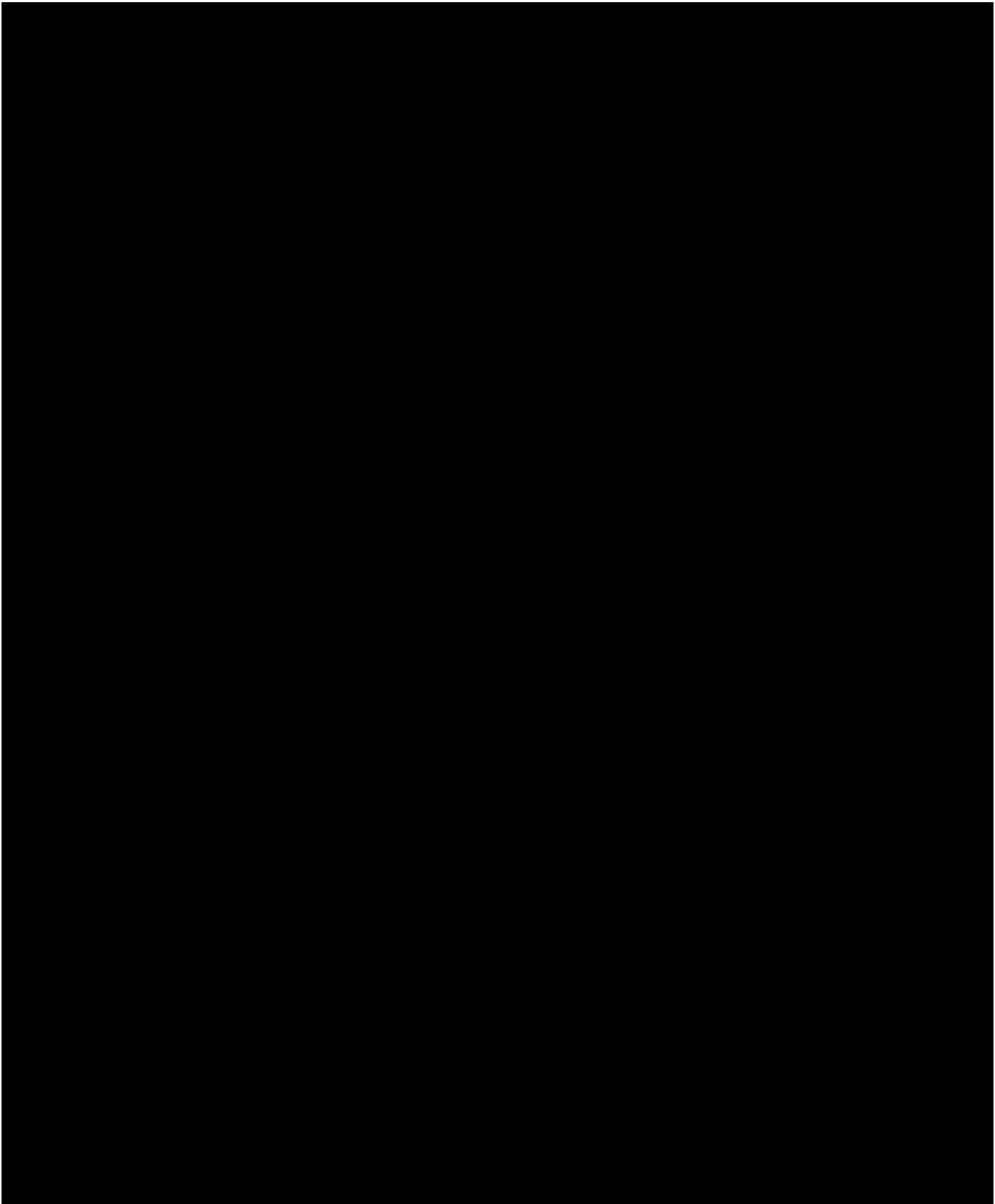
Approval Date: 15-Jul-2016



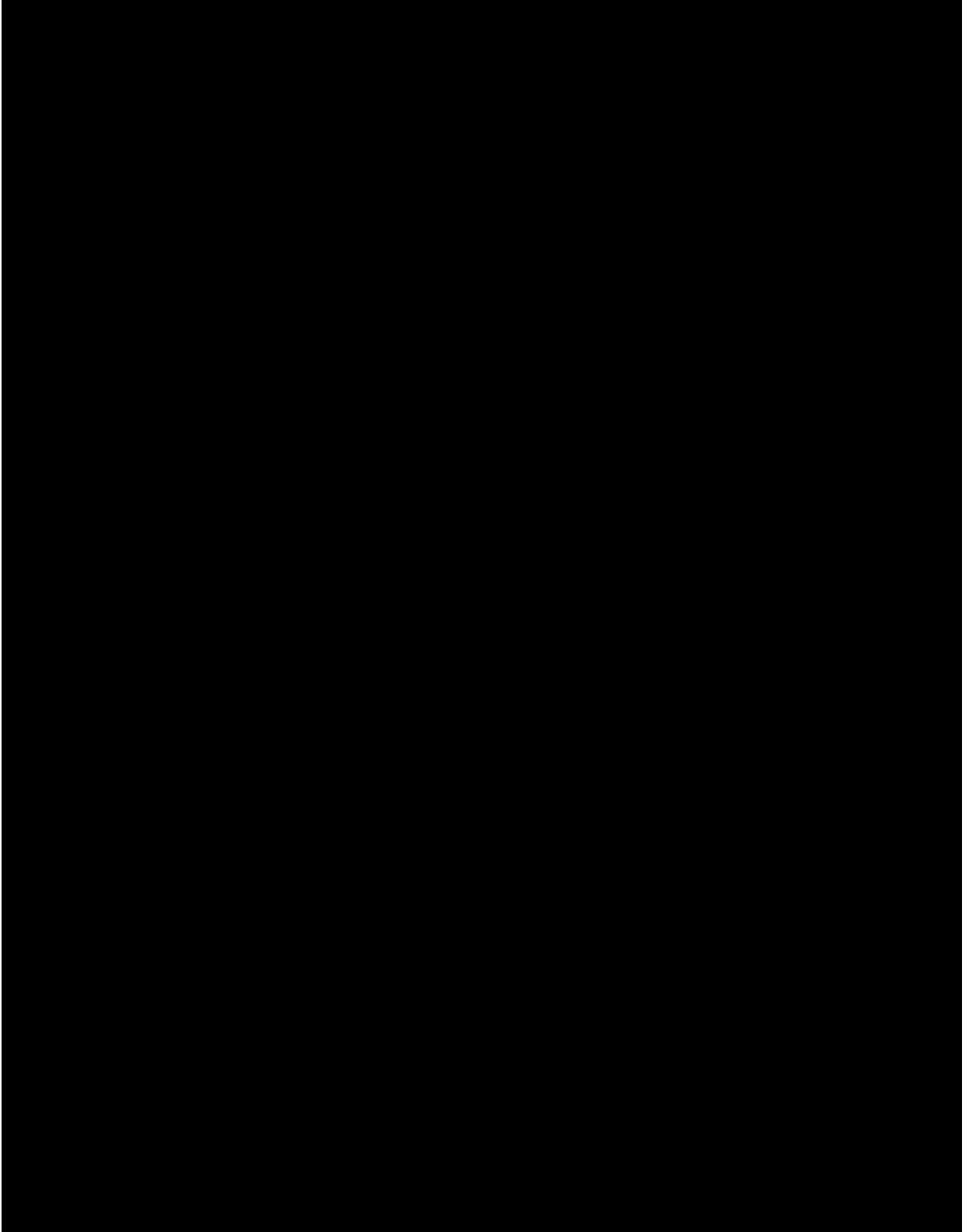
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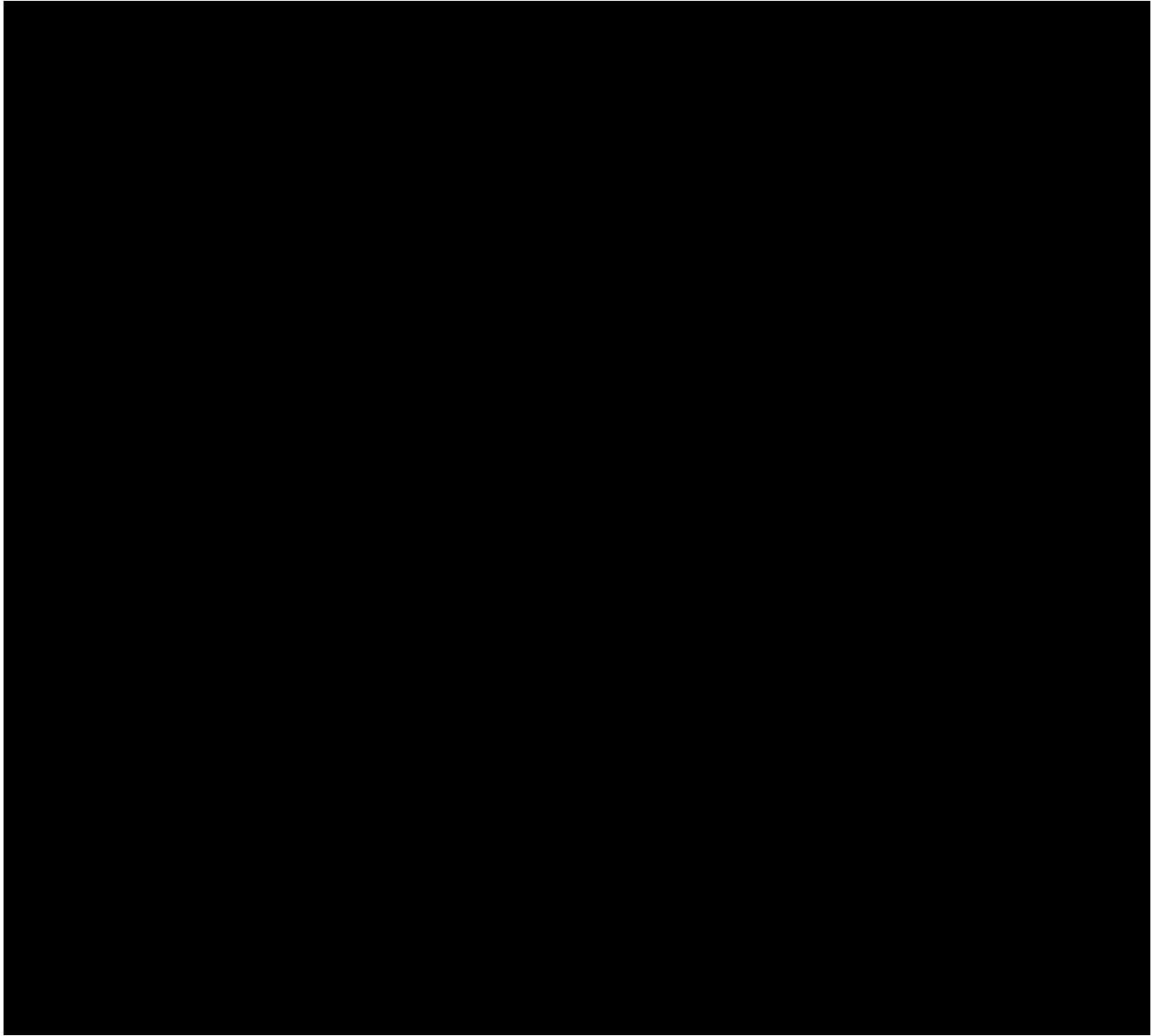


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## 12.2 Sexual Intercourse Diary

The SID will be completed by the patient and/or their female partner after any vaginal sexual activity during the screening visit and for 12 weeks following study treatment.

Study sites should adhere to the following general instructions:

- at each clinic visit, the SID is collected and reviewed for completeness and not content by the study site personnel in the patient's presence. Study site personnel will verify that all corrections made by the patient are initialed/dated by the patient. Study site personnel should not change information on the diary.
- review of SID is to occur after completion of questionnaires
- if information is not completely filled out in the diary, the patient/female partner should not be asked to recall the information
- instruct patients to refrain from altering their sexual activities (see Section 4.6) and refrain from condom usage (see Section 4.5.1.1)
- at the screening visit and each posttreatment clinic visit, the collected SID is filed as source document at the site
- completed only by the patient and/or female partner (no other outside influences such as family or study personnel)
- initialed and dated by the patient completing the diary
- completed for all attempted vaginal intercourse events
- completed only for vaginal intercourse events
- patient/female partner should call the site with any questions concerning completion of SID

Study sites should adhere to the following instructions during the screening period:

- provide initial stopwatch and SID training during the screening visit
- remind patient not to begin recording IELT in SID until after 28 days of washout has been completed (if applicable)
- instruct patients to provide at least 4 evaluable events (in a maximum of 28 days) during screening collection period

Study sites should adhere to the following instructions posttreatment:

- at the treatment visit and at each posttreatment clinic visit, SID and stopwatch training should be provided, as applicable, with emphasis on addressing corrective actions on any errors that were noted during SID review
- remind patient to wait at least 48 hours after treatment before engaging in vaginal intercourse
- instruct patients to aim for a minimum of 4 vaginal intercourse events per month for the duration of the study. For the open-label portion of the study, no minimum number of events per month is needed.

See Section 6.3.4 for additional details for patients for completing and reviewing the SID for IELT assessment.

[Redacted text block]

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- [Redacted list item 1]
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Approval Date: 15-Jul-2016

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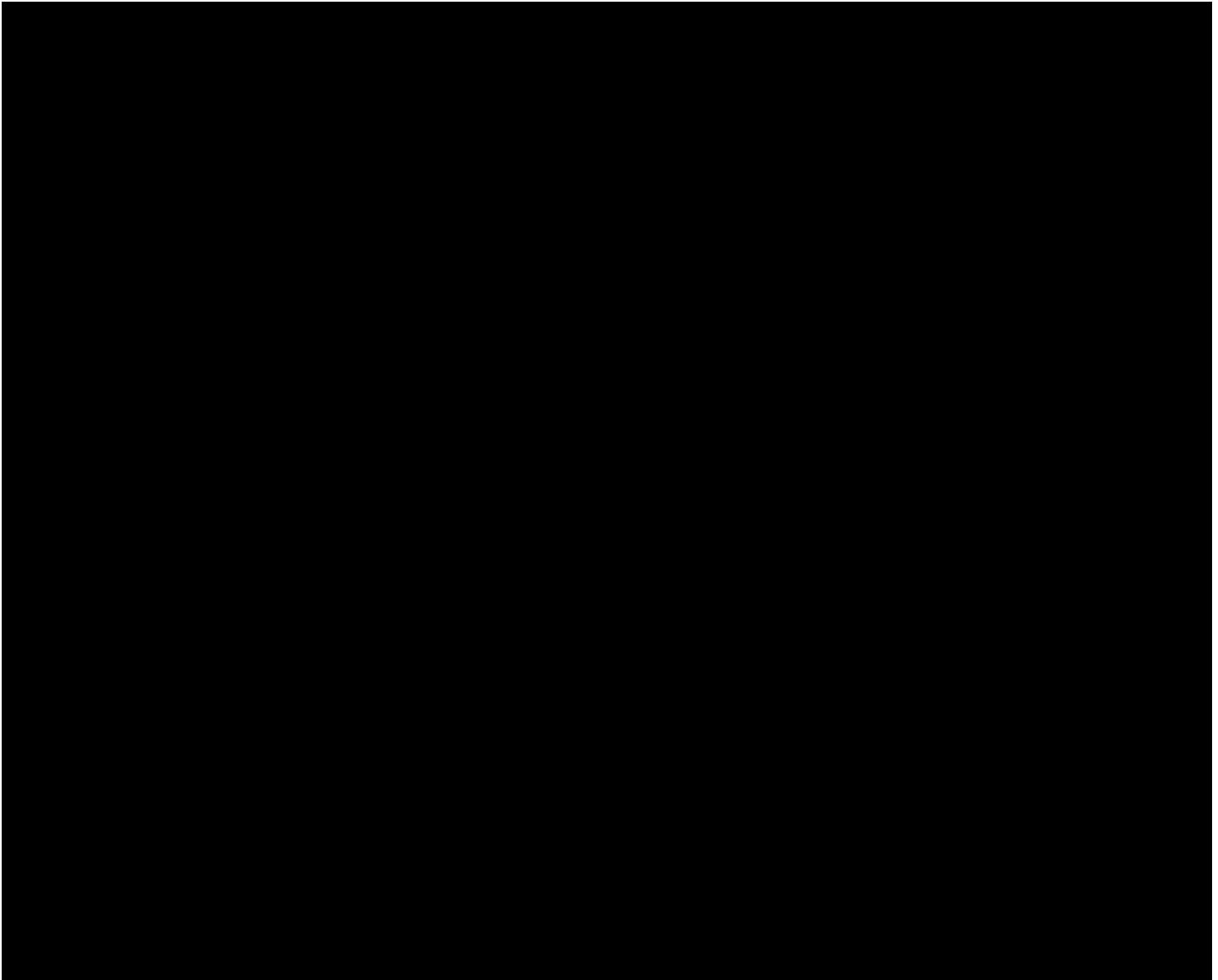
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Approval Date: 15-Jul-2016



View shows patient in lithotomy position

Approval Date: 15-Jul-2016

## **12.5 Package Insert**

The appropriate Package Insert/Summary of Product Characteristics will be supplied to investigators in countries where the product is marketed.

## 12.6 Glossary of Abbreviations

Term/Abbreviation	Definition
ANCOVA	analysis of covariance
BOTOX	Botulinum Toxin Type A Purified Neurotoxin Complex (US Adopted Name is OnabotulinumtoxinA)
BSM	bulbospongiosus muscle
[REDACTED]	[REDACTED]
DRC	Data Review Committee
eCRF	electronic case report form
CV	coefficient of variation
DR	drug reconstitutor
ED	erectile dysfunction
GCP	Good Clinical Practices
HIPAA	Health Insurance Portability and Accountability Act
HSA	human serum albumin
ICH	International Council on Harmonisation
IEC	Independent Ethics Committee
IELT	intravaginal ejaculatory latency time
[REDACTED]	[REDACTED]
IM	intramuscular
IRB	Institutional Review Board
ISSM	International Society of Sexual Medicine
IV	intravenously
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
LOAEL	lowest observable adverse effect level
mITT	modified intent-to-treat
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
NOAEL	no observed adverse effect level
PDE-5	phosphodiesterase type 5
PE	premature ejaculation
[REDACTED]	[REDACTED]
PP	per protocol
RBC	red blood cell
SID	sexual intercourse diary
SNRI	serotonin norepinephrine reuptake inhibitor
SSRI	selective serotonin reuptake inhibitor
UK	United Kingdom
US	United States



US FDA  
WBC

United States Food and Drug Administration  
white blood cell

Approval Date: 15-Jul-2016

## 12.7 Protocol Amendment 1 Summary

Protocol 191622-133 Amendment 1




Date of amendment: April 2015

The rationale for this amendment is to assess and visualize the direct effect on the bulbospongiosus muscle's ability to contract at baseline and then after the injection.

The following table summarizes changes to Protocol 191622-133. It includes content-oriented changes that were made to each section of the protocol and a brief rationale for these changes. Minor editorial and document formatting revisions are not summarized in the table.

Section	Revision	Rationale
Title Page	Revised emergency telephone numbers	Administrative change
	Revised name and contact information for Allergan Medical Safety Physician	Administrative change
Protocol Summary/ Response Measures/ Exploratory	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	Same as above
[REDACTED]	[REDACTED]	Same as above
6.5 Summary of Methods of Data Collection	[REDACTED]	Same as above

Approval Date: 15-Jul-2016

<b>Section</b>	<b>Revision</b>	<b>Rationale</b>
7.2.2 Secondary Efficacy Variables		Same as above
		Same as above

## 12.8 Protocol Amendment 2 Summary

Protocol 191622-133 Amendment 2

Date of amendment: July 2016

The rationale for this amendment is to 1) specify Cohort 6 with 24 patients (no sentinel dosing) randomized 1:1 to receive BTX [REDACTED] or placebo, 2) add an open-label period following the 12-week randomized period, 3) increase the maximum inclusion age from 50 to 60 years, 4) add additional study sites in the United States, and 5) remove [REDACTED]  
[REDACTED]

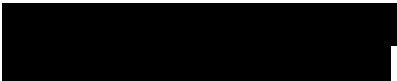
The following table summarizes changes to Protocol 191622-133 Amendment 1. It includes content-oriented changes that were made to each section of the protocol and a brief rationale for these changes. Minor editorial and document formatting revisions including the addition of wording such as “(Cohorts 1-5 only)” and clarification that “partner” refers to a “female partner” were added throughout the document for clarity and are not summarized in the table.

Section	Revision	Rationale
Title Page	Revised sponsor’s address	Administrative change
Investigator Signature Page	Revised to current company wording	Updated to current template wording
Protocol Summary, Section 3 (Study Design)	The study design was updated to include an open-label period and study visits during the randomized period and the open-label period were clarified	To address DRC request to change dosing and sample size for Cohort 6
Protocol Summary	Changed the study duration from up to 12 weeks to up to 24 weeks	To add an open-label period for Cohort 6
Protocol Summary, Section 5.6 (Treatment Regimen and Dosing)	Changed the maximum BOTOX total dose from [REDACTED]	To address DRC request to change dosing

Approval Date: 15-Jul-2016

<b>Section</b>	<b>Revision</b>	<b>Rationale</b>
Protocol Summary, Section 3 (Study Design), Table 3-1, Section 5.4 (Treatment Allocation Ratio and Stratification)	Added dosing information for Cohort 6 where 24 subjects will be randomized 1:1 to receive a single dose of BOTOX [REDACTED] or placebo	To address DRC request to change dosing and sample size for Cohort 6
Protocol Summary	Added a visit schedule for Cohort 6 during the randomized period and the open-label period	To accommodate the added open-label period
Protocol Summary, Section 4.1 (Number of Patients)	Updated the anticipated total number of subjects from 60 to 74	To address DRC request to change sample size of Cohort 6
Protocol Summary, Section 4.2 (Study Population Characteristics), Section 4.3 (Inclusion Criteria)	Changed the maximum patient age from 50 years to 60 years	Required to enroll a sufficient number of subjects
Protocol Summary, Section 4.6 (Sexual Activity and Practices), Section 5.9.4 (Posttreatment Instructions for Patients)	[REDACTED]	[REDACTED]
Protocol Summary, Section 4.4 (Exclusion Criteria)	[REDACTED]	To accurately define the exclusion criteria
Protocol Summary, Section 6.1.3 (Exploratory Measure), Section 6.3.6.4 (Clinical Global Impression of Change), Section 7.3.5 (Exploratory Analyses)	[REDACTED]	[REDACTED]

<b>Section</b>	<b>Revision</b>	<b>Rationale</b>
Protocol Summary	Clarified that the safety response measures will be assessed in both randomized and open-label periods	To confirm that safety measures do not change regardless of the cohort or the period of the study
Protocol Summary, Section 7.5 (Sample Size Calculation)	Specified the number of subjects to be enrolled by cohort	To address DRC request to change sample size
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
Section 3.2 (Data Review Committee)	Added that no data review of Cohort 6 will be conducted by the data review committee	To clarify that the DRC is not scheduled to review Cohort 6 as this is the final cohort
Section 3.3 (Open-label Period)	Added that at week 12, during the randomized period exit visit, patients who complete the double-blind period of the study will be eligible to enroll into the open-label period of the study	To clarify the criteria for entry into the open-label period for Cohort 6 and the dosing information
Section 4.1 (Number of Patients)	Updated the total number of study sites from 10 to 15	To support enrollment
Section 6.3.1.2 (Physical Examination)	Added wording for the physical exam of Cohort 6 to be performed at week 12 of the open-label period	To accommodate Cohort 6 activities and timelines
Section 6.3.2.1 (Hematology), Section 6.3.2.2 (Serum Chemistry), Section 6.3.3.1 (Central Laboratory Urine Analysis)	Added clarification that hematology, serum chemistry, and urine samples will be collected at both the randomized period and the open-label period	For clarity

<b>Section</b>	<b>Revision</b>	<b>Rationale</b>
Section 6.3.6.1 (International Index of Erectile Function - Erectile Function)		To accurately define the exclusion criteria
Section 7.2.1 (Primary Efficacy Variable)	Adding wording to clarify that IELT was assessed during the randomized period of the study only	To clarify the primary endpoint timelines
Section 7.6 (Interim Analyses)	Deleted that a data review committee will perform ongoing unblinded review of safety and efficacy	To clarify that no additional DRC activities are scheduled
Attachment 12.2 (Sexual Intercourse Diary)	Updated the diary instructions to clarify that no minimum number of events per month is needed for the open-label period	To clarify that there is no need for a minimum of vaginal intercourses for the open-label period

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Date (DD/MMM/YYYY)/Time (PT)

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Signed by:

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Justification

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