CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

BLA 103000/S-5050

Trade Name: Botox

Generic Name: onabotulinumtoxinA

Sponsor: Allergan, Inc.

Approval Date: July 19, 2004

Indications: Indicated for the treatment of primary axillary hyperhidrosis.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 103000/S-5050

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 103000/S-5050

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20852

Our STN: BL 103000/5050

JUL 19 2004

Allergan, Incorporated
Attention: Adelbert L. Stagg, Ph.D.
Senior Director, Worldwide Regulatory Affairs
2525 Dupont Drive
Irvine, CA 92623-9534

Dear Dr. Stagg:

Your request to supplement your biologics license application for Botulinum Toxin Type A to include a new indication for primary axillary hyperhidrosis has been approved.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred.

Your supplement was submitted without studies in pediatric patients less than 11 years of age. We are waiving the pediatric study requirement for ages 11 years and below.

We acknowledge your written commitments to provide additional information on ongoing studies and to conduct postmarketing studies as described in your letter of July 7, 2004 as outlined below:

Postmarketing Studies subject to reporting requirements of 21 CFR 601.70.

1. To conduct an open-label, repeated treatment, pediatric study in 130 patients, 12-16 years of age with severe axillary hyperhidrosis that is inadequately managed with topical agents. The final study protocol will be submitted by May 31, 2005. Patient enrollment will be initiated by August 30, 2005 and the last patient will be enrolled by August 30, 2006. The last patient will leave the study by August 30, 2007, and the study will be completed by October 31, 2007. The final study report will be completed by February 28, 2008 and submitted to the Agency (including SAS data and revised labeling) by May 30, 2008.

2. To conduct an open-label, three-year safety study (USA) in at least 150 patients, 17 to 64 years of age with severe primary axillary hyperhidrosis. The final study protocol was submitted on December 21, 2001. Patient enrollment has been completed. The last patient will leave the study on December 31, 2005. The study will be completed by February 28, 2006. The final study report will be completed by June 30, 2006, and submitted to the Agency (including SAS data and revised labeling, if appropriate) by September 30, 2006.

3. To conduct an open-label, three-year safety study (non-USA) in at least 150 patients, 17 to 64 years of age with persistent severe primary hyperhidrosis of the axillae. The final study protocol was submitted on May 9, 2003. Patient enrollment has been completed. The last patient will leave the study on April 30, 2007. The study will be completed by June 30, 2007. The final study report will be completed by November 30, 2007, and submitted to the Agency (including SAS data and revised labeling, if appropriate) by September 30, 2008.

4. To conduct a double-blind, placebo-controlled, repeat treatment study in 300 patients, 12 to 75 years of age with severe primary palmar hyperhidrosis that is inadequately managed with topical agents, with onset at least one year prior to study enrollment. The final study protocol will be submitted by September 30, 2005. Patient enrollment will be initiated by November 30, 2005 and the last patient will be enrolled by August 30, 2006. The last patient will leave the study by August 30, 2007, and the study will be completed by October 31, 2007. The final study report will be completed by February 28, 2008 and submitted to the Agency (including SAS data and revised labeling) by May 30, 2008.

5. To include the text from the Warning Section on Hypersensitivity Reactions in the Botox Cosmetic label at the time of next printing in July, 2004 to be made available for production to use with product manufactured starting in July, 2004 and then distributed. This label will be submitted to the Agency as a Changes Being Effected (CBE) at printing by July 31, 2004.

We request that you submit clinical protocols to your IND, with a cross-reference letter to this biologics license application (BLA), STN BL 103000. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to your BLA STN BL 103000. Please use the following designators to label prominently all submissions, including supplements, relating to these postmarketing study commitments as appropriate:

- Postmarketing Study Protocol
- Postmarketing Study Final Report
- Postmarketing Study Correspondence
- Annual Report on Postmarketing Studies

For each postmarketing study subject to the reporting requirements of 21 CFR 601.70, you must describe the status in an annual report on postmarketing studies for this product. The status report for each study should include:

- information to identify and describe the postmarketing commitment,
- the original schedule for the commitment,
- the status of the commitment (i.e. pending, ongoing, delayed, terminated, or submitted), and
- an explanation of the status including, for clinical studies, the patient accrual rate (i.e. number enrolled to date and the total planned enrollment).

As described in 21 CFR 601.70(e), we may publicly disclose information regarding these postmarketing studies on our Web site (http://www.fda.gov/cder/pmc/default.htm). Please refer to the April 2001 Draft Guidance for Industry: Reports on the Status of Postmarketing Studies - Implementation of Section 130 of the Food and Drug Administration Modernization Act of 1997 (see http://www.fda.gov/cber/gdlns/post040401.htm) for further information.

Please submit all final printed labeling at the time of use and include implementation information on FDA Form 356h. Please provide a PDF-format electronic copy as well as original paper copies (ten for circulars and five for other labels). In addition, you may wish to submit draft copies of the proposed introductory advertising and promotional labeling with a cover letter requesting advisory comments to the Division of Drug Marketing, Advertising and Communication (HFD-42), Center for Drug Evaluation and Research, 5600 Fishers Lane/Room 8B45, Rockville, MD 20857. Final printed advertising and promotional labeling should be submitted at the time of initial dissemination, accompanied by an FDA Form 2253.

All promotional claims must be consistent with and not contrary to approved labeling. You should not make a comparative promotional claim or claim of superiority over other products unless you have substantial evidence to support that claim.

The regulatory responsibility for review and continuing oversight for this product transferred from the Center for Biologics Evaluation and Research to the Center for Drug Evaluation and Research effective June 30, 2003. For further information about the transfer, please see http://www.fda.gov/cder/biologics/default.htm. Until further notice, however, all correspondence, except as provided elsewhere in this letter, should continue to be addressed to:

CBER Document Control Center
Attn: Office of Therapeutics Research and Review
Suite 200N (HFM-99)
1401 Rockville Pike
Rockville, Maryland 20852-1448

This information will be included in your biologics license application file.

Sincerely,

(b)(6)

Marc Walton, M.D., Ph.D.
Director
Division of Therapeutic Biological Internal Medicine Products
Office of Drug Evaluation VI
Center for Drug Evaluation and Research

Enclosures: Package Insert

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 103000/S-5050

LABELING

BOTOX® (Botulinum Toxin Type A)
Purified Neurotoxin complex

Manufactured by:
Allergan Pharmaceuticals Ireland
a subsidiary of
Allergan, Inc., 2525 Dupont Drive, Irvine, CA 92612

DESCRIPTION: BOTOX® (Botulinum Toxin Type A) Purified Neurotoxin Complex is a sterile, vacuum-dried purified botulinum toxin type A, produced from fermentation of Hall strain *Clostridium botulinum* type A grown in a medium containing casein hydrolysate, glucose and yeast extract. It is purified from the culture solution by dialysis and a series of acid precipitations to a complex consisting of the neurotoxin, and several accessory proteins. The complex is dissolved in sterile sodium chloride solution containing Albumin (Human) and is sterile filtered (0.2 microns) prior to filling and vacuum-drying.

One Unit of **BOTOX®** corresponds to the calculated median intraperitoneal lethal dose (LD_{50}) in mice. The method utilized for performing the assay is specific to Allergan's product, **BOTOX®**. Due to specific details of this assay such as the vehicle, dilution scheme and laboratory protocols for the various mouse LD_{50} assays, Units of biological activity of **BOTOX®** cannot be compared to nor converted into Units of any other botulinum toxin or any toxin assessed with any other specific assay method. Therefore, differences in species sensitivities to different botulinum neurotoxin serotypes precludes extrapolation of animal-dose activity relationships to human dose estimates. The specific activity of **BOTOX®** is approximately 20 Units/nanogram of neurotoxin protein complex.

Each vial of **BOTOX®** contains 100 Units (U) of *Clostridium botulinum* type A neurotoxin complex, 0.5 milligrams of Albumin (Human), and 0.9 milligrams of sodium chloride in a sterile, vacuum-dried form without a preservative.

CLINICAL PHARMACOLOGY: BOTOX® blocks neuromuscular transmission by binding to acceptor sites on motor or sympathetic nerve terminals, entering the nerve terminals, and inhibiting the release of acetylcholine. This inhibition occurs as the neurotoxin cleaves SNAP-25, a protein integral to the successful docking and release of acetylcholine from vesicles situated within nerve endings.

When injected intramuscularly at therapeutic doses, **BOTOX®** produces partial chemical denervation of the muscle resulting in a localized reduction in muscle activity. In addition, the muscle may atrophy, axonal sprouting may occur, and extrajunctional acetylcholine receptors may develop. There is evidence that reinnervation of the muscle may occur, thus slowly reversing muscle denervation produced by **BOTOX®**.

When injected intradermally, **BOTOX®** produces temporary chemical denervation of the sweat gland resulting in local reduction in sweating.

Pharmacokinetics

Botulinum Toxin Type A is not expected to be present in the peripheral blood at measurable levels following IM or intradermal injection at the recommended doses. The recommended quantities of neurotoxin administered at each treatment session are not expected to result in systemic, overt distant clinical effects, i.e. muscle weakness, in patients without other neuromuscular dysfunction. However,

sub-clinical systemic effects have been shown by single-fiber electromyography after IM doses of botulinum toxins appropriate to produce clinically observable local muscle weakness.

Clinical Studies:

Cervical Dystonia:

A phase 3 randomized, multi-center, double blind, placebo-controlled study of the treatment of cervical dystonia was conducted.[1] This study enrolled adult patients with cervical dystonia and a history of having received **BOTOX®** in an open label manner with perceived good response and tolerable side effects. Patients were excluded if they had previously received surgical or other denervation treatment for their symptoms or had a known history of neuromuscular disorder. Subjects participated in an open label enrichment period where they received their previously employed dose of **BOTOX®**. Only patients who were again perceived as showing a response were advanced to the randomized evaluation period. The muscles in which the blinded study agent injections were to be administered were determined on an individual patient basis.

There were 214 subjects evaluated for the open label period, of which 170 progressed into the randomized, blinded treatment period (88 in the **BOTOX**® group, 82 in the placebo group). Patient evaluations continued for at least 10 weeks post-injection. The primary outcome for the study was a dual endpoint, requiring evidence of both a change in the Cervical Dystonia Severity Scale (CDSS) and an increase in the percentage of patients showing any improvement on the Physicians Global Assessment Scale at 6 weeks after the injection session. The CDSS quantifies the severity of abnormal head positioning and was newly devised for this study. CDSS allots 1 point for each 5 degrees (or part thereof) of head deviation in each of the three planes of head movement (range of scores up to theoretical maximum of 54). The Physician Global Assessment Scale is a 9 category scale scoring the physician's evaluation of the patients' status compared to baseline, ranging from –4 to +4 (very marked worsening to complete improvement), with 0 indicating no change from baseline and +1 slight improvement. Pain is also an important symptom of cervical dystonia and was evaluated by separate assessments of pain frequency and severity on scales of 0 (no pain) to 4 (constant in frequency or extremely severe in intensity). Study results on the primary endpoints and the pain-related secondary endpoints are shown in Table 1.

Table 1: Efficacy Outcomes of The Phase 3 Cervical Dystonia Study (Group Means)

	Placebo N=82	**BOTOX®** N=88	95% Cl on Difference
Baseline CDSS	9.3	9.2	
Change in CDSS at Week 6	-0.3	-1.3	(-2.3, 0.3)[a,b]
Percentage Patients with Any Improvement on Physicians Global Assessment	31%	51%	(5%, 34%)[a]
Pain Intensity Baseline	1.8	1.8	
Change in Pain Intensity at Week 6	-0.1	-0.4	(-0.7, -0.2)[c]
Pain Frequency Baseline	1.9	1.8	
Change in Pain Frequency at Week 6	-0.0	-0.3	(-0.5, -0.0)[c]

[a] Confidence intervals are constructed from the analysis of covariance table with treatment and investigational site as main effects, and baseline CDSS as a covariate.
[b] These values represent the prospectively planned method for missing data imputation and statistical test. Sensitivity analyses indicated that the 95% confidence interval excluded the value of no difference between groups and the p-value was less than 0.05. These analyses included several alternative missing data imputation methods and non-parametric statistical tests.
[c] Confidence intervals are based on the t-distribution

Exploratory analyses of this study suggested that the majority of patients who had shown a beneficial response by week 6 had returned to their baseline status by 3 months after treatment. Exploratory analyses of subsets by patient sex and age suggest that both sexes receive benefit, although female patients may receive somewhat greater amounts than male patients. There is a consistent treatment-associated effect between subsets greater than and less than age 65 (see also **PRECAUTIONS**: **Geriatrics**). There were too few non-Caucasian patients enrolled to draw any conclusions regarding relative efficacy in racial subsets.

There were several randomized studies conducted prior to the phase 3 study which were supportive but not adequately designed to assess or quantitatively estimate the efficacy of **BOTOX®**.

In the phase 3 study the median total **BOTOX®** dose in patients randomized to receive **BOTOX®** (n=88) was 236 Units, with 25^{th} to 75^{th} percentile ranges of 198 to 300 Units. Of these 88 patients, most received injections to 3 or 4 muscles; 38 received injections to 3 muscles, 28 to 4 muscles, 5 to 5 muscles and 5 to 2 muscles. The dose was divided amongst the affected muscles in quantities shown in Table 2. The total dose and muscles selected were tailored to meet individual patient needs.

Table 2: Number of Patients Treated Per Muscle And Fraction Of Total Dose Injected Into Involved Muscles

Muscle*	**Number of Patients Treated in this Muscle (N=88)**	**Mean % Dose per Muscle**	**Mid-Range of % Dose per Muscle***
Splenius capitis/cervicis	83	38	25-50
Sternocleidomastoid	77	25	17-31
Levator scapulae	52	20	16-25
Trapezius	49	29	18-33
Semispinalis	16	21	13-25
Scalene	15	15	6-21
Longissimus	8	29	17-41

*The mid-range of dose is calculated as the 25^{th} to 75^{th} percentiles.

NOTE: There were 16 patients who had additional muscles injected.

Primary Axillary Hyperhidrosis:

The efficacy and safety of **BOTOX®** for the treatment of primary axillary hyperhidrosis were evaluated in two randomized, multi-center, double-blind, placebo-controlled studies.

Study 1 included adult patients with persistent primary axillary hyperhidrosis who scored 3 or 4 on a Hyperhidrosis Disease Severity Scale (HDSS) and who produced at least 50mg of sweat in each axilla at rest over 5 minutes. HDSS is a 4-point scale with 1= "underarm sweating is never noticeable and never interferes with my daily activities"; to 4 = "underarm sweating is intolerable and always interferes with my daily activities". A total of 322 patients were randomized in a 1:1:1 ratio to treatment in both axillae with either 50 Units of **BOTOX®**, 75 Units of **BOTOX®**, or placebo. Patients were evaluated at 4-week intervals. Patients who responded to the first injection were re-injected when they reported a re-increase in HDSS score to 3 or 4 and produced at least 50mg sweat in each axilla by gravimetric measurement, but no sooner than 8 weeks after the initial injection.

Study responders were defined as patients who showed at least a 2-grade improvement from baseline value on the HDSS 4 weeks after both of the first two treatment sessions or had a sustained response after their first treatment session and did not receive re-treatment during the study. Spontaneous resting axillary sweat production was assessed by weighing a filter paper held in the axilla over a period of 5 minutes (gravimetric measurement). Sweat production responders were those patients who demonstrated a reduction in axillary sweating from baseline of at least 50% at week 4.

In the three study groups the percentage of patients with baseline HDSS score of 3 ranged from 50% to 54% and from 46 % to 50% for a score of 4. The median amount of sweat production (averaged for each axilla) was 102g, 123 g, and 114 g for the placebo, 50 Units and 75 Units groups respectively.

The percentage of responders based on at least a 2-grade decrease from baseline in HDSS or based on a >50% decrease from baseline in axillary sweat production was greater in both **BOTOX®** groups than in the placebo group ($p < 0.001$), but was not significantly different between the 2 **BOTOX®** doses (See Table 3).

Table 3: Study 1. Study Outcomes

Treatment Response	**Botox 50 Units** N = 104	**Botox 75 Units** N=110	**Placebo** N= 108	**Botox 50-placebo (95% CI)**	**Botox 75-placebo (95% CI)**
HDSS Score change ≥2 % (n)[a]	55% (57)	49% (54)	6% (6)	49.3% (38.8, 59.7)	43% (33.2, 53.8)
>50% decrease in axillary sweat production % (n)	81% (84)	86% (94)	41% (44)	40% (28.1, 52.0)	45% (33.3, 56.1)

[a] Patients who showed at least a 2-grade improvement from baseline value on the HDSS 4 weeks after both of the first two treatment sessions or had a sustained response after their first treatment session and did not receive re-treatment during the study.

Duration of response was calculated as the number of days between injection and the date of the first visit at which patients returned to 3 or 4 on the HDSS scale. The median duration of response following the first treatment in BOTOX®-treated patients with either dose was 201 days. Among those who received a second **BOTOX®** injection, the median duration of response was similar to that observed after the first treatment.

In study 2, 320 adults with bilateral axillary primary hyperhidrosis were randomized to receive either 50 Units of **BOTOX®** (n=242) or placebo (n=78). Treatment responders were defined as subjects showing at least a 50% reduction from baseline in axillary sweating measured by gravimetric measurement at 4 weeks. At week 4 post-injection, the percentages of responders were 91% (219/242) in the **BOTOX®** group and 36% (28/78) in the placebo group, $p < 0.001$.The difference in percentage of responders between **BOTOX®** and placebo was 55% (95% CI = 43.3, 65.9).

Blepharospasm:

Botulinum toxin has been investigated for use in patients with blepharospasm in several studies. In an open label uncontrolled study, 27 patients with essential blepharospasm were injected with 2.0 Units of **BOTOX®** at each of six sites on each side. One patient had not received any prior treatment. Twenty-six of the patients had not responded to therapy with benztropine mesylate, clonazepam and/or baclofen. Three of the 26 patients continued to experience spasms following muscle stripping surgery. Twenty-five of the 27 patients treated with botulinum toxin reported improvement within 48 hours. One patient was controlled with a higher dosage at 13 weeks post initial injection and one patient reported mild improvement but remained functionally impaired.[2]

In another study, 12 patients with blepharospasm were evaluated in a double-blind, placebo-controlled study. Patients receiving botulinum toxin (n=8) improved compared with the placebo group (n=4). The mean dystonia score improved by 72%, the self-assessment score rating improved by 61%, and a videotape evaluation rating improved by 39%. The effects of the treatment lasted a mean of 12.5 weeks.[3]

One thousand six hundred eighty-four patients with blepharospasm who were evaluated in an open label trial showed clinical improvement as evaluated by measured eyelid force and clinically observed intensity of lid spasm, lasting an average of 12.5 weeks prior to the need for re-treatment.[4]

Strabismus:

It is postulated that when used for the treatment of strabismus, the administration of **BOTOX®** affects muscle pairs by inducing an atrophic lengthening of the injected muscle and a corresponding shortening of the muscle's antagonist; it was on the basis of this hypothesis that clinical studies were conducted. Six hundred seventy-seven patients with strabismus treated with one or more injections of **BOTOX®** were evaluated in an open label trial. Fifty-five percent of these patients improved to an alignment of 10 prism diopters or less when evaluated six months or more following injection.[5] These results are consistent with results from additional open label trials which were conducted for this indication.[4]

INDICATIONS AND USAGE:

BOTOX® is indicated for the treatment of cervical dystonia in adults to decrease the severity of abnormal head position and neck pain associated with cervical dystonia**.**

BOTOX® is indicated for the treatment of severe primary axillary hyperhidrosis that is inadequately managed with topical agents.

BOTOX® is indicated for the treatment of strabismus and blepharospasm associated with dystonia, including benign essential blepharospasm or VII nerve disorders in patients 12 years of age and above.

The efficacy of **BOTOX®** treatment in deviations over 50 prism diopters, in restrictive strabismus, in Duane's syndrome with lateral rectus weakness, and in secondary strabismus caused by prior surgical over-recession of the antagonist has not been established. **BOTOX®** is ineffective in chronic paralytic strabismus except when used in conjunction with surgical repair to reduce antagonist contracture.

CONTRAINDICATIONS: **BOTOX®** is contraindicated in the presence of infection at the proposed injection site(s) and in individuals with known hypersensitivity to any ingredient in the formulation.

WARNINGS:

The recommended dosage and frequency of administration for **BOTOX®** should not be exceeded. Risks resulting from administration at higher dosages are not known.

Hypersensitivity Reactions

Serious and/or immediate hypersensitivity reactions have been rarely reported. These reactions include anaphylaxis, urticaria, soft tissue edema, and dyspnea. One fatal case of anaphylaxis has been reported in which lidocaine was used as the diluent, and consequently the causal agent cannot be reliably determined. If such a reaction occurs further injection of **BOTOX®** should be discontinued and appropriate medical therapy immediately instituted.

Pre-Existing Neuromuscular Disorders

Individuals with peripheral motor neuropathic diseases (e.g., amyotrophic lateral sclerosis, or motor neuropathy) or neuromuscular junctional disorders (e.g., myasthenia gravis or Lambert-Eaton syndrome) should only receive **BOTOX®** with caution. Patients with neuromuscular disorders may be at increased risk of clinically significant systemic effects including severe dysphagia and respiratory compromise from typical doses of **BOTOX®**. Published medical literature has reported rare cases of administration of a botulinum toxin to patients with known or unrecognized neuromuscular disorders where the patients have shown extreme sensitivity to the systemic effects of typical clinical doses. In some of these cases, dysphagia has lasted several months and required placement of a gastric feeding tube.

Dysphagia

Dysphagia is a commonly reported adverse event following treatment of cervical dystonia patients with all botulinum toxins. In these patients, there are reports of rare cases of dysphagia severe enough to warrant the insertion of a gastric feeding tube. There are also rare case reports where subsequent to the finding of dysphagia a patient developed aspiration pneumonia and died.

Human Albumin

This product contains albumin, a derivative of human blood. Based on effective donor screening and product manufacturing processes, it carries an extremely remote risk for transmission of viral diseases. A theoretical risk for transmission of Creutzfeldt-Jakob disease (CJD) also is considered extremely remote. No cases of transmission of viral diseases or CJD have ever been identified for albumin.

PRECAUTIONS:

The safe and effective use of **BOTOX®** depends upon proper storage of the product, selection of the correct dose, and proper reconstitution and administration techniques. Physicians administering **BOTOX®** must understand the relevant neuromuscular and/or orbital anatomy of the area involved and any alterations to the anatomy due to prior surgical procedures. An understanding of standard electromyographic techniques is also required for treatment of strabismus and may be useful for the treatment of cervical dystonia.

Caution should be used when **BOTOX®** treatment is used in the presence of inflammation at the proposed injection site(s) or when excessive weakness or atrophy is present in the target muscle(s).

Cervical Dystonia:

Patients with smaller neck muscle mass and patients who require bilateral injections into the sternocleidomastoid muscle have been reported to be at greater risk for dysphagia. Limiting the dose injected into the sternocleidomastoid muscle may reduce the occurrence of dysphagia. Injections into the levator scapulae may be associated with an increased risk of upper respiratory infection and dysphagia.

Primary Axillary Hyperhidrosis:

Patients should be evaluated for potential causes of secondary hyperhidrosis (e.g. hyperthyroidism) to avoid symptomatic treatment of hyperhidrosis without the diagnosis and/or treatment of the underlying disease. The safety and effectiveness of **BOTOX®** for hyperhidrosis in other body areas have not been established. Weakness of hand muscles and blepharoptosis may occur in patients who receive BOTOX® for palmar hyperhidrosis and facial hyperhidrosis, respectively**.**

Blepharospasm:

Reduced blinking from **BOTOX®** injection of the orbicularis muscle can lead to corneal exposure, persistent epithelial defect and corneal ulceration, especially in patients with VII nerve disorders. One case of corneal perforation in an aphakic eye requiring corneal grafting has occurred because of this effect. Careful testing of corneal sensation in eyes previously operated upon, avoidance of injection into the lower lid area to avoid ectropion, and vigorous treatment of any epithelial defect should be employed. This may require protective drops, ointment, therapeutic soft contact lenses, or closure of the eye by patching or other means.

Strabismus:

During the administration of **BOTOX®** for the treatment of strabismus, retrobulbar hemorrhages sufficient to compromise retinal circulation have occurred from needle penetrations into the orbit. It is recommended that appropriate instruments to decompress the orbit be accessible. Ocular (globe) penetrations by needles have also occurred. An ophthalmoscope to diagnose this condition should be available. Inducing paralysis in one or more extraocular muscles may produce spatial disorientation, double vision or past pointing. Covering the affected eye may alleviate these symptoms.

Information for Patients:

Patients or caregivers should be advised to seek immediate medical attention if swallowing, speech or respiratory disorders arise.

Patients with cervical dystonia should be informed of the possibility of experiencing dysphagia, which is typically mild to moderate, but could be severe. Rare consequences of severe dysphagia include aspiration, dyspnea, pneumonia, and the need to reestablish an airway.

As with any treatment with the potential to allow previously sedentary patients to resume activities, the sedentary patient should be cautioned to resume activity gradually following the administration of **BOTOX®.**

Drug Interactions:

Co-administration of **BOTOX®** and aminoglycosides or other agents interfering with neuromuscular transmission (e.g., curare-like compounds) should only be performed with caution as the effect of the toxin may be potentiated.

The effect of administering different botulinum neurotoxin serotypes at the same time or within several months of each other is unknown. Excessive neuromuscular weakness may be exacerbated by administration of another botulinum toxin prior to the resolution of the effects of a previously administered botulinum toxin.

Pregnancy*:* Pregnancy Category C

When pregnant mice and rats were injected intramuscularly during the period of organogenesis, the developmental NOEL of **BOTOX®** was 4 U/kg. Higher doses (8 or 16 U/kg) were associated with reductions in fetal body weights and/or delayed ossification which may be reversible.

In a range finding study in rabbits, daily injection of 0.125 U/kg/day (days 6 to 18 of gestation) and 2 U/kg (days 6 and 13 of gestation) produced severe maternal toxicity, abortions and/or fetal malformations. Higher doses resulted in death of the dams. The rabbit appears to be a very sensitive species to **BOTOX®**.

There are no adequate and well-controlled studies of **BOTOX®** in pregnant women. Because animal reproductive studies are not always predictive of human response, **BOTOX®** should be administered during pregnancy only if the potential benefit justifies the potential risk to the fetus. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential risks, including abortion or fetal malformations which have been observed in rabbits.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long term studies in animals have not been performed to evaluate carcinogenic potential of **BOTOX®**.

The reproductive NOEL following intramuscular injection of 0, 4, 8, and 16 U/kg was 4 U/kg in male rats and 8 U/kg in female rats. Higher doses were associated with dose-dependent reductions in fertility in male rats (where limb weakness resulted in the inability to mate), and an altered estrous cycle in female rats. There were no adverse effects on the viability of the embryos.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when **BOTOX®** is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children below the age of 12 have not been established for blepharospasm or strabismus, below the age of 16 for cervical dystonia or 18 for hyperhidrosis.

Geriatric Use: Clinical studies of **BOTOX®** did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. There were too few patients over the age of 75 to enable any comparisons. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

ADVERSE REACTIONS:

General:

There have been rare spontaneous reports of death, sometimes associated with dysphagia, pneumonia, and/or other significant debility or anaphylaxis, after treatment with botulinum toxin.

There have also been rare reports of adverse events involving the cardiovascular system, including arrhythmia and myocardial infarction, some with fatal outcomes. Some of these patients had risk factors including cardiovascular disease. The exact relationship of these events to the botulinum toxin injection has not been established.

The following events have been reported since the drug has been marketed and a causal relationship to the botulinum toxin injected is unknown: skin rash (including erythema multiforme, urticaria and psoriasiform eruption), pruritus, and allergic reaction.

In general, adverse events occur within the first week following injection of **BOTOX®** and while generally transient may have a duration of several months. Localized pain, tenderness and/or bruising may be associated with the injection. Local weakness of the injected muscle(s) represents the expected pharmacological action of botulinum toxin. However, weakness of adjacent muscles may also occur due to spread of toxin.

Cervical Dystonia:

In cervical dystonia patients evaluated for safety in double-blind and open-label studies following injection of **BOTOX®**, the most frequently reported adverse reactions were dysphagia (19%), upper respiratory infection (12%), neck pain (11%), and headache (11%).[7]

Other events reported in 2-10% of patients in any one study in decreasing order of incidence include: increased cough, flu syndrome, back pain, rhinitis, dizziness, hypertonia, soreness at injection site, asthenia, oral dryness, speech disorder, fever, nausea, and drowsiness. Stiffness, numbness, diplopia, ptosis, and dyspnea have been reported rarely.

Dysphagia and symptomatic general weakness may be attributable to an extension of the pharmacology of **BOTOX®** resulting from the spread of the toxin outside the injected muscles.

The most common severe adverse event associated with the use of **BOTOX®** injection in patients with cervical dystonia is dysphagia with about 20% of these cases also reporting dyspnea. (See **Warnings**). Most dysphagia is reported as mild or moderate in severity. However, it may rarely be associated with more severe signs and symptoms (See **Warnings**).

Additionally, reports in the literature include a case of a female patient who developed brachial plexopathy two days after injection of 120 Units of **BOTOX®** for the treatment of cervical dystonia, and reports of dysphonia in patients who have been treated for cervical dystonia.

Primary Axillary Hyperhidrosis:

The most frequently reported adverse events (3 - 10% of patients) following injection of **BOTOX®** in double-blind studies included injection site pain and hemorrhage, non-axillary sweating, infection, pharyngitis, flu syndrome, headache, fever, neck or back pain, pruritus, and anxiety.

The data reflect 346 patients exposed to **BOTOX®** 50 Units and 110 patients exposed to **BOTOX®** 75 Units in each axilla.

Because clinical trials are conducted under widely varying conditions, adverse events observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not be predictive of rates observed in practice.

Blepharospasm:

In a study of blepharospasm patients who received an average dose per eye of 33 Units (injected at 3 to 5 sites) of the currently manufactured **BOTOX®**, the most frequently reported treatment-related adverse reactions were ptosis (20.8%), superficial punctate keratitis (6.3%) and eye dryness (6.3%).[8]

In this study, the rate for ptosis in the current **BOTOX®** treated group (20.8% of patients) was significantly higher than the original **BOTOX®** treated group (4.0% of patients) (p=0.014%). All of these events were mild or moderate except for one case of ptosis which was rated severe.

Other events reported in prior clinical studies in decreasing order of incidence include: irritation, tearing, lagophthalmos, photophobia, ectropion, keratitis, diplopia and entropion, diffuse skin rash and local swelling of the eyelid skin lasting for several days following eyelid injection.

In two cases of VII nerve disorder (one case of an aphakic eye), reduced blinking from **BOTOX®** injection of the orbicularis muscle led to serious corneal exposure, persistent epithelial defect, and corneal ulceration. Perforation occurred in the aphakic eye and required corneal grafting.

A report of acute angle closure glaucoma one day after receiving an injection of botulinum toxin for blepharospasm was received, with recovery four months later after laser iridotomy and trabeculectomy. Focal facial paralysis, syncope and exacerbation of myasthenia gravis have also been reported after treatment of blepharospasm.

Strabismus:

Extraocular muscles adjacent to the injection site can be affected, causing ptosis or vertical deviation, especially with higher doses of **BOTOX®**. The incidence rates of these adverse effects in 2058 adults who received a total of 3650 injections for horizontal strabismus are 15.7% and 16.9%, respectively.[4]

Inducing paralysis in one or more extraocular muscles may produce spatial disorientation, double vision, or past-pointing. Covering the affected eye may alleviate these symptoms.

The incidence of ptosis was 0.9% after inferior rectus injection and 37.7% after superior rectus injection.

Ptosis (0.3%) and vertical deviation greater than two prism diopters (2.1%) were reported to persist for over six months in a larger series of 5587 injections of horizontal muscles in 3104 patients.

In these patients, the injection procedure itself caused nine scleral perforations. A vitreous hemorrhage occurred in one case and later cleared. No retinal detachment or visual loss occurred in any case. Sixteen retrobulbar hemorrhages occurred without visual loss. Decompression of the orbit after five minutes was done to restore retinal circulation in one case. Five eyes had pupillary change consistent with ciliary ganglion damage (Adie's pupil).

One patient developed anterior segment ischemia after receiving **BOTOX®** injection into the medial rectus muscle under direct visualization for esotropia.

Immunogenicity:

Formation of neutralizing antibodies to botulinum toxin type A may reduce the effectiveness of **BOTOX®** treatment by inactivating the biological activity of the toxin. The rate of formation of neutralizing antibodies in patients receiving **BOTOX®** has not been well studied.

In the phase 3 cervical dystonia study[1] that enrolled only patients with a history of receiving **BOTOX®** for multiple treatment sessions, at study entry there were 192 patients with antibody assay results, of whom 33 (17%) had a positive assay for neutralizing activity. There were 96 patients in the randomized period of the phase 3 study with valid assays at both study entry and end and who were neutralizing activity negative at entry. Of these 96, 2 patients (2%) converted to positive for neutralizing activity. Both of these converting patients were among the 52 who had received two **BOTOX®** treatments between the two assays; none were in the group randomized to placebo in the controlled comparison period of the study.

In the randomized period of the cervical dystonia study, patients in the **BOTOX®** group whose baseline assays were neutralizing antibody negative showed improvements on CDSS (n=64, mean CDSS change -2.1) while patients whose baseline assays were neutralizing antibody positive did not (n=14, mean CDSS change +1.1). However, in uncontrolled studies there are also individual patients who are perceived as continuing to respond to treatments despite the presence of neutralizing activity. Not all patients who become non-responsive to **BOTOX®** after an initial period of clinical response have demonstrable levels of neutralizing activity.

One patient among the 445 hyperhidrosis patients with analyzed specimens showed the presence of neutralizing antibodies.

The data reflect the patients whose test results were considered positive or negative for neutralizing activity to **BOTOX®** in a mouse protection assay. The results of these tests are highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of neutralizing activity in an assay may be influenced by several factors including sample handling, concomitant medications and underlying disease. For these reasons, comparison of the incidence of neutralizing activity to **BOTOX®** with the incidence reported to other products may be misleading.

The critical factors for neutralizing antibody formation have not been well characterized. The results from some studies suggest that **BOTOX®** injections at more frequent intervals or at higher doses may lead to greater incidence of antibody formation. The potential for antibody formation may be minimized by injecting with the lowest effective dose given at the longest feasible intervals between injections.

OVERDOSAGE:

Signs and symptoms of overdose are not apparent immediately post-injection. Should accidental injection or oral ingestion occur, the person should be medically supervised for up to several weeks for signs or symptoms of systemic weakness or muscle paralysis.

An antitoxin is available in the event of immediate knowledge of an overdose or misinjection. In the event of an overdose or injection into the wrong muscle, immediately contact Allergan for additional information at (800) 433-8871 from 8:00 a.m. to 4:00 p.m. Pacific Time, or at (714) 246-5954 for a recorded message at other times. The antitoxin will not reverse any botulinum toxin induced muscle weakness effects already apparent by the time of antitoxin administration.

DOSAGE AND ADMINISTRATION:

BOTOX® is supplied in a single use vial. Because the product and diluent do not contain a preservative, once opened and reconstituted, store in a refrigerator and use within four hours. Discard any remaining solution. Do not freeze reconstituted **BOTOX®**.

BOTOX® is to be reconstituted with sterile, non-preserved saline prior to intramuscular injection.

General:

An injection of **BOTOX®** is prepared by drawing into an appropriately sized sterile syringe an amount of the properly reconstituted toxin (see Dilution Table) slightly greater than the intended dose. Air bubbles in the syringe barrel are expelled and the syringe is attached to an appropriate injection needle. Patency of the needle should be confirmed. A new, sterile, needle and syringe should be used to enter the vial on each occasion for removal of **BOTOX®**.

The method utilized for performing the potency assay is specific to Allergan's Botulinum Toxin Type A. Due to specific details of this assay such as the vehicle, dilution scheme and laboratory protocols for the various potency assays, Units of biological activity of Botulinum Toxin Type A cannot be compared to nor converted into Units of any other botulinum toxin or any toxin assessed with any other specific assay method. Therefore, differences in species sensitivities to different botulinum neurotoxin serotypes precludes extrapolation of animal dose-activity relationships to human dose relationships.

Cervical Dystonia:

The phase 3 study enrolled patients who had extended histories of receiving and tolerating **BOTOX®** injections, with prior individualized adjustment of dose. The mean **BOTOX®** dose administered to patients in the phase 3 study was 236 Units (25^{th} to 75^{th} percentile range 198 Units to 300 Units). The **BOTOX®** dose was divided among the affected muscles (see Clinical Studies: Cervical Dystonia). Dosing in initial and sequential treatment sessions should be tailored to the individual patient based on the patient's head and neck position, localization of pain, muscle hypertrophy, patient response and adverse event history.

The initial dose for a patient without prior use of **BOTOX®** should be at a lower dose, with subsequent dosing adjusted based on individual response. Limiting the total dose injected into the sternocleidomastoid muscles to 100 Units or less may decrease the occurrence of dysphagia (see Precautions: Cervical Dystonia).

A 25, 27 or 30 gauge needle may be used for superficial muscles, and a longer 22 gauge needle may be used for deeper musculature. Localization of the involved muscles with electromyographic guidance may be useful.

Clinical improvement generally begins within the first two weeks after injection with maximum clinical benefit at approximately six weeks post-injection. In the phase 3 study most subjects were observed to have returned to pre-treatment status by 3 months post-treatment.

Primary Axillary Hyperhidrosis

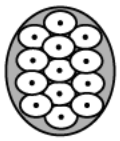
The recommended dose is 50 Units per axilla. The hyperhidrotic area to be injected should be defined using standard staining techniques, e.g., Minor's Iodine-Starch Test. **BOTOX®** is reconstituted with 0.9% non-preserved sterile saline (100 Units/4 mL). Using a 30 gauge needle, 50 Units of **BOTOX®** (2mL) is injected intradermally in 0.1 to 0.2 mL aliquots to each axilla evenly distributed in multiple sites (10-15) approximately 1-2 cm apart.

Repeat injections for hyperhidrosis should be administered when the clinical effect of a previous injection diminishes.

Instructions for the Minor's Iodine Starch Test Procedure

Patients should shave underarms and abstain from use of over-the-counter deodorants or antiperspirants for 24 hours prior to the test. Patient should be resting comfortably without exercise, hot drinks, etc. for approximately 30 minutes prior to the test. Dry the underarm area and then immediately paint it with iodine solution. Allow the area to dry, then lightly sprinkle the area with starch powder. Gently blow off any excess starch powder. The hyperhidrotic area will develop a deep blue-black color over approximately 10 minutes.

Each injection site has a ring of effect of up to approximately 2 cm in diameter. To minimize the area of no effect, the injection sites should be evenly spaced as shown in Figure 1:

Figure 1: 

Each dose is injected to a depth of approximately 2mm and at a 45° angle to the skin surface with the bevel side up to minimize leakage and to ensure the injections remain intradermal.

If injection sites are marked in ink do not inject **BOTOX®** directly through the ink mark to avoid a permanent tattoo effect.

Blepharospasm*:*

For blepharospasm, reconstituted **BOTOX®** (see Dilution Table) is injected using a sterile, 27 - 30 gauge needle without electromyographic guidance. The initial recommended dose is 1.25 - 2.5 Units (0.05 mL to 0.1 mL volume at each site) injected into the medial and lateral pre-tarsal orbicularis oculi of the upper lid and into the lateral pre-tarsal orbicularis oculi of the lower lid. Avoiding injection near the levator palpebrae superioris may reduce the complication of ptosis. Avoiding medial lower lid injections, and thereby reducing diffusion into the inferior oblique, may reduce the complication of diplopia. Ecchymosis occurs easily in the soft eyelid tissues. This can be prevented by applying pressure at the injection site immediately after the injection.

In general, the initial effect of the injections is seen within three days and reaches a peak at one to two weeks post-treatment. Each treatment lasts approximately three months, following which the procedure can be repeated. At repeat treatment sessions, the dose may be increased up to two-fold if the response from the initial treatment is considered insufficient-usually defined as an effect that does not last longer than two months. However there appears to be little benefit obtainable from injecting more than 5.0 Units per site. Some tolerance may be found when **BOTOX®** is used in treating blepharospasm if treatments are given any more frequently than every three months, and is rare to have the effect be permanent.

The cumulative dose of **BOTOX®** treatment in a 30-day period should not exceed 200 Units.

Strabismus:

BOTOX® is intended for injection into extraocular muscles utilizing the electrical activity recorded from the tip of the injection needle as a guide to placement within the target muscle. Injection without surgical exposure or electromyographic guidance should not be attempted. Physicians should be familiar with electromyographic technique.

To prepare the eye for **BOTOX®** injection, it is recommended that several drops of a local anesthetic and an ocular decongestant be given several minutes prior to injection.

Note: The volume of **BOTOX®** injected for treatment of strabismus should be between 0.05 - 0.15 mL per muscle.

The initial listed doses of the reconstituted **BOTOX®** (see Dilution Table below) typically create paralysis of injected muscles beginning one to two days after injection and increasing in intensity during the first week. The paralysis lasts for 2-6 weeks and gradually resolves over a similar time period. Overcorrections lasting over six months have been rare. About one half of patients will require subsequent doses because of inadequate paralytic response of the muscle to the initial dose, or because of mechanical factors such as large deviations or restrictions, or because of the lack of binocular motor fusion to stabilize the alignment.

I. Initial doses in Units. Use the lower listed doses for treatment of small deviations. Use the larger doses only for large deviations.
   A. For vertical muscles, and for horizontal strabismus of less than 20 prism diopters: 1.25 - 2.5 Units in any one muscle.
   B. For horizontal strabismus of 20 prism diopters to 50 prism diopters: 2.5 - 5.0 Units in any one muscle.

C. For persistent VI nerve palsy of one month or longer duration: 1.25 - 2.5 Units in the medial rectus muscle.

II. Subsequent doses for residual or recurrent strabismus.

A. It is recommended that patients be re-examined 7-14 days after each injection to assess the effect of that dose.

B. Patients experiencing adequate paralysis of the target muscle that require subsequent injections should receive a dose comparable to the initial dose.

C. Subsequent doses for patients experiencing incomplete paralysis of the target muscle may be increased up to two-fold compared to the previously administered dose.

D. Subsequent injections should not be administered until the effects of the previous dose have dissipated as evidenced by substantial function in the injected and adjacent muscles.

E. The maximum recommended dose as a single injection for any one muscle is 25 Units.

Dilution Technique:

Prior to injection, reconstitute vacuum-dried **BOTOX®**, with sterile normal saline **without** a preservative; 0.9% Sodium Chloride Injection is the only recommended diluent. Draw up the proper amount of diluent in the appropriate size syringe, and slowly inject the diluent into the vial. Discard the vial if a vacuum does not pull the diluent into the vial. Gently mix **BOTOX®** with the saline by rotating the vial. Record the date and time of reconstitution on the space on the label. **BOTOX®** should be administered within four hours after reconstitution.

During this time period, reconstituted **BOTOX®** should be stored in a refrigerator (2° to 8°C). Reconstituted **BOTOX®** should be clear, colorless and free of particulate matter. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration and whenever the solution and the container permit.

Dilution Table

Diluent Added (0.9% Sodium Chloride Injection)	**Resulting dose Units per 0.1 mL**
1.0 mL	10.0 Units
2.0 mL	5.0 Units
4.0 mL	2.5 Units
8.0 mL	1.25 Units

Note: These dilutions are calculated for an injection volume of 0.1 mL. A decrease or increase in the **BOTOX®** dose is also possible by administering a smaller or larger injection volume - from 0.05 mL (50% decrease in dose) to 0.15 mL (50% increase in dose.)

HOW SUPPLIED: BOTOX® is supplied in a single use vial. Each vial contains 100 Units of vacuum-dried *Clostridium botulinum* type A neurotoxin complex. NDC 0023-1145-01.

Vials of BOTOX® have a holographic film on the vial label that contains the name "Allergan" within horizontal lines of rainbow color. In order to see the hologram, rotate the vial back and forth between your fingers under a desk lamp or fluorescent light source. (Note: the holographic film on the label is absent in the date/batch area.) If you do not see the lines of rainbow color or the name "Allergan", do not use the product and contact Allergan for additional information at (800) 890-4345 from 8:00 a.m. to 4:00 p.m. Pacific time.

Rx Only

Single use vial.

Storage:

Unopened vials of **BOTOX®** should be stored in a refrigerator (2° to 8°C) for up to 24 months. Do not use after the expiration date on the vial. Administer **BOTOX®** within 4 hours of reconstitution; during this period reconstituted **BOTOX®** should be stored in a refrigerator (2° to 8°C). Reconstituted **BOTOX®** should be clear, colorless and free of particulate matter.

All vials, including expired vials, or equipment used with the drug should be disposed of carefully as is done with all medical waste.

Revised: May 2004

Manufactured by: Allergan Pharmaceuticals Ireland
a subsidiary of: Allergan, Inc., 2525 Dupont Dr., Irvine, CA 92612

References:

1. Data on file, Allergan, Inc. A randomized, multicenter, double-blind, placebo-controlled study of intramuscular **BOTOX®** (botulinum toxin type A) purified neurotoxin complex (original 79-11 **BOTOX®**) for the treatment of cervical dystonia. 1998.
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3. Jankovic J, Orman J. Botulinum A toxin for cranial-cervical dystonia: A double-blind , placebo-controlled study. Neurology 1987;37:616-623.
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8. Data on file, Allergan, Inc. A randomized, multicenter, double-blind, parallel clinical trial to compare the safety and efficacy of **BOTOX®** (botulinum toxin type A) purified neurotoxin complex manufactured from neurotoxin complex batch BCB2024 to that manufactured from neurotoxin complex batch 79-11 in blepharospasm patients. 1997.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 103000/S-5050

MEDICAL REVIEW(S)

STN 103000/5050 CLINICAL REVIEW

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service

Memorandum

Food and Drug Administration
Center for Drug Evaluation and Research
1401 Rockville Pike
Rockville, MD 20852
July 19, 2004

From:

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Division of Therapeutic Biologic Internal Medicine Products
Office of Drug Evaluation 6, CDER
And
Elizabeth M. Sutkowski, Ph.D.
Division of Vaccines and Related Products Applications,
Office of Vaccines Research and Review, CBER

Through:

Marc Walton, M.D., Ph.D., Director,
Division of Therapeutic Biologic Internal Medicine Products,
Office of Drug Evaluation 6,
CDER, FDA

To:

STN 103000\5050

Topic:

Clinical Review of Labeling Supplement

Product: Botulinum Toxin Type A Purified Neurotoxin Complex (BTA)

Indication: Treatment of Severe Primary Axillary Hyperhidrosis that is Inadequately Managed with Topical Agents

Sponsor: Allergan, Inc.

Table of Contents

Clinical Review for Supplemental BLA STN BL 103000/5050

Executive Summary

I. Recommendations

A. Recommendation on Approvability

The two phase 3 trials showed consistent treatment effect of Botulinum Toxin Type A (BTA) demonstrated by the proportion of patients achieving clinically significant improvement in hyperhydrosis disease severity score and reduction of axillary sweat production.

The totality of the data show that BTA is safe and effective for the treatment of adults with severe axillary hyperhydrosis that is inadequately managed with topical agents. The reviewers recommend that the supplemental application by Allergan for marketing of BTA in this patient population be approved.

The recommended dose of BTA is 50 U per axilla.

B. Recommendation on Phase 4 Studies and/or Risk Management Steps

This License Supplement:

- Contains limited data on long-term safety following repeated use.
- Does not contain data on appropriate dosing, safety, and efficacy of the product in hyperhidrosis affecting other body areas.
- Does not contain data on use of BTA in adolescents.

Therefore, the following post-marketing commitments are recommended:

- Complete two open-label, three-year studies (191622-046 and 191622-513) of the safety of multiple treatment cycles in at least 300 patients, submit updates on the study progress in the annual report, and submit the final study reports to the Agency when the studies are completed.

- Develop and execute a long-term, open-label safety clinical repeated treatment study in a statistically meaningful number of post-pubescence (12-16 years of age) pediatric patients with severe primary axillary hyperhidrosis that is inadequately managed with topical agents.

- Develop and execute a clinical study program in palmar hyperhidrosis patients leading to an expansion of the label to include palmar hyperhidrosis. The development plan should include a sufficient number of patients evaluated in a double blind, placebo controlled study with more than one treatment cycle and appropriate clinically relevant measures of treatment outcome.

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

Botulinum Toxin Type A (BTA) Purified Neurotoxin Complex is a purified BTA that blocks neuromuscular transmission by binding to acceptor sites on motor or sympathetic nerve terminals, entering the nerve terminals, and inhibiting the release of acetylcholine. This inhibition occurs as the neurotoxin cleaves SNAP-25, a protein integral to the successful docking and release of acetylcholine from vesicles situated within nerve endings. The drug product is produced from fermentation of the Hall strain of *Clostridium botulinum* type A.

The mechanism of action of BTA in hyperhidrosis is thought to be the inhibition of cholinergically-induced sweating by blockage of autonomic sympathetic nerve fibers innervating sweat glands. The product was administered intradermally in each axilla. The intended use was the treatment of primary axillary hyperhidrosis.

Clinical Studies

Table 1 lists the studies that provide the basis for the assessment of safety and efficacy of BTA for axillary hyperhidrosis. Study -016 is the pivotal US phase 3 study. This was a double-blind, randomized, placebo-controlled, dose-optimization study. The study used a principal efficacy endpoint of the proportion of responders with a substantial improvement in hyperhidrosis severity measured with a global assessment scale. The pivotal study is supported by a second double-blind, randomized, placebo-controlled study (Study -505) conducted in Europe. Study -505 used a pharmacodynamic primary efficacy endpoint, namely the proportion of responders with a 50% decrease in the production of axillary sweat at rest. The European study was a non-IND study and was designed without input from the Agency. Study -506 was an open-label continuation study evaluating retreatment with follow up for 52 weeks. Two single-arm, open-label studies (046 and 513) are evaluating the safety, activity, and durability of multiple treatment cycles of BTA with follow up for up to three years.

Table 1 Listing of Studies of BTA Administered Intradermally for Axillary Hyperhidrosis

Study #	Study Design	BTA Dose[a] (U)	n	Treatments F/U
191622-016	Multi-center, double- blind, randomized, placebo-controlled	0, 50, 75	322	≤ 6 treatments FU: ≤ 52 weeks
191622-046 (ongoing)	Multi-center, open-label, single group	50	322	≤ 12 treatments FU: 24-36 months
191622-505	Multi-center, double- blind, randomized, vehicle-controlled	0, 50	320	1 treatment FU: 16 weeks
191622-506	Multi-center, open-label, single group	50	242	≤3 treatments FU: 52 weeks
191622-513 (ongoing)	Multi-center, open-label, single group	50	350	≤ 4 treatments FU: 36 months

[a]Dose for each axilla

Table 2 lists three retrospective studies. The agency requested these data from the sponsor to assess the safety of off-label uses of the product in hyperhidrosis. Of particular interest were the dosages, safety, and activity of uses of BTA in other anatomic sites such as face, hands, and feet. It was also of interest to determine if higher doses than were studied in the clinical programs are being used off-label and whether or not these higher doses show evidence of serious adverse events (SAEs). The studies are discussed in the Appendix at the end of this review.

Table 2 Retrospective Studies of BTA Injected Intradermally for Hyperhidrosis

Study Identifier	Aims	Study Design	Dose	n	Indication	Treatments F/U
US study 191622-059	Safety	Retrospective chart review no control	Variable	122	hyperhidrosis	Variable
German observational study	Safety and activity	Single-center retrospective chart review no control	mean 36 U range 20 -40 U	29	axillary, palmar, plantar or facial hyperhidrosis	≤4 treatments FU ≤ 21 months
Swedish observational study	Safety and activity	Single-center retrospective chart review no control	mean 56 U range 17-130 U	157	axillary, palmar, plantar, genital, facial or other hyperhidrosis	≤ 5 treatments FU ≤ 15 months

The sponsor has also provided reports of two studies to assess the validity of the gravimetric measurements of hyperhidrosis. In addition, the sponsor has provided reports of surveys to assess the prevalence of hyperhidrosis in Germany and the US (**Table 3**).

Table 3 Other Studies

Study Identifier	Objective(s)	Study Design	n	Study Population
191622-015	Inter- and intra-rater reliability of gravimetric measurement	Multicenter randomized low sweat control group	50 (26 low sweat, 24 high sweat)	Patients clinically diagnosed with primary axillary hyperhidrosis or subjects without hyperhydrosis
Normal volunteer study	Axillary sweat production in normal adult volunteers	Single center non-randomized no control group	46	Healthy volunteers with normal rate of sweating in their own opinion
Burden of disease study	Impact of disease of hyperhidrosis in Germany	Single center non-randomized survey control group of normal population	345 patients 154 controls	Patients with hyperhidrosis or non-hyperhidrotic subjects
Epidemi-ologic study	Number of patients under treatment	Database of outpatient visits in Europe	887,130	Patients in MediPlus database in Germany
Epidemi-ologic study	Population prevalence of hyperhidrosis	Consumer panel survey in US	150,000 house-holds	Representative population of US households

The clinical studies were conducted according to the protocol and protection of patients was adequate. Source data were compared to CRF entries and no discrepancies were identified.

B. Overall Summary of Efficacy

The efficacy of BTA for the treatment of primary axillary hyperhidrosis was evaluated in two randomized, multi-center, double-blind, placebo-controlled studies. In Study -016, a total of 322 adults were randomized 1:1:1 to 50 Units of BTA, 75 U of BTA or placebo and were eligible to receive one or more treatments over the course of one year of study. In Study -505, 320 adults were randomized 3:1 to receive a single treatment of 50 Units of BTA or placebo. In total, 346 patients were exposed to 50 Units and 110 patients were exposed to 75 Units of BTA.

- Studies -505 and -016 were consistent in showing a clinically significant treatment effect of BTA. The designs of the two studies including the primary efficacy outcomes were different and pooled analyses of the data were not considered to be appropriate.

- For Study -016, a global assessment scale, the Hyperhidrosis Disease Severity Scale (HDSS), was the primary efficacy outcome. Study responders were defined as patients who showed at least a 2-grade improvement from baseline value on the HDSS at 4 weeks after both of the first two treatment sessions or had a sustained response after their first treatment session and did not receive re-treatment during the study. The percentage of responders based on at least a 2-grade decrease from baseline in HDSS or based on a >50% decrease from baseline in axillary sweat production was greater in both BTA groups than in the placebo group ($p < 0.001$). The difference between the BTA groups and placebo (95% C.I.) was 49% (38.8, 59.7) for the 50U and 43% (33.2, 53.8) for the 75 U group.

- The proportion of treatment responders and the durability of response appeared to be similar between the 50 U and 75 U dose groups.

- For Study -505, treatment responders were defined as subjects showing at least a 50% reduction from baseline in axillary sweating measured by gravimetric measurement at 4 weeks. At week 4 post-injection, the percentages of responders were 91% (219/242) in the BTA group and 36% (28/78) in the placebo group, $p < 0.001$. The difference in percentage of responders between BTA and placebo was 55% (95% CI = 43.3, 65.9).

- There was no suggestion of loss of treatment effect upon repeated dosing.

- Treatment response was similar for patients with HDSS score of 3 or 4 at baseline.

- There are no data on efficacy of doses lower than 50 U. However, in view of lack of safety concerns from data with doses up to 75 U, the rationale for exploring lower doses is weak. The possibility exists that doses lower than 50 U might result in lower proportion of responders and/or shorter duration of response.

- Few non-Caucasians and elderly were enrolled in the clinical studies to reliably assess treatment responses in these subgroups. Men and women appeared to respond similarly to treatment

- The study of children was deferred. Given that most patients report the onset of hyperhidrosis in adolescence, the study of post-pubertal children might be considered.

- Observational studies reported in this submission and literature reports provide evidence of off-label use of BTA for hyperhidrosis in several anatomic sites, in particular the palmar aspect of hands, digits, and plantar aspect of feet. Face and genitalia are less common treatment sites. Hands and face are associated with frequent significant weakness of adjoining muscles. A postmarketing study of hyperhidrosis of the hands to develop a safe and effective dose seems warranted.

C. Overall Summary of Safety

- No serious adverse events related to treatment have been observed to date in the patients with axillary hyperhidrosis. The database is small and the potential for rare serious adverse events cannot be judged.

- There is little information on the safety of repeated treatment cycles with respect to local tolerance and development of anhydrosis. It is not known if intradermal injection will prove to be more sensitizing than intramuscular injection. The sponsor has ongoing open-label studies of repeated treatment cycles and completion and reporting of these studies will be stipulated by PMC.

- Rare but serious immediate hypersensitivity reactions including urticaria, soft tissue edema, and one case of anaphylaxisis resulting in death were observed postmarketing in non-hyperhidrosis indications. The most frequently reported adverse events (3-10% of patients) following injection of BTA in double-blind studies included injection site pain and hemorrhage, non-axillary sweating, infection, pharyngitis, flu syndrome, headache, fever, neck or back pain, pruritus, and anxiety.

- One patient among the 445 hyperhidrosis patients with analyzed specimens showed the presence of neutralizing antibodies.

D. Dosing

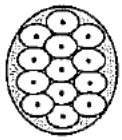
The recommended dose is 50 Units per axilla. The hyperhidrotic area to be injected should be defined using standard staining techniques, e.g., Minor's Iodine-Starch Test. BTA is reconstituted with 0.9% non-preserved sterile saline (100 Units/4 mL). Using a 30 gauge needle, 50 Units of BTA (2mL) is injected intradermally in 0.1 to 0.2 mL aliquots to each axilla evenly distributed in multiple sites (10-15) approximately 1-2 cm apart. Repeat injections for hyperhidrosis may be administered when the clinical effect of a previous injection diminishes.

Instructions for the Minor's Iodine Starch Test Procedure

Patients should shave underarms and abstain from use of over-the-counter deodorants or antiperspirants for 24 hours prior to the test. Patient should be resting comfortably without exercise, hot drinks, etc. for approximately 30 minutes prior to the test. Dry the underarm area and then immediately paint it with iodine solution. Allow the area to dry, then lightly sprinkle the area with starch powder. Gently blow off any excess starch powder. The hyperhidrotic area will develop a deep blue-black color over approximately 10 minutes.

Each injection site has a ring of effect of up to approximately 2 cm in diameter. To minimize the area of no effect, the injection sites should be evenly spaced as shown in **Figure 1**:

Figure 1:



Each dose is injected to a depth of approximately 2 mm and at a 45° angle to the skin surface with the bevel side up to minimize leakage and to ensure the injections remain intradermal. If injection sites are marked in ink, do not inject BTA directly through the ink mark to avoid a permanent tattoo effect.

E. Special Populations

The assessment of gender effects in the clinical program was judged to be satisfactory. In Study -016, overall, 54% (174/322) of subjects were male and 46% (148/322) were female. As shown in **Table 4** below, analysis of efficacy by gender showed statistically significant differences in the responder rates between both active groups and placebo for both males and females, although the response rates were higher for females receiving BTA than for males.

Table 4 Study -016. Responder Rates Based on HDSS by Gender

Gender	BTA 75U (n=110)	BTA 50U (n=104)	Placebo (n=108)	BTA 75U vs Placebo[a]	BTA 50U vs Placebo[a]	BTA 75U vs 50U[a]
Male	43% (26/60)	47% (27/57)	7% (4/57)	< 0.001	< 0.001	0.650
Female	56% (28/50)	64% (30/47)	4% (2/51)	< 0.001	< 0.001	0.412

[a] P-value based on Cochran-Mantel-Haenszel test stratified by study baseline HDSS score.

In Study -505, there was no appreciable difference in responder rates based on gender (**Table 5**).

Table 5 Study -505. Responder Rates Based on Gravimetric Assessment by Gender

	Male				Female			
	BTA 50U n=113		Vehicle n=35		BTA 50U n=129		Vehicle n=43	
Responders	n	%	n	%	n	%	n	%
Week 1	107	95.5%	10	29.4%	123	95.3%	15	34.9%
Week 4	99	92.5%	14	42.4%	120	95.2%	14	33.3%

It was concluded that both men and women showed clinically significant treatment responses.

Response by Age

In Study -016, overall, 78% (241/322) of subjects were <40 years old, 24% (78/322) were 40 to 64 years old, and 0.9% (3/322) were ≥65 years old. There were too few subjects > 65 years (n = 3) to evaluate efficacy in this age group. As shown in **Table 6** below, analysis of efficacy by age

group showed response rates to be similar for the under 40 and over 40 age group in the active groups. In the placebo group, responder rates were higher in the over 40 than in the under 40-year-old subjects.

Table 6 Responder Rates Based on HDSS by Age Group

Age Group	BTA 75U (n=110)	BTA 50U (n=104)	Placebo (n=108)
< 40 years	53% (42/79)	55% (43/78)	4% (3/84)
40 to 64 years	41% (12/29)	56% (14/25)	13% (3/24)
≥ 65 years	0% (0/2)	0% (0/1)	-- (-/0)

In Study -505, there was no apparent difference in response rates based on age of subjects. In a subgroup analysis comparing patients ≤ 35 years and > 35 years of age, treatment responses at 4 weeks post-treatment were 93% and 97%, respectively, in patients receiving BTA 50 U and 38% and 36%, respectively, in patients receiving placebo.

Response by Race

In Study -016, overall, 84% (262/322) of subjects were Caucasian and 19% (60/322) of subjects were non-Caucasian. Responder rates based on HDSS by race are shown in **Table 7**. Statistically significant differences in favor of both active groups over placebo were shown for both Caucasians and non-Caucasians, although response rates were numerically higher for Caucasians receiving BTA than for non-Caucasians.

Table 7 Responder Rates Based on HDSS by Race Group

Race Group	BTA 75U (n=110)	BTA 50U (n=104)	Placebo (n=108)	BTA 75U vs Placebo[a]	BTA 50U vs Placebo[a]	BTA 75U vs 50U[a]
Caucasian	51% (44/86)	56% (49/87)	7% (6/89)	< 0.001	< 0.001	0.469
Non-Caucasian	42% (10/24)	47% (8/17)	0% (0/19)	0.002	< 0.001	0.738

[a] P-value based on Cochran-Mantel-Haenszel test stratified by study baseline HDSS score.

It was concluded that there was no appreciable difference in treatment response based on age. There was very limited data on non-Caucasians; the available data suggested that non-Caucasians also responded to treatment.

Clinical Review

I. Introduction and Background

A. Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups

Botulinum Toxin Type A (BTA) Purified Neurotoxin Complex is a purified BTA that blocks neuromuscular transmission by binding to acceptor sites on motor or sympathetic nerve terminals, entering the nerve terminals, and inhibiting the release of acetylcholine. This inhibition occurs as the neurotoxin cleaves SNAP-25, a protein integral to the successful docking and release of acetylcholine from vesicles situated within nerve endings. The eccrine sweat-producing gland is innervated by the sympathetic nervous system, but its principal periglandular neurotransmitter is acetylcholine. The mechanism of action of BTA in hyperhidrosis is thought to be the inhibition of cholinergically-induced sweating by blockage of autonomic sympathetic nerve fibers innervating sweat glands.

The drug product is produced from fermentation of the Hall strain of *Clostridium botulinum* type A. The product is purified from the culture solution by dialysis and a series of acid precipitations to a complex consisting of neurotoxin and several accessory proteins. The complex is dissolved in sterile sodium chloride solution containing human serum albumin and is sterile filtered before filling and vacuum-drying.

The product is intended for intracutaneous administration in the sweat producing area of the axillae in adults with primary axillary hyperhydrosis that is severe and inadequately managed with topical agents.

The sponsor proposes 50 Units per axilla as the recommended dose. The hyperhidrotic area to be injected should be defined using standard staining techniques, e.g., Minor's Iodine-Starch Test. BTA is reconstituted with 0.9% non-preserved sterile saline (100 Units/4 mL). Using a 30 gauge needle, 50 Units of BTA (2mL) is injected intradermally in 0.1 to 0.2 mL aliquots to each axilla evenly distributed in multiple sites (10-15) approximately 1-2 cm apart. Repeat injections for hyperhidrosis should be administered when the clinical effect of a previous injection diminishes.

Each vial of BTA contains 100 Units (U) of Clostridium botulinum type A neurotoxin complex, 0.5 mg of albumin, and 0.9 mg of sodium chloride in a sterile, vacuum-dried form without a preservative and the specific activity is approximately 20 units/nanogram of neurotoxin protein complex. One unit (U) corresponds to the calculated median intraperitoneal lethal dose (LD50) in mice. Due to specific details of this assay such as the vehicle, dilution scheme and laboratory protocols for the various mouse LD50 assays, units of biological activity of BTA cannot be compared to nor converted into units of any other botulinum toxin or any toxin assessed with any other specific assay method. Therefore, differences in species sensitivities to different botulinum neurotoxin serotypes preclude extrapolation of animal-dose activity relationships to human dose estimates.

At the time this application was submitted, BTA was licensed in the U.S. for treatment of cervical dystonia, blepharospasm, strabismus, and glabellar lines. At the time of submission, BTA was also licensed in over 70 other countries for the indications listed above and for a variety of other indications.

B. State of Armamentarium for Indication(s)

Hyperhidrosis is a disorder of excessive sweating that may affect any body part, particularly the axillae, the palms of the hands, the soles of the feet, and the face. The principal treatment for hyperhydrosis consists of over the counter deodorants and antiperspirants. When over the counter preparations aren't effective, prescription versions with high concentrations of aluminum chlorides may be helpful for sweating from the hands, feet and underarms if applied nightly. An example is Drysol. Experimental agents in medical use include beta blockers and anticholinergic drugs. Anticholinergic drugs such as Robinul, block the action of the neurotransmitter that causes sweating. These medications dry the entire body and can cause side effects including blurred vision, dry mouth and urination problems. Also, use of surgical interventions has been reported such as denervation (open thoracic or endoscopic sympathectomy), sweat gland excision or curettage/suction. Iontophoresis consists of placing an electrical device that emits low-voltage current against the skin, generally for 20 minutes three to four times a week. It is thought that the current passing through the body temporarily blocks the opening of sweat pores. One brand, Drionic, was cleared by the FDA in 1984. BTA is currently approved for the treatment of axillary hyperhidrosis in 26 countries. In addition, off-label use of BTA has been reported in the literature in the U.S.

C. Important Milestones in Product Development

Agreements were reached to develop a clinical endpoint that would be more readily interpretable clinically than measurement of axillary sweat production. A 4-point global disease severity scale was used to assess treatment response. Treatment success was defined as the ability to achieve at least a 2-point improvement in score after two consecutive treatment sessions. Responders also included patients who responded to the first treatment but were precluded from a second treatment because of continued response.

On July 7, 2003, Allergan submitted to the Center for Biologics Evaluation and Research a Supplemental Biologics License Application (STN BL 103000/5050) to the existing marketing application for BOTOX (Botulinum Toxin Type A Purified Neurotoxin Complex) [STN BL 103000 (ELN 1145)], designated BTA, for an additional clinical indication to treat primary axillary hyperhidrosis. This application was transferred to CDER on October 2003 with the transfer of jurisdiction of many biological products to CDER.

D. Other Relevant Information

At the time this application was submitted, BTA was licensed in the U.S. for treatment of cervical dystonia, blepharospasm, strabismus, and glabellar lines. At the time of submission, BTA was also licensed in over 70 other countries for the indications listed above and for a variety of other indications including axillary hyperhidrosis.

E. Important Issues with Pharmacologically Related Agents

One unit (U) of product corresponds to the calculated median intraperitoneal lethal dose (LD_{50}) in mice. Due to specific details of this assay such as the vehicle, dilution scheme and laboratory protocols for the various mouse LD_{50} assays, Units of biological activity of BTA cannot be compared to nor converted into Units of any other botulinum toxin or any toxin assessed with any other specific assay method. Differences in species sensitivities to different botulinum neurotoxin serotypes preclude extrapolation of animal-dose activity relationships to human dose estimates.

II. Clinically Relevant Findings From Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews

No chemistry or animal pharmacology or toxicology data were contained in the submission. The statistical reviewers in collaboration with the clinical reviewers verified selected raw and derived datasets by comparing them to CRF entries. The statistical reviewer confirmed the validity of key efficacy analyses.

III. Human Pharmacokinetics and Pharmacodynamics

A. Pharmacokinetics

The toxin is administered intramuscularly or intradermally and systemic spread is not intended. No traditional PK studies are possible.

B. Pharmacodynamics

The sponsor conducted testing showing that 1U of BTA in 0.1 mL of diluent injected subdermally into the forearm resulted in a circle of anhydrosis 1.5 cm in diameter. In the hyperhidrotic axilla, doses of 5-10 U in 0.05-0.1 mL increased the diameter of this zone of hyperhidrosis to a maximum of 1.9 cm, thus suggesting that the injections should be spaced every 1 to 2 cm, depending on the individual injection site dose.

IV. Description of Clinical Data and Sources

A. Overall Data

The main support for this supplement comes from randomized clinical trials. Additional information was obtained from retrospective studies. Literature reports were an additional important source of safety information.

B. Tables Listing the Clinical Trials

Table 8 lists the adequate and well controlled studies that form the basis for the findings of safety and efficacy of this supplement.

Table 8 Listing of Studies of BTA Administered Intradermally for Axillary Hyperhidrosis

Study #	Study Design	BTA Dose (U)	n	Treatments F/U
191622-016	Multi-center, double- blind, randomized, placebo-controlled	0, 50, 75	322	$\leq$ 6 treatments FU: $\leq$ 52 weeks
191622-505	Multi-center, double- blind, randomized, vehicle-controlled	0, 50	320	1 treatment FU: 16 weeks

Table 9 lists retrospective studies that were reviewed for the main purpose of assessing safety.

Table 9 Retrospective Studies of BTA Injected Intradermally for Hyperhydrosis

Study Identifier	Aims	Study Design	Dose	n	Indication	Treatments F/U
US study 191622-059	Safety	Retrospective chart review no control	Variable	122	hyperhydrosis	Variable
German observational study	Safety and activity	Single-center retrospective chart review no control	mean 36 U range 20 -40 U	29	axillary, palmar, plantar or facial hyperhidrosis	$\leq$ 4 treatments FU $\leq$ 21 months
Swedish observational study	Safety and activity	Single-center retrospective chart review no control	mean 56 U range 17-130 U	157	axillary, palmar, plantar, genital, facial or other hyperhidrosis	$\leq$ 5 treatments FU $\leq$ 15 months

C. Postmarketing Experience

Postmarketing safety data were provided as a 120-day safety update.

D. Literature Review

All the reprints provided by the sponsor were reviewed to assess product safety and product activity in hyperhidrosis.

V. Clinical Review Methods

A. How the Review was Conducted

The two phase 3 trials were reviewed in their entirety including original protocols, protocol amendments, case report forms, clinical summaries, data listings, integrated summaries of efficacy and safety and full study reports. The following additional analyses were required for the review.

Regarding Study -016, the following analyses were performed:

- Response rates by investigator for each of the three arms.
- A list of the concurrent medications, categorized into analgesics, anti-inflammatory agents, anti-infectives, sedatives/psychotropics/anti-depressants, topical agents (to the axillae)
- Regarding the Primary Efficacy Variable(s), patients with at least a 2-grade improvement in HDSS score at week 4 of treatment session 1 who completed the 52-week study observation period but were precluded from a second injection because of a continuing

The numbers of protocol deviations, serious adverse events and treatment responders for the double-blind, randomized, placebo-controlled portion of Studies -016 and -505 were examined by study center. In consultation with the Division of Scientific Investigations, five study centers (sites 3167, 1901, 3166, 3157, and 2941) were selected for inspection based on numbers of patients enrolled, response rates, protocol deviations and/or adverse event rates. The inspections determined that the studies were conducted according to the protocol and that protection of patients was adequate. Source data were compared to CRF entries and no discrepancies were identified. It was concluded that the audits revealed no evidence of important deviations from good clinical practice in the conduct of the clinical trials. The clinical data were judged to be of good quality and were considered acceptable for supporting the license application.

Additional Review of Data From Study -059 to Address Allegations of Data Falsification

FDA was informed (b) (4) that a missing treatment date for a patient (4143) in this retrospective chart review Study -059 may have been falsely entered. The (b) (4) also questioned the utility of the data from this chart review study given the amount of missing data and the likelihood that there was bias in the selection of study sites. The reviewers examined the datasets for study 059 for the data variable called TXDT containing the raw treatment date variables and the data variable called ITXDT, which had imputed treatment dates. Treatment dates for two subjects 4108 and 4113 were imputed.

To verify the data, the reviewers requested the following information for Study -059 from the sponsor:

- All the data sets and variable definitions.
- All the case report forms for screened subjects.
- A description of the process for handling missing data.
- Verification that the treatment dates for subjects 4108 and 4113 and verification whether these two subjects were the only two for which treatment dates were imputed.
- Verification of the dates for the following eligible subjects (chosen to include the subject with the alleged made-up treatment date): Subjects 4108, 4113, 4127, 4141, and 4143.
- Copies of the original protocol for study 059 and the amended protocol 059-01
- Process for screening and selection of study sites.

The sponsor provided a description of the criteria and process used to screen and select the sites. The sponsor screened 10 potential sites over the phone, of which 7 met the criteria in that they had sufficient patients and could accurately identify the patients they had treated. Only 5 sites ultimately participated. The others did not participate either because they had no paper log, electronic spreadsheet or electronic database of potential patients (and were not considered further by the sponsor) or they withdrew because of concerns about patient privacy during the chart review study.

The sponsor verified that subjects 4108 and 4113 were the only two subjects with treatment dates that had to be imputed. They referenced the rules used to impute the dates that were submitted in the December 03, 2003 submission. The rules indicate that when the month and year are provided, the treatment date should be imputed as the first day of that month. This response was acceptable and the sponsor's approach seemed reasonable.

response to treatment, were considered responders. A re-analysis of the treatment response and duration of response excluding patients with HDSS score ≥3 but gravimetric measurement ≤50 mg was performed.

- An additional analysis was performed for the duration of the primary response by HDSS in which the interval was defined from the time of injection to the last visit at which response was observed, rather than from injection to the first recording of a score of 3 or 4 on the HDSS or discontinuation of a patient from the study prior to a score of 3 or 4.
- Analyses of Agreement Between HDSS and Gravimetric Assessment were performed using a scatter plot of HDSS versus the gravimetric assessment and a tabular cross-correlation of response/lack of response using HDSS score and gravimetric measurement.

Regarding Study -505, the following analyses were performed:

- Response rates by investigator.
- A list of the concurrent medications, which has been categorized into larger classes of medications to include analgesics, anti-inflammatory agents or drugs, anti-infectives, sedatives/psychotropics/anti-depressants, topical agents (to the axillae).
- Additional, conservative (ITT) analyses of the primary efficacy endpoint (responders based on a 50% reduction from baseline in axillary sweating).
- For each responder, the duration of response was calculated using the following rules:
    - onset of response: week 4
    - loss of response: sweat production ≤50% reduction from baseline or missing data
    - onset of loss of response:
        - first visit where loss of response criteria are met,
        - last visit where response documented, and
        - interpolations, e.g., mid-point, between the visits defined above.

In addition, SAS datasets were examined to verify data entries against CRF and to assess distribution of variables and amounts of missing data.

Observational studies were reviewed primarily for safety and the reviews are included in the Appendix.

B. Overview of Materials Consulted in Review

The submission was in electronic format. In addition to the original submission and the 120-day safety supplement, during the review cycle the sponsor submitted a final abbreviated clinical study report for Study -059 (Retrospective Chart Review Study).

C. Overview of Methods Used to Evaluate Data Quality and Integrity

The sponsor provided the scanned Case Report forms (CRFs) for each subject screened in the study, including a "Comments" page with a listing of missing data and Data Clarification Forms sent by the sponsor to the investigator site with queries about discrepancies or missing data. This standard data clarification process was used for some subjects to confirm missing treatment dates. For a total of 20 subjects, it was confirmed by reviewing the CRFs versus the SAS data sets that the correct treatment date and adverse event information was entered into the SAS data sets.

Conclusions
The reviewers verified the process of entry of treatment dates from CRF into CRT and for imputing missing treatment dates. No evidence of falsification of data was found.

D. Were Trials Conducted in Accordance with Accepted Ethical Standards

The investigators in the studies complied with applicable patients protection laws including obtaining informed consent, and obtaining IRB approval of the studies.

E. Evaluation of Financial Disclosure

1. Disclosure of Financial Interests and Arrangements of Clinical Investigators

In both (b) (6), some clinical investigators certified the presence of financial interests or proprietary interest in BTA, or a significant equity in Allergan as defined in 21 CFR 54.2(b). The investigators disclosed the receipt of significant payments of other sorts as defined in 21 CFR 54.2(f).

In Study (b) (6), one investigator declared the presence of financial interests (site (b) (6) with (b) (6) subjects). In Study (b) (6), the following study sites had investigator(s) with financial interest: Site (b) (6) subjects; Site (b) (6) subjects; Site (b) (6) subjects; Site (b) (6) subjects; Site (b) (6) subjects; and Site (b) (6) subjects. **Tables 10** and **11** show the treatment responder rates at the sites with investigators that disclosed financial interests for studies (b) (6) respectively.

Table 10 Study (b) (6) - Treatment Responder Rates Based on (b) (6) at Sites with Certified Financial Interests

Study Site Number	BTA 50U	Placebo
(b) (6)		
Mean at Other Sites	(b) (6)	
Mean Overall		

Table 11 Study -(b) (6)- Treatment Responder Rates Based on (b) (6) at Sites with Certified Financial Interests

Study Site Number	BTA 75U	BTA 50U	Placebo
(b) (6)			
Mean at Other Sites			(b) (6)
Mean Overall			

Reviewers' comments
In Study (b) (6) only one site certified the presence of financial interest. In Study (b) (6), a large number of sites relative to the total number certified the presence of financial interest. In the BTA 50 U group, the mean treatment effect was numerically similar for sites with financial interest (57%) compared to sites without financial interest (54%).

It was concluded that the presence of financial interests had no impact on the results of the studies.

2. Debarment Certification

The sponsor certifies that they have not used nor will they use the services of any clinical investigators debarred under section 306 (a) or (b) in conjunction with this license application.

VI. Integrated Review of Efficacy

A. Brief Statement of Conclusions

- For Study -016, a global assessment scale, the Hyperhydrosis Disease Severity Scale (HDSS), was the primary efficacy outcome. Study responders were defined as patients who showed at least a 2-grade improvement from baseline value on the HDSS at 4 weeks after both of the first two treatment sessions or had a sustained response after their first treatment session and did not receive re-treatment during the study. The percentage of responders based on at least a 2-grade decrease from baseline in HDSS or based on a >50% decrease from baseline in axillary sweat production was greater in both BTA groups than in the placebo group ($p < 0.001$). The difference in response by HDSS between the BTA groups and placebo (95% C.I.) was 49% (39, 60) for the 50U and 43% (33, 54) for the 75 U group.

- The proportion of treatment responders and the durability of response appeared to be similar between the 50 and 75 U dose.
- For Study -505, treatment responders were defined as subjects showing at least a 50% reduction from baseline in axillary sweating measured by gravimetric measurement at 4 weeks. At week 4 post-injection, the percentages of responders were 91% (219/242) in the BTA group and 36% (28/78) in the placebo group, $p < 0.001$. The difference in percentage of responders between BTA and placebo was 55% (95% CI = 43, 66).
- There was no suggestion of loss of treatment effect upon repeated dosing.
- Treatment response was similar for patients with HDSS score of 3 or 4 at baseline.
- There are no data on efficacy of doses lower than 50 U. However, in view of lack of safety concerns from data with doses up to 75 U, the rationale for exploring lower doses is weak. The possibility exists that doses lower than 50 U might result in lower proportion of responders and/or shorter duration of response.
- There were too few non-Caucasians and elderly enrolled in the clinical studies to reliably assess response rates in these subgroups. Men and women appeared to respond similarly to treatment.
- The study of children was deferred. Given that most patients report the onset of hyperhidrosis in adolescence, the study of post-pubertal children might be considered.
- Observational studies reported in this submission and literature reports provide evidence of off-label use of BTA for hyperhidrosis in several anatomic sites, in particular the palmar aspect of hands, digits, and plantar aspect of feet. Face and genitalia are less common treatment sites. A postmarketing study of hyperhidrosis of the hands to develop a safe and effective dose seems warranted.

B. General Approach to Review of the Efficacy of the Drug

Studies -016 and -505 were two adequate and well controlled studies, which were reviewed in detail. Included in the submission were a number of observational studies that were reviewed primarily for safety. The results of the latter studies are presented in the Appendix.

C. Detailed Review of Trials by Indication

1. Study -016 (US IND Study)

Title

A Multicenter, Double-Blind, Randomized, Placebo-Controlled, Parallel Study of the Safety and Efficacy of Repeated Treatment with One of Two Dosages of Botox® Purified Neurotoxin Complex for the Treatment of Primary Axillary Hyperhidrosis

Study Objectives

The objective of the study was to assess the safety and efficacy of repeated treatment with either one of 2 dosages of BTA (50U or 75U) compared with placebo (saline) for the treatment of primary axillary hyperhidrosis.

a. Study -016 Protocol

Study Design

This was a multicenter, double-blind, randomized, placebo-controlled, parallel group study of BTA in patients with hyperhidrosis. Patients were randomized to treatment with either placebo, 50U, or 75U of BTA (ratio of 1:1:1) at the first treatment session. Assignment to treatment group was stratified within investigational site and by disease severity at day 0 as assessed by the Hyperhydrosis Disease Severity Scale (HDSS). Patients were followed for up to 52 weeks after the first treatment. Patients who responded to the first treatment and relapsed were eligible to receive a second treatment. Planned enrollment was approximately 291 subjects at approximately 20 investigational sites for an expected sample size of 231 (77 per treatment group) to complete the second treatment session. The anticipated attrition was 20% following the second treatment session.

Reviewers' comments

This study was designed to assess the benefit of intermittent treatment with BTA over the course of one year. The expected median duration of response to treatment based on previous data was approximately six months. Therefore the study was designed to assess response to two treatment courses for patients who responded to the first treatment and relapsed during the study observation period. The composition of the placebo solution was different in this study compared to Study -505 and -506. Two placebo groups (high volume and low volume) were employed to maintain the blind.

Test Product, Dose, Mode of Administration, Formulation Number

Botulinum Toxin A (BTA) Purified Neurotoxin Complex (formulation No. 9060X, lots 11955, R12665, R12750, R12808, R12893, R13044) was reconstituted with either 2.67 mL (75 U group) or 4.0 mL (50 U group) of 0.9% sterile non-preserved saline. At each treatment session, each axilla would be injected with either 75U or 50U of BTA or placebo, for a total dose of 150 U, 100 U, or 0 U, respectively. The hyperhidrotic area of each axilla was identified using Minor's iodine-starch test. Using a syringe fitted with a 30 gauge needle each axilla was injected intradermally with 2 mL of study medication, evenly distributed among 10 to 15 sites (each designed to have a ring effect of approximately 2 cm in diameter) within the outlined

hyperhidrotic area. The volume at each injection site was determined by the total number of injection sites. The sponsor conducted testing showing that 1U of BTA in 0.1 mL of diluent injected subdermally into the forearm resulted in a circle of anhidrosis 1.5 cm in diameter. In the hyperhidrotic axilla, doses of 5-10 U in 0.05-0.1 mL had increased the diameter of this zone of hyperhidrosis to a maximum of 1.9 cm, thus suggesting that the injections should be given every 1 to 2 cm, depending on the individual injection site dose. Each subject was to receive up to 6 treatment sessions, depending upon the response to treatment and duration of response.

Reviewers' comment
The distribution and spacing of injections appears to be reasonable based on diffusion characteristics of intradermal injections.

Placebo (non HSA) (Formulation No. 9379X, lots R12714, R12751, R12810, R12840, R13330) was reconstituted with either 2.67 mL or 4.0 mL of 0.9% sterile non-preserved saline. Two milliliters of reconstituted placebo was administered in an identical way to that described for the test product.

Following the initial treatment session, subjects would be evaluated at a telephone visit 1 week post-injection, an office visit 4 weeks post-injection, and at alternating office and telephone visits every 4 weeks thereafter until they would be eligible for reinjection or exited the study. Subjects would be eligible for reinjection when they reported a HDSS score of 3 or 4 but not sooner than 8 weeks from the prior treatment session, and not later than 44 weeks from the initial treatment session. If eligibility for retreatment was determined at an office visit, subjects would be reinjected at that office visit. If eligibility was determined at a phone visit, an office visit was scheduled within 7 to 14 days for the reinjection. After reinjection, follow-up would be as described above for the initial treatment session.

Concurrent treatments
Use of over-the-counter antiperspirants or deodorants was allowed. Such treatments were to be withheld for at least 24 hrs before a study visit. Treatments for hyperhidrosis, including prescription antiperspirants, were not allowed.

Key Inclusion Criteria
The following were the principal criteria required for entry in to the study.
- Male or female subjects, 18 to 75 years of age.
- Persistent bilateral primary axillary hyperhidrosis as measured by an HDSS score of 3 or 4
- Production of at least 0.05 g spontaneous resting axillary sweat in each axilla measured over 5 minutes at room temperature by gravimetric measurement at both the screening visit and the initial treatment session.

Key Exclusion Criteria
The following were the main exclusion criteria.
- Any medical condition that may put the subject at increased risk with exposure to BTA.
- Concurrent use of agents that might interfere with neuromuscular function.
- Known allergy or sensitivity to BTA or iodine,

- Secondary hyperhidrosis, concurrent use or use within 7 days of the initial treatment session of any treatment for hyperhidrosis, previous botulinum toxin treatment of any serotype for hyperhidrosis.

Primary Efficacy Measure

The primary efficacy variable was the subject's assessment of the severity of hyperhidrosis using the following 4 point Hyperhidrosis Disorder Severity Scale (HDSS):

1 = My underarm sweating is never noticeable and never interferes with my daily activities.
2 = My underarm sweating is tolerable but sometimes interferes with my daily activities.
3 = My underarm sweating is barely tolerable and frequently interferes with my daily activities.
4 = My underarm sweating is intolerable and always interferes with my daily activities.

The primary endpoint would be the proportion of responders defined as subjects who, after each of the first two treatment sessions, report at least a 2-grade improvement on the HDSS at 4 weeks postinjection compared to baseline. In addition, the following patients were also considered to be treatment responders:

- Patients who enrolled in the study with an HDSS score of 4, showed only a 2-grade improvement following the first treatment session, and were reinjected with an HDSS score of 3 needed only a 1-grade improvement 4 weeks following the second treatment session.

- Patients with at least a 2-grade improvement in HDSS score at week 4 of treatment session 1 who completed the 52-week study observation in remission defined as:

    - HDSS scores of 1 or 2 at all visits through week 44

    - HDSS score 3 or 4 but gravimetric measurements < 50 mg

Reviewers' comment
Treatment response and duration of remission were also analyzed excluding patients with HDSS scores ≥3 but gravimetric measurement <50 mg.

Secondary Efficacy Measures

Gravimetric measurement of sweat production:
The principal secondary efficacy variable was the measurement of spontaneous resting axillary sweat production using a filter paper weighed before and after placement in the axilla. This measurement was carried out for each axilla at room temperature over 5 minutes. There were two endpoints using the gravimetric measurement of sweat production:

1) the proportion of responders (defined as subjects who achieved at least a 50% reduction in spontaneous resting axillary sweat production at week 4 postinjection for the first two treatment sessions) and
2) the percentage change in spontaneous resting axillary sweat production at week 4 postinjection for the first two treatment sessions.

Bilateral measurements of axillary sweat production were averaged for each patient at each timepoint. If the value for one axilla was missing, then the value from the contralateral axilla was used. If both values were missing, the patient's average at a visit was imputed by the median average at that visit of patients with the same study baseline HDSS score, regardless of treatment group.

Reviewers' comments
The measurement of axillary sweat production can, in general, be performed reliably and reproducibly. However the relationship of the baseline measurement to severity of hyperhidrosis and quantitative relationship between decreased sweat production and patient satisfaction is not well understood. For these reasons a global patient's assessment was considered a more meaningful measure of treatment response and was designated as the primary efficacy outcome for the present study. As discussed previously, axillary sweat production was the primary endpoint for Study -505.

Neverthless, axillary sweat production is an objective and useful measure of treatment response and, as an important corroborative outcome, it was designated as the principal secondary endpoint. The proportion of patients achieving a 50% or better improvement from baseline in axillary sweat production is considered a more clinically interpretable outcome than mean percentage change in axillary sweat production.

Subject Daily Diary:
Patients completed a Subject Daily Diary (SDD) for the 7 days immediately before each office visit (except the screening visit), and for the 7 days immediately following the completion of a visit at which a patient was first considered a non-responder. Questions 1, 2, and 3 assessed the effect of hyperhidrosis on daily activities. Patients reported the frequency and time devoted to activities performed due to hyperhidrosis (e.g. time to treat the condition, frequency of showering and clothes changing) on a daily basis. Questions 4, 5, and 6 related to work productivity. Patients reported the effect of hyperhidrosis symptoms on work productivity, i.e. number of days affected and percent of normal work effectiveness. Question 7 contained 8 parts and dealt with limitations on various activities (e.g. social activities and relationships).

Questions 1-3 allowed 4 levels of scoring. Questions 4-5 required entry of a number (for the number of hours worked/affected). Questions 6-7 allowed 5 levels of scoring ranging from "not at all" to "extremely".

For question 1-3 median scores for the responses over the 7 days were determined for each subject. For questions 4-5 the proportion of working hours affected by hyperhidrosis was

determined for each subject. Each of the parts in question 7 was evaluated independently and median scores over 7 days were determined for each subjects. The treatment groups would be compared by rank testing.

The SDD is shown below.

Subject Daily Diary (Page 1 of 2)	Subject Initials (use '-' if no middle initial)	Subject Number	Study Number 191622-016
Investigator Name	Investigator No.	Begin completing diary on: Month / Day / Year	

Question	Choices	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
1. How long yesterday did you spend treating your hyperhidrosis?	Less than 15 minutes 15-30 minutes 31-60 minutes More than 60 minutes	☐ ☐ ☐ ☐	☐ ☐ ☐ ☐	☐ ☐ ☐ ☐	☐ ☐ ☐ ☐	☐ ☐ ☐ ☐	☐ ☐ ☐ ☐	☐ ☐ ☐ ☐
2. How many times yesterday did you change your shirt or other clothes due to the effects of your hyperhidrosis?	Not at all Once Twice 3 times or more	☐ ☐ ☐ ☐	☐ ☐ ☐ ☐	☐ ☐ ☐ ☐	☐ ☐ ☐ ☐	☐ ☐ ☐ ☐	☐ ☐ ☐ ☐	☐ ☐ ☐ ☐
3. How many times yesterday did you shower or take a bath?	Not at all Once Twice 3 times or more	☐ ☐ ☐ ☐	☐ ☐ ☐ ☐	☐ ☐ ☐ ☐	☐ ☐ ☐ ☐	☐ ☐ ☐ ☐	☐ ☐ ☐ ☐	☐ ☐ ☐ ☐
4. How many hours were you supposed to work yesterday?	Please enter whole numbers ONLY	☐	☐	☐	☐	☐	☐	☐
5. How many hours did hyperhidrosis keep you from work yesterday?	Please enter whole numbers ONLY	☐	☐	☐	☐	☐	☐	☐
6. How much do you think your hyperhidrosis symptoms influenced your effectiveness at work yesterday?	Not applicable Not at all A little Moderately Quite a bit Extremely	☐ ☐ ☐ ☐ ☐ ☐	☐ ☐ ☐ ☐ ☐ ☐	☐ ☐ ☐ ☐ ☐ ☐	☐ ☐ ☐ ☐ ☐ ☐	☐ ☐ ☐ ☐ ☐ ☐	☐ ☐ ☐ ☐ ☐ ☐	☐ ☐ ☐ ☐ ☐ ☐
7. How limited do you feel you were yesterday in each of these activities / situations due to your hyperhidrosis?	*If you did not have the opportunity to do the activity yesterday due to reasons other than hyperhidrosis please mark: "Did not have opportunity to do."*							
7a. Being in public places	Did not have opportunity to do	☐	☐	☐	☐	☐	☐	☐
	Not limited Somewhat limited Moderately limited Quite a bit limited Extremely limited	☐ ☐ ☐ ☐ ☐	☐ ☐ ☐ ☐ ☐	☐ ☐ ☐ ☐ ☐	☐ ☐ ☐ ☐ ☐	☐ ☐ ☐ ☐ ☐	☐ ☐ ☐ ☐ ☐	☐ ☐ ☐ ☐ ☐
7b. When meeting or being introduced to people for the first time	Did not have opportunity to do	☐	☐	☐	☐	☐	☐	☐
	Not limited Somewhat limited Moderately limited Quite a bit limited Extremely limited	☐ ☐ ☐ ☐ ☐	☐ ☐ ☐ ☐ ☐	☐ ☐ ☐ ☐ ☐	☐ ☐ ☐ ☐ ☐	☐ ☐ ☐ ☐ ☐	☐ ☐ ☐ ☐ ☐	☐ ☐ ☐ ☐ ☐

Subject Daily Diary (Page 2 of 2)	Subject Initials (use "-" if no middle initial)	Subject Number	Study Number 191622-016

Question	Choices	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
7. (Cont'd) How limited do you feel you were yesterday in each of these activities / situations due to your hyperhidrosis?		*If you did not have the opportunity to do the activity yesterday due to reasons other than hyperhidrosis please mark: "Did not have opportunity to do."*						
7c. On family occassions or with friends	Did not have opportunity to do	☐	☐	☐	☐	☐	☐	☐
	Not limited	☐	☐	☐	☐	☐	☐	☐
	Somewhat limited	☐	☐	☐	☐	☐	☐	☐
	Moderately limited	☐	☐	☐	☐	☐	☐	☐
	Quite a bit limited	☐	☐	☐	☐	☐	☐	☐
	Extremely limited	☐	☐	☐	☐	☐	☐	☐
7d. When shaking hands	Did not have opportunity to do	☐	☐	☐	☐	☐	☐	☐
	Not limited	☐	☐	☐	☐	☐	☐	☐
	Somewhat limited	☐	☐	☐	☐	☐	☐	☐
	Moderately limited	☐	☐	☐	☐	☐	☐	☐
	Quite a bit limited	☐	☐	☐	☐	☐	☐	☐
	Extremely limited	☐	☐	☐	☐	☐	☐	☐
7e. In developing personal relationships	Did not have opportunity to do	☐	☐	☐	☐	☐	☐	☐
	Not limited	☐	☐	☐	☐	☐	☐	☐
	Somewhat limited	☐	☐	☐	☐	☐	☐	☐
	Moderately limited	☐	☐	☐	☐	☐	☐	☐
	Quite a bit limited	☐	☐	☐	☐	☐	☐	☐
	Extremely limited	☐	☐	☐	☐	☐	☐	☐
7f. In sexual activities	Did not have opportunity to do	☐	☐	☐	☐	☐	☐	☐
	Not limited	☐	☐	☐	☐	☐	☐	☐
	Somewhat limited	☐	☐	☐	☐	☐	☐	☐
	Moderately limited	☐	☐	☐	☐	☐	☐	☐
	Quite a bit limited	☐	☐	☐	☐	☐	☐	☐
	Extremely limited	☐	☐	☐	☐	☐	☐	☐
7g. In sport	Did not have opportunity to do	☐	☐	☐	☐	☐	☐	☐
	Not limited	☐	☐	☐	☐	☐	☐	☐
	Somewhat limited	☐	☐	☐	☐	☐	☐	☐
	Moderately limited	☐	☐	☐	☐	☐	☐	☐
	Quite a bit limited	☐	☐	☐	☐	☐	☐	☐
	Extremely limited	☐	☐	☐	☐	☐	☐	☐
7h. Other situations (please list):	Did not have opportunity to do	☐	☐	☐	☐	☐	☐	☐
	Not limited	☐	☐	☐	☐	☐	☐	☐
	Somewhat limited	☐	☐	☐	☐	☐	☐	☐
	Moderately limited	☐	☐	☐	☐	☐	☐	☐
	Quite a bit limited	☐	☐	☐	☐	☐	☐	☐
	Extremely limited	☐	☐	☐	☐	☐	☐	☐

Reviewers' comment

The purpose of the diary was to corroborate the patient's global assessment of treatment response. This tool is not validated and interpretation of the results is difficult.

Minor's Iodine-Starch Test:
Minor's iodine starch test was performed to assess the surface area of excessive sweating. The test was performed at every injection/reinjection visit (before injection and after gravimetric measurement) to identify the sweat producing area (blue colored area of skin) and to serve as the baseline measurement. The test was repeated at the 4-week postinjection/reinjection visit (after gravimetric measurement) and compared to baseline. Photographs of the affected area were obtained. Change in area from baseline would be compared between groups.

Reviewers' comment
This test was used to outline the area in the axilla producing sweat and requiring treatment. It would be of interest to determine if a treatment effect would be demonstrable by a decrease in sweat production as well as by a reduction in the sweat producing area (e.g. by development of anhydrosis) based on the colorimetric test.

Hyperhidrosis Impact Questionnaire:
The Hyperhidrosis Impact Questionnaire (HHIQ) was designed to assess the impact of the condition and treatment effect in the study patients. The HHIQ is a 41-item self-administered baseline questionnaire and a 10-item follow-up questionnaire. The baseline questionnaire is divided into 4 sections: Resource Utilization and Perceived Effectiveness of Treatment, Effect on Daily Activities, Productivity and Activity, and Treatment Satisfaction.

The follow-up questionnaire is divided into 2 sections: Effect of Hyperhidrosis on Daily Activities and Effect of Hyperhidrosis on Activities/Productivity and Emotion. The follow-up questionnaire is shown below. Note the similarity in content between the HHIQ and the SDD.

Reviewers' comment
The Hyperhydrosis Impact Questionnaire was developed and previously tested by the sponsor who makes no claim for its validity or sensitivity. The scale contains items that are identical or similar to the items in the Patient Daily Diary.

HYPERHYDROSIS IMPACT FOLLOW UP QUESTIONNAIRE

Please check your overall level of satisfaction with the following:						
	Very satisfied	Somewhat satisfied	Neutral	Somewhat dissatisfied	Very dissatisfied	Does not apply
Your ability to perform your current work activities due to your hyperhidrosis						
Your ability to perform your current non-work (e.g. social and leisure) activities due to your hyperhidrosis						

HYPERHYDROSIS IMPACT FOLLOW UP QUESTIONNAIRE (continued)

EFFECT OF HYPERHIDROSIS ON DAILY ACTIVITIES IN THE PAST THREE MONTHS

5. Is an unpleasant smell associated with your sweating?

- ☐ No
- ☐ Yes. If yes, how much limitation in your activities or situations is due to the sweating and how much is due to the smell?
  - ☐ All due to the sweating alone
  - ☐ Mostly due to the sweating alone
  - ☐ Due equally to sweating and smell
  - ☐ Mostly due to the smell alone
  - ☐ All due to the smell alone
  - ☐ I am not limited in my activities or situations due to sweating or smell

. How long per day on average do you spend treating your hyperhidrosis?

☐ Less than 15 minutes ☐ 15-30 minutes ☐ 31-60 minutes ☐ More than 60 minutes

How frequently must you change your shirt or other clothes due to the effects of your hyperhidrosis?

- ☐ I can wear my clothing for several days
- ☐ Daily
- ☐ Twice per day
- ☐ 3 times or more per day

How frequently do you shower or take a bath?

- ☐ Less than daily
- ☐ Daily
- ☐ Twice a day
- ☐ 3 times or more per day

During the past 3 months, how many days did hyperhidrosis keep you from work for half a day or more?
(Please write in number of days)

☐☐ days

Over the past 3 months, on the days you continued working, how much do you think your hyperhidrosis symptoms influenced your effectiveness at work?

☐ Extremely ☐ Quite a bit ☐ Moderately ☐ A little ☐ Not at all

HYPERHYDROSIS IMPACT FOLLOW UP QUESTIONNAIRE (continued)

EFFECT OF HYPERHIDROSIS ON ACTIVITIES & PRODUCTIVITY AND EMOTION

10. **Do you feel emotionally damaged/injured by your hyperhidrosis?**

- ☐ Not effected emotionally
- ☐ Effected emotionally to a small extent
- ☐ Effected emotionally moderately
- ☐ Effected emotionally significantly

11. **How limited do you feel you currently are in each of these activities/situations due to your hyperhidrosis?**

Activity / Situation	Not limited	Somewhat limited	Moderately limited	Quite a bit limited	Extremely limited
At work					
Being in public places					
When meeting or being introduced to people for the first time					
On family occasions or with friends					
When shaking hands					
In developing personal relationships					
In sexual activities					
In sport					
Other situations: Please list: _____					

Dermatology Life Quality Index:
The Dermatology Life Quality Index (DLQI) is a general scale for assessment of the effect of dermatologic disorders on patient's activities, emotions and relationships. The scale (see below) requires responses to 10 questions in 6 domains: Symptoms and Feelings, Daily Activities, Leisure, Work and School, Personal Relationships, and Treatment. Questions were answered on a 4-point scale ranging from very much to not at all.

Reviewers' comment
This scale has not been validated for hyperhidrosis.

DERMATOLOGY LIFE QUALITY INDEX

The aim of this questionnaire is to measure how much your skin problem has affected your life OVER THE LAST WEEK. Please check one box for each question.

1. **Over the last week, how itchy, sore, painful or stinging has your skin been?**	Very much ☐ A lot ☐ A little ☐ Not at all ☐	
2. **Over the last week, how embarrassed or self conscious have you been because of your skin?**	Very much ☐ A lot ☐ A little ☐ Not at all ☐	
3. **Over the last week, how much has your skin interfered with you going shopping or looking after your home or garden?**	Very much ☐ A lot ☐ A little ☐ Not at all ☐	Not relevant ☐
4. **Over the last week, how much has your skin influenced the clothes you wear?**	Very much ☐ A lot ☐ A little ☐ Not at all ☐	Not relevant ☐
5. **Over the last week, how much has your skin affected any social or leisure activities?**	Very much ☐ A lot ☐ A little ☐ Not at all ☐	Not relevant ☐
6. **Over the last week, how much has your skin made it difficult for you to do any sport?**	Very much ☐ A lot ☐ A little ☐ Not at all ☐	Not relevant ☐

7. Over the last week, has your skin prevented you from working or studying?	Yes No	☐ ☐	Not relevant ☐
If "No", over the last week how much has your skin been a problem at work or studying?	A lot A little Not at all	☐ ☐ ☐	
8. Over the last week, how much has your skin created problems with your partner or any of your close friends or relatives?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐
9. Over the last week, how much has your skin caused any sexual difficulties?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐
10. Over the last week, how much of a problem has the treatment for your skin been, for example by making your home messy, or by taking up time?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐

Other Clinical Assessments

Clinical assessments included physical examination, vital signs, urine pregnancy tests (the latter for women of childbearing potential), laboratory tests (hematology and blood chemistry), adverse events, and serum test for anti-BTA antibodies. The schedule of visits is shown below.

Table 12 Schedule of Assessments

Assessment	Screening	Injection Reinjection[a] Day 0	Phone Contact Day 7	Visit Week 4	Monthly Office Visits or Phone [b] Week 8-52	Exit Visit Week 16-52
History & physical	X					X
Vital signs	X	X		X	X[c]	X
Pregnancy test		X				
HDSS	X	X	X	X	X	X
Gravimetric meas.	X	X		X		
Minor s test		X		X		
injection/ reinjection		X				
Subject Daily Diary		X		X	X[c]	X
DLQI	X	X		X	X[c]	X
Hyperhidrosis Impact Questionnaire-	X	X		X	X[c]	X
Adverse events		X	X	X	X	X
Concurrent procedures		X	X	X	X	X
Concomitant meds	X	X	X	X	X	X
antibody test		X				X
CBC/chemistry	X					X

a Patients eligible for reinjection had the same follow-up as after the first treatment session.
b Office and telephone visits alternated monthly.
c Only at office visits.

Study -016 Statistical Analyses

All efficacy analyses included all subjects randomized, with subjects analyzed as randomized. All safety analyses included all subjects randomized and treated, with subjects analyzed as treated. A per protocol analysis of the primary efficacy variable was performed as a secondary analysis. Subjects who met the evaluability criteria as specified in the analysis plan, and who received study medication with at least one follow-up visit were included in the per protocol analysis. The primary analysis would be performed at week 4 following the second injection.

Primary Efficacy Variable

Subjects missing primary outcomes, i.e., HDSS assessment 4 weeks following either of the first or second treatment session, would be considered non-responders regardless of reasons for the missing data. HDSS evaluation at week 4 would be considered valid only if collected between 2 weeks and 6 weeks postinjection. If there were multiple valid HDSS scores in the window of 2-6 weeks post injection, the one closest to the week 4 time mark would be used as the primary outcome. If multiple valid HDSS scores were equidistant from the week 4 time mark, the latter one would be considered the primary outcome. Subjects discontinued from the study before the week 4 postinjection visit of the second injection would be treated as non-responders. Subjects with a continued response (at least a 2-grade improvement on the HDSS 4 weeks following the first treatment session followed by a score of 1 or 2 at all subsequent evaluations) from the first injection to greater than or equal to 44 weeks would be considered responders. An analysis of the actual score would be provided as a secondary analysis.

The primary analysis would be performed on the responder data at week 4 following the second injection. A Mantel-Haenzel test stratified by baseline severity of HDSS would be performed to evaluate the equality of the proportions of responders between groups. Two pairwise tests, each BTA group versus placebo, would be performed and the Hochberg procedure would be used to adjust for multiplicity.

Duration of effect would be based on the HDSS and provided for the first and second injections only. Entry time would be defined as the date of injection. The criteria for end of effect would be a score of 3 or 4 on the HDSS. The analysis of duration of effect following the second injection would only include subjects receiving a second injection.

Secondary Efficacy Variables

Gravimetric measurement of spontaneous resting axillary sweat production:

The percentage change in spontaneous resting axillary sweat production as measured by the gravimetric measurement would be analyzed at week 4 postinjection for the first two treatment sessions. Percent change from baseline would be calculated for each axilla, and then averaged within each time point for each subject. If data for a single axilla were missing then the value from the contralateral axilla was to be used in the calculations. As with the primary endpoint, only measurements collected between weeks 2 and 6 would be considered valid for the analyses at week 4. Multiple valid measurements within the window would be handled similarly as for the HDSS analyses. Missing percentage change values at week 4 postinjection would be

imputed according to baseline HDSS score. Missing percentage change values at a visit would be imputed by the median percentage change among all subjects with the same baseline HDSS score, across all treatment groups at that visit. The 2-sample t-test would be performed, one for each BTA dose group versus placebo, and the Hochberg procedure used to adjust for multiplicity at each of the time points. A responder analysis would be performed for comparison with the results of the primary analysis of the clinical study report. A treatment responder based on gravimetric assessment was defined as a subject showing at least 50% reduction from baseline in axillary sweating. The percentage of treatment responders in each treatment group would be determined and Fisher's exact test would be performed for all pairwise between-group comparisons.

Iodine starch test:
Measurements of axillary hyperhidrotic areas were performed on photographs of axillae to which Minor's iodine starch had been applied. Wilcoxon rank sum test was used for between group comparisons.

Subject Daily Diary (SDD):
A Wilcoxon rank sum analysis would be performed on each BTA dose group versus placebo, and the Hochberg procedure used to adjust for multiplicity at each visit. Windows were applied to the Subject Daily Diaries (SDD) completed 7 days immediately prior to each office visit and 7 days immediately following the visit at which a patient was classified as a non-responder. Only data from days within the windows were used in the analyses. These questions would be analyzed at the week 4 post injection visit of each of the first two treatment sessions. Determination of valid visits, and handling of missing values and multiple values for the week 4 assessments, would be performed similarly as for the gravimetric measurement. For the pre-visit diaries, missing values were imputed according to baseline HDSS score. For patients who did not submit a post-visit diary, their pre-visit diary for the same visit was substituted. No additional imputation of missing data was performed if both diaries were missing.

Question 1, 2 and 3 of SDD
The analysis of question 1, 2, and 3 of the SDD was based on the ITT population. At each visit, the median score of the observed data collected during the 7 days prior to the scheduled visit would be determined for each subject for each question.

Questions 4 and 5
The analysis of these questions would exclude non-evaluable subjects, i.e., subjects who, for all 7 days prior to the scheduled visit, did not work at all, or had a combination of 0 hours and missing values. For evaluable subjects at each visit, the proportion of missed work hours for the 8 days prior to the scheduled visit would be calculated: total number of hours not worked (according to question 5)/the total number of hours supposed to have worked (according to question 4) over all non-zero, non-missing days.

Questions 7a – 7h
Each of these questions would be analyzed independently in the following manner: The analysis of each question would exclude non-evaluable subjects, i.e., subjects who, for all 7 days prior to

the scheduled visit, checked only "Did not have opportunity to do", or had a combination of only "Did not have opportunity to do" and missing values for each question. For each evaluable subject at each visit, the median score of the observed data (excluding missing and "Did not have opportunity to do") collected during the 7 days would be determined.

Analysis of Time To Event Variables

Kaplan-Meier estimates would be provided for time-to-event data for the purposes of evaluating duration of effect. Confidence intervals would be constructed using Greenwood's formula for the standard error. Between-group tests for differences in duration of effect would be performed using the log-rank test.

Null hypothesis and adjustment for multiplicity

The primary null hypothesis was that the BTA doses and placebo are equally effective in reducing spontaneous resting axillary sweat production as measured by the HDSS.

Statistical tests would include 2 pair-wise tests of each of BTA dose group versus placebo. For the evaluation of the efficacy variables, the Hochberg procedure would be used to adjust for multiplicity; the larger p-value of the hypothesis tests would be compared to the critical value of 0.05, if significant, the results of both tests would be considered significant, otherwise, the smaller p-value would be compared to the critical value of 0.025 (adjusted according to the procedure).

Sample Size Calculation

The primary efficacy variable used to calculate the pre-study estimate of power was the HDSS dichotomized to represent responders and non-responders.

A minimum sample size of 77 subjects per treatment group was calculated based on the following assumptions: Detection of a 25-percentage point difference in the incidence of responders based on the HDSS between at least one BTA treatment group compared with the placebo group. Bonferroni adjustment of the significance level for the 2 pairwise comparisons of BTA to placebo: Alpha=0.05/2. Power=80%. 2-sided Fisher's exact test for 50% versus 25%. Therefore, 291 subjects (97 per treatment group) would be required given a drop out rate expected to be 20% following the second injection.

Protocol Amendments

The original protocol was dated 21 December 1999. There were two protocol amendments (February 2001 and July 2001). The protocol amendments were made before unblinding of data and resulted in the following changes to the protocol

- clarified the method for treatment assignment
- allowed for prior botulinum toxin exposure for indications other than hyperhidrosis but limited to no more than 5% of the patients enrolled
- added the Subject Daily Diary as a secondary efficacy variable
- added the Dermatology Life Quality Index as a health outcomes measure
- clarified the process for maintaining the blind during study drug preparation

- clarified the procedures for unmasking study medication
- expanded the statistical analysis section to cover missing data, Subject Daily Diary, and various efficacy variables
- added production of at least 50 mg spontaneous resting axillary sweat in each axilla over 5 minutes as a requirement for reinjection

Amendments to the Analysis Plan

- inclusion as responders of those patients who responded to the first treatment by HDSS score and by gravimetric measurement, at a later office visit reported an HDSS score of 3 or 4 but did not produce at least 50 mg of sweat on the gravimetric measurement and were therefore precluded from receiving a second treatment, provided they completed the 52-week study observation period
- percentage change in gravimetric measurement of spontaneous resting axillary sweat production was calculated after averaging bilateral raw values for each patient rather than calculating the percent change by axilla and then averaging the changes in each axilla for the patient
- summary statistics for change from screening to baseline of responses to the DLQI questions, and correlation between results at those 2 visits
- between-group comparisons of dichotomized responses to the HHIQ based on Fisher's exact test
- duration of effect analyses for subgroup of patients with at least a 2-grade decrease in HDSS score from baseline to week 4 of treatment session 1

Reviewers' comments
The changes made to the analysis plan for Study -016 were entitled " Analysis Plan Amendment 1". The amendment was dated October 30, 2002 and it was received on October 31, 2002. The database was locked and the study was unblinded on November 13, 2002.

b. Study -016 Results

Study Centers
A total of 18 centers participated in the study (US: 17 centers, Canada: 1 center)

Study Period
The study was begun on April 17, 2001 and was completed on October 10, 2002.

Study conduct
Several mostly minor deviations from the protocol were observed in all centers. These included:

- visit outside window or missing
- diary/questionnaire deviations
- injection deviation (a small number of subjects had lower and greater number of injections)
- Patient room temperature at study site was outside range

- Consent issues (outdated version used, required re-consent); Screening assessments done before consent form signed
- Antibody sampling deviation (e.g. storage at room temp, missing, incorrect sampling time)
- Safety lab deviation (e.g. data missing; data not reviewed before injection)
- Tertiary assessments not performed or performed incorrectly

Major protocol deviations were:

- Seven patients at 5 study centers did not meet entry criteria of axillary sweat production > 50 mg at baseline.
- One patient 3166-3161 had concurrently enrolled in a second trial and was discontinued from study.
- Six patients at 2 study centers were mis-randomized because of error in stratification based on baseline HDSS score. These patients were analyzed as randomized or were analyzed in the stratum from which they should have been randomized (i.e. according to their actual study baseline HDSS score) (Patients 2941-3085, placebo; 2941-3086, 75 U; 2941-3088, 2941-3089, 50U; 2941-3090, 75U; 3270-3057, 50U)
- Two patients at 2 sites became pregnant during the study; each woman delivered a healthy baby (Patients 3278-3061 and 3646-3038)
- Several negative values for gravimetric assessments were reported during the study. These may indicate measurement error.

Only one patient had prior exposure to botulinum toxin (3166-4176 for cosmetic treatment). Only previous botulinum toxin treatment for hyperhydrosis was excluded per protocol.

Patient Disposition

A total of 322 patients were enrolled and 252 of the patients completed the study.

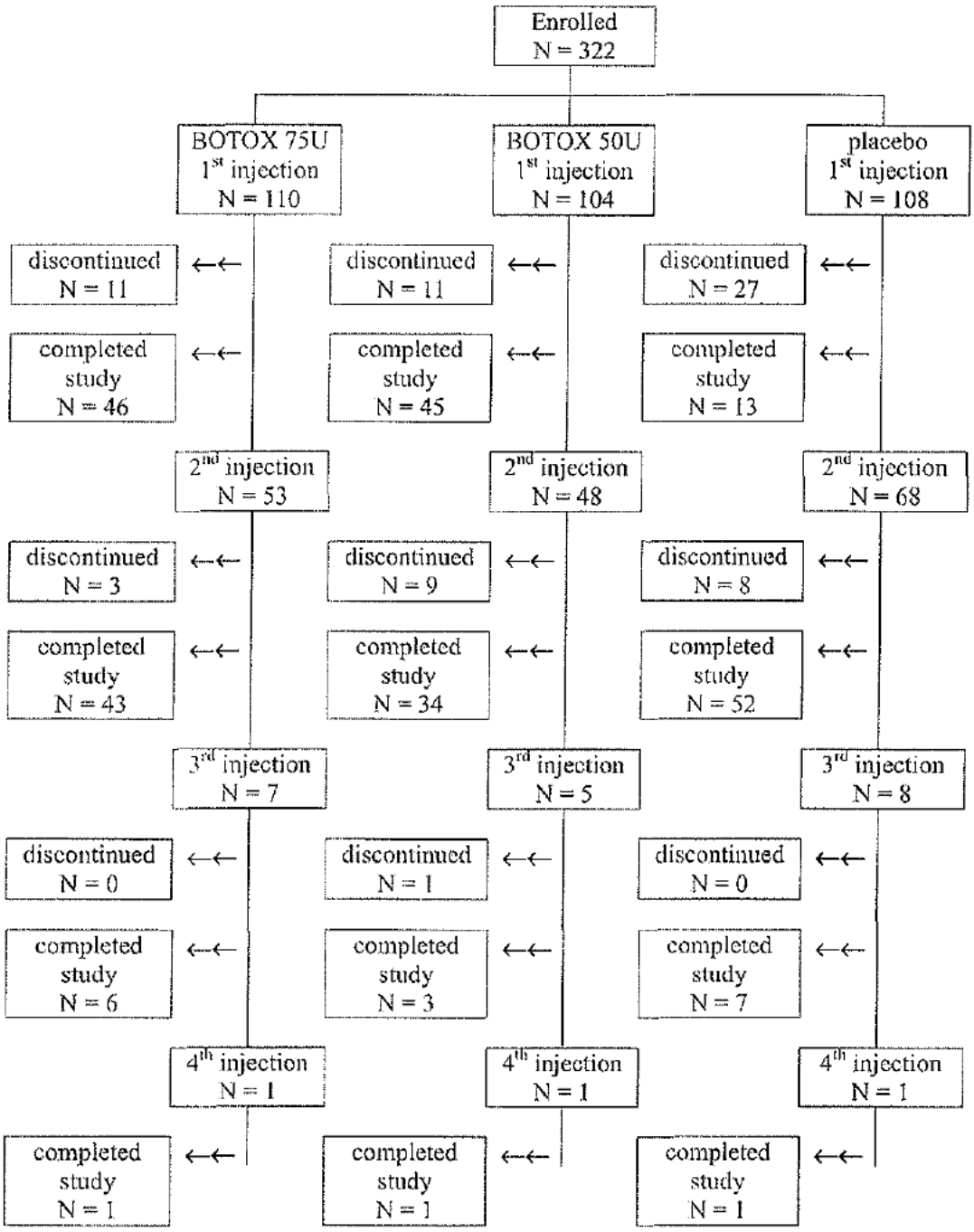
Discontinued Subjects

Subjects were discontinued from the study early due to adverse events, protocol violations, administrative reasons (e.g., inability to continue, loss to follow-up), failure to continue to satisfy inclusion/exclusion requirements.

Completed Subjects

A completed subject was one who completed 52 weeks of follow-up (from the time of the initial treatment session) or who was considered to be a non-responder. Subjects considered to be non-responders were exited from the study 8 weeks following the second consecutive treatment session at which they failed to show at least a 2-grade improvement in HDSS score 4 weeks post-injection. All exit visits were to have occurred at an office visit.

The following figure shows the disposition of patients following each injection by study treatment and by injection number. Note that few patients received more than two injections.



Source: Table 14.1-1.2

Note patients completed the study after as few as 1 treatment session or as many as 4 treatment sessions.

Table 13 shows the proportion of patients with status of discontinued or completed by treatment group and by monthly intervals. Note that the proportion of patients discontinuing is higher in the placebo group than in the active groups.

Table 13 Cumulative Patient Disposition

Study Days	Cumulative Status	BTA 75U (n=110)	BTA 50U (n=104)	Placebo (n=108)
30	Completed	0	0	0
	Continuing	109 (99)	104 (100)	108 (100)
	Discontinued	1 (1)	0	0
60	Completed	0	0	0
	Continuing	108 (98)	103 (99)	103 (95)
	Discontinued	2 (2)	1 (1)	5 (5)
90	Completed	0	0	0
	Continuing	107 (97)	102 (98)	95 (88)
	Discontinued	3 (3)	2 (2)	13 (12)
120	Completed	1 (1)	0	6 (6)
	Continuing	105 (96)	102 (98)	83 (77)
	Discontinued	4 (4)	2 (2)	19 (18)
150	Completed	4 (4)	1 (1)	23 (21)
	Continuing	102 (93)	98 (94)	61 (57)
	Discontinued	4 (4)	5 (5)	24 (22)
180	Completed	5 (5)	1 (1)	29 (27)
	Continuing	100 (91)	96 (92)	54 (50)
	Discontinued	5 (5)	7 (7)	25 (23)
210	Completed	6 (6)	1 (1)	34 (32)
	Continuing	97 (88)	94 (90)	45 (42)
	Discontinued	7 (6)	9 (9)	29 (27)
240	Completed	7 (6)	1 (1)	37 (34)
	Continuing	93 (84)	92 (89)	39 (36)
	Discontinued	10 (9)	11 (11)	32 (30)
270	Completed	8 (7)	1 (1)	39 (36)
	Continuing	92 (84)	91 (88)	37 (34)
	Discontinued	10 (9)	12 (12)	32 (30)
300	Completed	8 (7)	1 (1)	41 (38)
	Continuing	92 (84)	89 (86)	34 (32)
	Discontinued	10 (9)	14 (14)	33 (31)
330	Completed	8 (7)	3 (3)	44 (41)
	Continuing	90 (82)	85 (82)	31 (29)
	Discontinued	12 (11)	16 (15)	33 (31)
350	Completed	13 (12)	6 (6)	45 (42)
	Continuing	85 (77)	81 (78)	30 (28)
	Discontinued	12 (11)	17 (16)	33 (31)
360	Completed	40 (36)	25 (24)	52 (48)
	Continuing	57 (52)	60 (58)	22 (20)
	Discontinued	13 (12)	19 (18)	34 (32)
360+	Completed	96 (87)	83 (80)	73 (68)
	Discontinued	14 (13)	21 (20)	35 (32)

350 and 360+ are windows for last study visit. Numbers is parentheses are percentages.

Table 14 shows the incidence and reasons for discontinuation by treatment group.

Table 14 Reasons for Discontinuation from Study

	BTA 75 U (n= 110)	BTA 50 U (n = 104)	Placebo (n= 108)
TOTAL	14 (12.7%)	21 (20.2%)	35 (32.4%)
Adverse Events	0 (0.0%)	1 (1.0%)	0 (0.0%)
Lost to Follow-Up	4 (3.6%)	11 (10.6%)	11 (10.2%)
after 1 to 60 days	0	3	6
after 61 to 120 days	0	1	2
after 121 to 180 days	1	3	1
after 181 to 240 days	1	1	1
after 241 to 300 days	0	2	0
after 301 to 360 days	2	1	1
Personal Reasons	8 (7.3%)	8 (7.7%)	19 (17.6%)
work/schedule conflict	3	4	3
moved	2	3	2
dissatisfied	1	0	11
other	2	1	3
Inability to follow study instructions	1 (0.9%)	0 (0.0%)	1 (0.9%)
Other	1 (0.9%)	1 (1.0%)	4 (3.7%)

Reviewers' comments
There was a relatively high proportion of discontinuations. Only one was due to adverse events. Total discontinuations were highest in placebo arm and lowest in 50 U group. The number of subjects discontinuing for "dissatisfaction" was highest in the placebo group. The listing of reasons for discontinuation was reviewed. It was confirmed that lack of treatment response was higher in the placebo group and that treatment discontinuation for adverse events was rare.

Patient Demographics

The treatment groups were balanced with respect to age. No children were studied. Median age was 31 years. There were very few (<1%) patients >65 years of age. There was nearly equal gender participation in the study (54% men). Most of the patients (81%) were Caucasian (**Table 15**).

Table 15 Patient Demographics

		BTA 75U (n=110)	BTA 50U (n=104)	Placebo (n=108)
Age (years)	Mean	34.0	32.2	31.8
	SD	11.64	10.77	9.71
	Median	33.0	29.5	30.0
	Min	18	18	18
	Max	69	65	61
	>=65	2 (1.8%)	1 (1.0%)	0
Gender	Male	60 (54.5%)	57 (54.8%)	57 (52.8%)
	Female	50 (45.5%)	47 (45.2%)	51 (47.2%)
Race	Caucasian	86 (78.2%)	87 (83.7%)	89 (82.4%)
	Black	10 (9.1%)	4 (3.8%)	7 (6.5%)
	Asian	2 (1.8%)	2 (1.9%)	4 (3.7%)
	Hispanic	10 (9.1%)	9 (8.7%)	7 (6.5%)
	Other	2 (1.8%)	2 (1.9%)	1 (0.9%)

There was no evidence of imbalance in hyperhidrosis characteristics at baseline. By history the median age of onset of hyperhidrosis was 15 years. The majority of patients (70%) were not on medical treatment for hyperhidrosis. Emotional factors, heat, and physical exertion were each identified by 80% of subjects as triggers for hyperhidrosis. Palms, soles, face and genitalia were each cited by roughly 30-40% of patients as other body sites affected by excessive sweat. Approximately half of the patients stated that hyperhidrosis had remained stable since its inception and half stated that the rate of sweating had increased (**Table 16**).

Table 16 Hyperhidrosis Characteristics at Baseline

		BTA 75U (n=110)	BTA 50U (n=104)	Placebo (n=108)
Age (years) at onset	n	94	90	90
	Mean	16.2	16.8	17.1
	Median	15.0	15.5	15.0
On hyperhidrosis medication that will NOT be continued	At least one	29 (26%)	22 (21%)	28 (26%)
	None	81 (73%)	82 (79%)	80 (74%)
Had previously used hyperhidrosis procedure	At least one	5 (5%)	5 (5%)	7 (7%)
	None	105 (96%)	98 (94%)	101 (94%)
Triggers of hyperhidrosis	Emotional	88 (80%)	80 (77%)	91 (84%)
	Cold	43 (39%)	44 (42%)	45 (42%)
	Heat	97 (88%)	79 (76%)	86 (80%)
	Exertion	94 (86%)	86 (83%)	95 (88%)
	Hot beverages	49 (44%)	47 (45%)	45 (42%)
	Alcohol	26 (24%)	26 (25%)	27 (25%)
	Spicy food	36 (33%)	42 (40%)	47 (44%)
	Other	13 (12%)	10 (10%)	9 (8%)
	Missing	5 (5%)	9 (9%)	5 (5%)
Change in rate of sweating From disease onset	Increased	53 (48%)	46 (44%)	59 (55%)
	Decreased	5 (5%)	4 (4%)	4 (4%)
	Same	52 (47%)	54 (52%)	45 (42%)
Parts of body (other than axillae) in which excessive sweating occurs	Palms	46 (42%)	33 (32%)	60 (56%)
	Soles	47 (43%)	40 (39%)	43 (40%)
	Face	44 (40%)	38 (37%)	38 (35%)
	Genitalia	35 (32%)	31 (30%)	35 (32%)
	Other	24 (22%)	29 (28%)	20 (19%)
	None	28 (26%)	38 (37%)	30 (28%)

At baseline, abnormal findings noted most frequently on medical examination were related to the skin (approximately 12% incidence) across all groups. At baseline approximately 20% of patients were using antihidrotics (exclusively the agent drysol); the use of this product was not allowed during the study. Beta blockers were the next most commonly used product category (0.3%). The baseline HDSS scores were similar across groups, approximately half the patients had scores of 3 and half had scores of 4 (**Table 21**). With respect to baseline gravimetric measurements the median axillary sweat production was 102g, 123g, and 114g for placebo, 50 Units and 75 Unit groups respectively (**Table 27**).

Use of Concomitant Medications During Study

Overall, 84% (272/322) of patients used concomitant medications during the study. The most frequently reported medications were analgesics, anti-inflammatories, anti-infectives, and psychotropic agents.

Table 17 Concomitant Medications by Selected Categories

Selected Grouping	Drug Class	BTA 75U (n=110)	BTA 50U (n=104)	Placebo (n=108)
Overall		96 (87.3%)	90 (86.5%)	86 (79.6%)
Analgesics	Overall	31 (28.2%)	31 (29.8%)	25 (23.1%)
	Anilides	23 (20.9%)	19 (18.3%)	21 (19.4%)
	Salicylic acid and derivatives	4 (3.6%)	5 (4.8%)	3 (2.8%)
	Opium alkaloids and derivatives	3 (2.7%)	2 (1.9%)	0 (0.0%)
	Natural opium alkaloids	1 (0.9%)	6 (5.8%)	2 (1.9%)
Anti-inflammatories	Overall	27 (24.5%)	34 (32.7%)	25 (23.1%)
	Propionic acid derivatives	14 (12.7%)	18 (17.3%)	11 (10.2%)
	Corticosteroids, potent (group iii)	3 (2.7%)	5 (4.8%)	3 (2.8%)
	Antiinflammatory and antirheumatic prod.	3 (2.7%)	5 (4.8%)	2 (1.9%)
	Antiinflammatory/antirheumatic prod.,non-steroids	3 (2.7%)	2 (1.9%)	2 (1.9%)
	Corticosteroids	3 (2.7%)	2 (1.9%)	2 (1.9%)
	Glucocorticoids	2 (1.8%)	6 (5.8%)	7 (6.5%)
Anti-infectives	Overall	33 (30.0%)	39 (37.5%)	21 (19.4%)
	Penicillins with extended spectrum	7 (6.4%)	7 (6.7%)	7 (6.5%)
	Macrolides	6 (5.5%)	11 (10.6%)	5 (4.6%)
	Fluoroquinolones	6 (5.5%)	3 (2.9%)	0 (0.0%)
	Cephalosporins and related substances	5 (4.5%)	7 (6.7%)	3 (2.8%)
	Tetracyclines	4 (3.6%)	4 (3.8%)	5 (4.6%)
	Combinationsof penicillins	4 (3.6%)	2 (1.9%)	0 (0.0%)
	Other antibiotics for topical use	2 (1.8%)	3 (2.9%)	1 (0.9%)
Sedatives/psychotropics/ anti-depressants	Overall	21 (19.1%)	30 (28.8%)	19 (17.6%)
	Selective serotonin reuptake inhibitors	13 (11.8%)	17 (16.3%)	12 (11.1%)
	Benzodiazepine derivatives	6 (5.5%)	4 (3.8%)	1 (0.9%)
	Other antidepressants	4 (3.6%)	8 (7.7%)	3 (2.8%)
	Non selective monoamine reuptake inhibitors	3 (2.7%)	5 (4.8%)	2 (1.9%)
Topical agents to axillae	Overall	2 (1.8%)	2 (1.9%)	0 (0.0%)
Other agents	Overall	84 (76.4%)	70 (67.3%)	66 (61.1%)
	Progestogens and estrogens, fixed combinations	19 (17.3%)	15 (14.4%)	13 (12.0%)
	Other antihistamines for systemic use	13 (11.8%)	6 (5.8%)	11 (10.2%)

Note: Concomitant medications include all medications continued from the time of study screening and any changes during the study.

Reviewers' comment

The predominant concomitant medications (analgesics, anti-inflammatories, and anti-infectives correlate with the predominant adverse reactions reported during the study (i.e., injection site pain, flu syndrome, headache, pharyngitis). The proportion of patients receiving sedative/anti-

depressant medications is notable and is consistent with the 27% incidence of psychiatric conditions (the most frequently reported medical condition) in the study population.

Primary Efficacy Outcome

The study met its primary endpoint. The percentage of responders based on the HDSS was significantly higher in the treatment groups than in placebo ($p<0.001$). The proportion of responders in the 75 U group was similar to the proportion of responders in the 50 U group.

Table 18 Percentage of Responders Based on HDSS (Hyperhidrosis Disease Severity Score)

	BTA 75 U	BTA 50 U	Placebo	75 U vs Placebo[a]	50 U vs Placebo[a]	75 U vs 50 U[a]
	n = 110	n = 104	n = 108			
Responder	54 (49%)	57 (55%)	6 (6%)	< 0.001	< 0.001	0.378
Failure	56 (51%)	47 (45%)	102 (94%)			

[a] P-value based on Cochran-Mantel-Haenszel test stratified by study baseline HDSS score.

A treatment response was observed in patients with baseline HDSS = 3 (50% and 40% for 50U and 75 U respectively) and in patients with baseline HDSS = 4 (60% and 58% for 50U and 75U respectively). The intent-to-treat (ITT) population included all patients randomized: 110 patients in the BTA 75 U group, 104 patients in the BTA 50 U group, and 108 patients in the placebo group.

As noted above, the statistical analysis plan was amended to allow inclusion as responders of those patients who responded to the first treatment by HDSS score and by gravimetric measurement, but at a later office visit reported an HDSS score of 3 or 4 and were precluded from receiving a second treatment because they did not produce at least 50 mg of sweat on the gravimetric measurement, provided they completed the 52-week study observation period. There were 16 such subjects in the study, 8 in each of the groups receiving BTA. The reason for the discrepancy between worsening HDSS score that is not confirmed by increased axillary sweat production is not understood, but may relate to sub-optimal reliability of a purely subjective scoring system.

The table below shows a sensitivity analysis with treatment responder rates based on HDSS regardless of gravimetric assessment. For the purpose of this analysis the 16 patients who qualified for retreatment but were not reinjected were considered treatment failures. The percentage of responders based solely on the HDSS was still significantly higher in the treatment groups than in placebo ($p<0.001$). The proportion of responders in the 75 U group was still similar to the proportion of responders in the 50 U group. If the 16 subjects are excluded from the analysis the proportion of responders in the 50 U and 75 U groups are 45% (46/102) and 51% (49/96), respectively.

Table 19 Percentage of Responders Based on HDSS Regardless of Gravimetric Assessment

	BTA 75U (n=110)	BTA 50U (n=104)	Placebo (n=108)	Difference (95% CI) 75U - Placebo[a]	Difference (95% CI) 50U - Placebo[a]	Difference (95% CI) 75U – 50U[b]
Responders[c]	46 (41.8%)	49 (47.1%)	6 (5.6%)	36.3 % (26.1, 46.4)	41.6% (31, 52.1)	-5.3% (-18.6, 8)

[a] P<0.001; b P= 0.4

[c] A responder is based on the HDSS results of treatment sessions 1 and 2, or treatment session 1 if no additional treatments given. Patients who qualified for second injection based on HDSS (score of 3 or 4), but were precluded from injection due to gravimetric assessment < 50 mg are categorized as non-responders.

Both the treatment-by- baseline HDSS score and the treatment-by-investigator site interactions were not statistically significant for any of the pairwise comparisons (p>0.2) as seen in the table below. For the number of study sites and patients per study sites see **Table 46**.

Table 20 Treatment Responder HDSS Interaction Analysis

Interaction	BTA 75U *vs* Placebo	BTA 50U *vs* Placebo	BTA 75U *vs* 50U
Treatment by Baseline HDSS Score	0.324	0.195	0.552
Treatment by Investigator Site	0.201	0.770	0.619

P-values for interaction are based on the Breslow-Day test.

Onset of Treatment Response

The tables below (**Tables 21 and 22**) show the distribution of scores for the HDSS scale by treatment group at study baseline and at weeks 1-12 after the first injection of study drug. Consistent with the entry criteria, all patients had a score ≥3 at baseline. The distribution of scores is similar across groups at baseline.

Note that at week 1 post-injection, evidence of treatment effect is seen in the active groups. By the first week post-treatment, there was evidence of treatment effect with approximately 45% of patients in the active groups reaching a score of 1 compared to 9% of patients in the placebo group. Note that in this table the distribution of scores within each group is based on the number of patients at each visit within that group.

Table 21 Hyperhidrosis Disease Severity Scale Frequency Distribution of Raw Scores by Visit Treatment Session 1

Visit		BTA 75U (n=110)	BTA 50U (n=104)	Placebo (n=108)
Baseline	n	110	104	108
	1	0 (0.0%)	0 (0.0%)	0 (0.0%)
	2	0 (0.0%)	0 (0.0%)	0 (0.0%)
	3	55 (50.0%)	54 (51.9%)	58 (53.7%)
	4	55 (50.0%)	50 (48.1%)	50 (46.3%)
Week 1	n	103	100	104
	1	49 (47.6%)	42 (42.0%)	9 (8.7%)
	2	32 (31.1%)	32 (32.0%)	29 (27.9%)
	3	19 (18.4%)	23 (23.0%)	43 (41.3%)
	4	3 (2.9%)	3 (3.0%)	23 (22.1%)
Week 4[a]	n	110	104	108
	1	65 (59.1%)	63 (60.6%)	7 (6.5%)
	2	33 (30.0%)	31 (29.8%)	49 (45.4%)
	3	10 (9.1%)	7 (6.7%)	32 (29.6%)
	4	2 (1.8%)	3 (2.9%)	20 (18.5%)
Week 8	n	100	88	86
	1	53 (53.0%)	52 (59.1%)	6 (7.0%)
	2	32 (32.0%)	27 (30.7%)	29 (33.7%)
	3	15 (15.0%)	8 (9.1%)	33 (38.4%)
	4	0 (0.0%)	1 (1.1%)	18 (20.9%)
Week 12	n	97	94	54
	1	38 (39.2%)	42 (44.7%)	7 (13.0%)
	2	39 (40.2%)	33 (35.1%)	23 (42.6%)
	3	20 (20.6%)	17 (18.1%)	16 (29.6%)
	4	0 (0.0%)	2 (2.1%)	8 (14.8%)

[a] imputation of missing data at week 4

There were 91/214 (42%) of patients in the BTA groups who completed the study and required only one injection and 22/214 (10%) of patients in the BTA groups who discontinued after receiving the first injection. The table below shows the distribution of scores for the HDSS scale by treatment group before the second injection of study drug and at weeks 1-12 in the subgroup of patients who underwent a second injection of study drug. Treatment effect is seen by the first week post-treatment; approximately 60% of patients in the active groups who received a second treatment achieved a HDDS score of 1. Only twelve percent of the subjects in the placebo group who received a second treatment achieved a HDSS score of 1 by week-1 post-treatment.

Table 22 Hyperhidrosis Disease Severity Scale - Frequency Distribution of Raw Scores by Visit Treatment Session 2

Visit		BTA 75U (n=53)	BTA 50U (n=48)	Placebo (n=68)
Pre-injection 2 score	n	53	48	68
	1	0 (0.0%)	0 (0.0%)	0 (0.0%)
	2	0 (0.0%)	0 (0.0%)	0 (0.0%)
	3	49 (92.5%)	38 (79.2%)	45 (66.2%)
	4	4 (7.5%)	10 (20.8%)	23 (33.8%)
Week 1	n	51	44	60
	1	34 (66.7%)	27 (61.4%)	7 (11.7%)
	2	12 (23.5%)	13 (29.5%)	16 (26.7%)
	3	4 (7.8%)	4 (9.1%)	21 (35.0%)
	4	1 (2.0%)	0 (0.0%)	16 (26.7%)
Week 4[a]	n	53	48	68
	1	28 (52.8%)	29 (60.4%)	7 (10.3%)
	2	19 (35.8%)	19 (39.6%)	27 (39.7%)
	3	5 (9.4%)	0 (0.0%)	19 (27.9%)
	4	1 (1.9%)	0 (0.0%)	15 (22.1%)
Week 8	n	46	33	55
	1	26 (56.5%)	21 (63.6%)	7 (12.7%)
	2	16 (34.8%)	12 (36.4%)	17 (30.9%)
	3	3 (6.5%)	0 (0.0%)	20 (36.4%)
	4	1 (2.2%)	0 (0.0%)	11 (20.0%)
Week 12	n	38	31	29
	1	16 (42.1%)	10 (32.3%)	0 (0%)
	2	12 (31.6%)	12 (38.7%)	15 (51.7%)
	3	10 (26.3%)	9 (29.0%)	7 (24.1%)
	4	0 (0.0%)	0 (0.0%)	7 (24.1%)

[a]imputation of missing data at week 4

Analyses of raw HDSS scores also showed evidence of treatment effect after both injections. **Table 23** shows that patients in the active groups achieved lower scores than patients in placebo after the first treatment. For the analysis of HDSS raw scores and percent change from baseline missing values at week 4 of each treatment session were imputed by the median score at that visit for patients with the same study baseline HDSS score, regardless of treatment group. Missing values at other visits were not imputed and the analysis was on the observed data only.

Table 23 Baseline and Change From Baseline in HDSS

Visit		BTA 75U (n=110)	BTA 50U (n=104)	Placebo (n=108)
Baseline	n	110	104	108
	Mean	3.5	3.5	3.5
	Median	3.5	3.0	3.0
Week 1	n	103	100	104
	Mean	-1.7	-1.6	-0.7
	Median	-2.0	-2.0	-0.5
Week 4	n	110	104	108
	Mean	-2.0	-2.0	-0.9
	Median	-2.0	-2.0	-1.0

Duration of Treatment Effect

The table below shows the duration of the treatment effect for patients who responded with at least a 2 grade drop from baseline to week 4 for the first treatment. The duration was defined as the number of days between injection and the date of the last visit before the first recording of a 3 or 4 on the HDSS. The median duration of response after the first treatment was 168, 173, and 63 days for BTA 75U, 50 U and placebo, respectively.

Table 24 Duration of Response: Time (Days) to Event for Treatment Sessions 1 For Patients Responding

Time to Event	BTA 75U (n=110)	BTA 50U (n=104)	Placebo (n=108)
N	80	74	21
Median	168	173	63
95% CI for Median	(141-197)	(142-227)	(54-88)
25th Percentile	100	113	41
75th Percentile	275	348	141
Censored	14 (17.5%)	18 (24.3%)	1(4.8%)

Parameters are estimated using the Kaplan-Meier procedure, and the 95% CI for the median is based on Greenwood's formula for the standard error.

Reviewers' comments

The median duration of treatment response using this conservative definition is approximately 6 months in the active groups compared to two months in the placebo group. It is important to note that the duration of response is similar in the two dose groups. This observation does not support the suggestion in the literature that higher doses of BTA than are needed to achieve treatment response may prolong the duration of the response. The number of patients who responded to the first injection is higher than the number of treatment responders.

In the BTA groups 75% of patients responded to the first injection (82/110 and 78/104 in the 75 Units and 50 Units groups respectively) compared to 25% (27/108) of patients in the placebo group. Of the patients who were eligible and received a second injection 74% (39/53) in the 75

Units group and 85% (41/48) in the 50 U groups responded compared to 25% (17/68) in the placebo group.

Secondary Efficacy Outcomes

Principal Secondary Endpoint: Treatment Responder Based on Gravimetric Assessment
Responder rates are presented by treatment group in the following table. A treatment response based on sweat production was defined as ≥ 50% reduction from baseline in axillary sweating at week 4 following the first treatment only. In this analysis missing percentage change values at a visit would be imputed by the median percentage change among all subjects with the same baseline HDSS score, across all treatment groups at that visit . The percentage of responders was significantly greater in both active groups than in the placebo group ($p < 0.001$), at week 4 following the first treatment and also following the second treatment. The proportion of responders was similar (about 90% after the first treatment) in the two active groups. The proportion of responders in the placebo group was high (50%) and the treatment effect was 34-40% after the first treatment session.

Using a post-hoc more stringent definition of gravimetric response, namely 80% reduction in sweat production, the placebo response was lower (23%).

Table 25 Percentage of Responders Based on Gravimetric Measurement

	>50% Decrease			>80% Decrease		
	BTA 75 U	**BTA 50 U**	**Placebo**	**BTA 75 U**	**BTA 50 U**	**Placebo**
Treatment Session 1	n=110	n=104	n=108			
Responder	104 (94%)	92 (88%)	58 (54%)	81 (74%)	74 (71%)	25 (23%)
Treatment Session 2	n=53	n=48	n=68			
Responder	50 (94%)	48 (100%)	31 (46%)	34 (64%)	35 (73%)	13 (19%)

[a]Measurement of spontaneous resting axillary sweat collected on a filter paper over 5 min at room temperature at before and 4 weeks after treatment.

As a sensitivity analysis, a responder was defined as a patient showing at least 50% reduction from baseline in axillary sweating, but where gravimetric assessment for both arms were missing or negative at baseline or at week 4, the patient was categorized as a non-responder. Also, if at any visit, assessments were missing or negative in only one arm, the contralateral value was used. The table below shows that the percentage of responders was significantly greater in both active groups than in the placebo group ($p < 0.001$), at week 4 following the first treatment. The P-value for between-group comparison is based on Fisher's exact test. The proportion of responders was similar (about 80-85% after the first treatment) in the two active groups. The treatment effect was 40-45% after the first treatment session. The same imputation (non-responder status for missing data) was used to also calculate treatment responder rates at week 4 after the second treatment session. The responder rates were 70% (37/53 ; *95% CI* 58%, 82%) and 67% (32/48; *95% CI* 53, 80) for the 75 U and 50U groups respectively. The responder rate for the placebo group was 28% (19/68; *95% CI* 17%, 39%).

Table 26 Sensitivity Analysis of Treatment Responder Rates Based on 50% Reduction in Gravimetric Measurement from Baseline to Week 4 for Treatment Session 1

	BTA 75U (n=110)	BTA 50U (n=104)	Placebo (n=108)	Difference (95% CI) 75 U – Placebo[a]	Difference (95% CI) 50 U – Placebo[a]	Difference (95% CI) 75 U – 50 U[b]
Responder	94 (85.5%)	84 (80.8%)	44 (40.7%)	44.7% (33.3, 56.1)	40.0% (28.1, 52)	4.7% (-5.4, 14.7)

[a] P< 0.001; [b] P= 0.37

Reviewers' comments
The results of the sensitivity analysis confirm the proportion of responders is greater in the BTA-treated groups compared to placebo.

Table 27 shows the measurement of sweat production at baseline and at 4 weeks post-treatment by treatment group for all study patients. Gravimetric measurements for these subgroups are shown before and after (4 weeks) each treatment session. Very few patients received more than two injections. In the 50 U group, median sweat production was 123 and 76 mg before the first and second treatment session respectively and was 8-10 fold lower at 4 weeks after treatment. In the placebo group median sweat production was 102 and 106mg before the first and second treatment session and was 50% lower at 4 weeks after treatment. The median sweat production after treatment was similar in the two BTA arms. The percentage changes in sweat production in the right and left axilla were similar.

Table 27 Gravimetric Measurements (mg) by Treatment Session

Treatment	Visit[a]		BTA 75U (n=110)	BTA 50U (n=104)	Placebo (n=108)
1	Baseline	n	110	104	108
		Mean	162.6	154.2	156.4
		Median	114.3	123.3	102.3
		Min	49.1	-299.8	51.2
		Max	598.2	766.7	1051.2
	Week 4	Mean	19.2	24.9	83.7
		Median	10.1	11.5	62.7
		Min	-60.4	-4.5	-137.7
		Max	230.1	335.2	754.7
2	Baseline	n	53	48	68
		Mean	122.6	109.8	126.7
		Median	91.8	76.1	105.9
		Min	51.6	51.8	53.1
		Max	396.8	710.0	497.1
	Week 4	Mean	20.5	11.4	80.4
		Median	15.4	10.0	59.1
		Min	-2.8	-2.6	1.2
		Max	125.8	34.8	601.7
3	Baseline	n	7	5	8
		Mean	83.5	64.5	168.7
		Median	79.0	64.8	117.0
		Min	58.5	56.8	56.9
		Max	112.2	71.0	439.
	Week 4	Mean	9.8	15.9	75.8
		Median	4.9	8.8	42.1
		Min	0.5	2.4	6.4
		Max	42.1	42.1	181.1
4	Baseline	n	1	1	1
			71.6	78.5	169.0
	Week 4		45.4	11.8	45.4

[a] Missing data at week 4 imputed

Agreement between Primary Efficacy Variable and Principal Secondary Variable:
There was a very low agreement between treatment responder defined by the HDSS and treatment responder defined by a 50% reduction in sweat production by gravimetric assessment. The kappa statistics were as shown below.

Table 28 Agreement Between Treatment Responder Defined by HDSS and by Gravimetry

	BTA 75U (n=110)	BTA 50U (n=104)	Placebo (n=108)
Kappa	<.001	0.065	0.027
95% CI	(-0.085, 0.082)	(-0.069, 0.200)	(-0.052, 0.106)

The low values for the kappa are in part attributable to differences between the endpoints namely one is a continuous and the other is a categorical variable. In addition, treatment response based on the HDSS was derived from data at week 4 of treatment sessions 1 and 2, whereas treatment response based on the gravimetric assessment was derived from data from week 4 of treatment session 1 only. As shown in **Table 29**, mean changes in sweat production in the three treatment groups combined (n=322) matched changes in the HDSS scores at week 4 of treatment session 1.

Table 29 Changes in Sweat Production by Changes in the HDSS Scores at Week 4 of Treatment Session 1

HDSS Change from Baseline	Reduction in Sweat (%)
-3	91 %
-2	80 %
-1	51 %
No Change	17 %

Iodine Starch Test

The area of blue-black color development in the axilla after the topical application of iodine starch was captured by photography and measured. **Table 30** shows that the affected areas were similar at baseline in the study arms. At 4 weeks after the first treatment the affected areas decreased numerically in the three groups. Using a 0.025 level of significance, there were no significant differences between groups by Wilcoxon rank test. Similarly no differences between groups were identified following the second treatment (data not shown).

Table 30 Iodine Starch Test Photography of Axillae (cm^2)

Visit		BTA 75U (n=110)	BTA 50U (n=104)	Placebo (n=108)
Baseline	n	92	82	91
	Mean	7.9 ±12.2	6.8±12.7	6.1±9.1
	Median	2.8	1.3	2.1
	Min	0.0	0.0	0.0
	Max	56.0	80.4	47.4
Week 4	n	88	80	78
	Mean	2.3±4.6	4.1±8.6	3.1±6.1
	Median	0.0	0.0	0.1
	Min	0.0	0.0	0.0
	Max	20.9	39.1	29.2

Values are cm^2

Reviewers' comments
A substantial number of patients had missing data. No validation of area measurement technique was provided. The variability is high. Given these limitation the results should be interpreted with caution. The decrease in sweat production shown by gravimetric measurement does not appear to correspond to a decrease in affected area as the placebo group shows a decrease in area similar to that of the BTA groups, but gravimetric measurement showed a far smaller change in placebo than BTA groups.

Subject Daily Diary Responses

The patient's daily diary was developed to provide support for the primary endpoint. Patients completed the daily diary for the 7 days preceding each office visit. In general the treatment groups scores were comparable at baseline. At 4 weeks after the first treatment session, mean scores were lower for the active groups compared to placebo in the following areas: time spent treating hyperhidrosis, number of clothing changes, adverse influence on effectiveness at work, and limitation on: being in public places, meeting people, being with family and friends, shaking hands, personal relationships, and sexual activities. At week 4 after the second treatment session, mean scores were numerically lower for active groups compared to placebo for clothing changes, effectiveness at work, and limitations being in public places, meeting people, being with family or friends and personal relationships.

Table 31 Summary of Mean Subject Daily Diary Responses at Week 4

Question number	BTA 75 U	BTA 50 U	Placebo
TREATMENT SESSION 1[d]	(n =110)	(n =104)	(n=108)
Q1 time spent treating disease[a]	0.1	0.1	0.3
Q2 clothing changes[b]	0.3	0.3	0.8
Q3 shower/bath frequency[b]	1.2	1.2	1.3
Q4/5 missed work hours (%)	2.6	2.0	4.2
Q6 effectiveness at work[c]	0.2	0.3	0.8
LIMITATIONS[c]			
Q7a being in public places	0.2	0.2	0.9
Q7b meeting people	0.3	0.2	0.8
Q7c with family or friends	0.1	0.2	0.6
Q7d shaking hands	0.5	0.2	0.6
Q7e personal relationships	0.2	0.2	0.5
Q7f sexual activities	0.1	0.1	0.4
Q7g sports	0.1	0.2	0.3
Q7h other situations	0.4	0.3	0.6
TREATMENT SESSION 2[d]	(n =53)	(n=48)	(n=68)
Q1 time spent treating disease[a]	0.2	0.1	0.3
Q2 clothing changes[b]	0.4	0.3	0.7
Q3 shower/bath frequency[b]	1.1	1.1	1.2
Q4/5 missed work hours (%)	0.1	0.4	1.8
Q6 effectiveness at work[c]	0.2	0.1	0.7
LIMITATIONS[c]			
Q7a being in public places	0.3	0.2	0.8
Q7b meeting people	0.3	0.2	0.8
Q7c with family or friends	0.2	0.1	0.5
Q7d shaking hands	0.6	0.3	0.6
Q7e personal relationships	0.3	0.1	0.6
Q7f sexual activities	0.2	0.1	0.2
Q7g sports	0.3	0.2	0.4
Q7h other situations	0.4	0.0	0.2

[a] responses scored from 0 (< 15 minutes) to 3 (> 60 minutes)
[b] responses scored from 0 (not at all) to 3 (3 times or more)
[c] responses scored from 0 (not at all) to 4 (extremely)
[d] analysis of questions 4 to 7 was based on evaluable patients defined as those who did not check the "Did not have opportunity to do" (not applicable) response.

Reviewer's comments
The scores at baseline indicated that the limitations induced by hyperhidrosis were on average mild. Numerical differences were observed between treatment arms for a number of measures but the magnitude was relatively small. The significance of these findings is not clear. The results of patient daily diary will be reviewed in detail because it was considered the principal patient reported outcome measure. The second patient reported outcome scale (Hyperhydrosis Impact Questionnaire) is very similar to the daily diary and assessments using the latter scale will be reported in less detail.

Tables 32-44 below show mean and median scores at baseline and at 4 weeks after treatment sessions 1 and 2 for all the questions on the Subject Daily Diary. For all the data, the week 4 values include imputation for missing median values.

Table 32 shows the results of question 1. Question 1 asked, "How long yesterday did you spend treating your hyperhydrosis?" The answers were scored as follows: 0='Less than 15 minutes', 1='15-30 minutes', 2='31-60 minutes' and 3='More than 60 minutes'. For each patient, median scores of the observed data were analyzed for each pre-visit diary. Week 4 values include imputation for missing median values. Patients spent less than 15 minutes per day (median score 0) dealing with their hyperhydrosis. Mean scores were similar across groups before each treatment and were numerically lower in the active groups compared to placebo after each of the two treatments. Median scores were not affected.

Table 32 Subject Daily Diary - Question 1

Treatment Session	Visit		BTA 75U (n=110)	BTA 50U (n=104)	Placebo (n=108)
1	Baseline	n	97	90	95
		Mean	0.47	0.47	0.46
		Median	0.00	0.00	0.00
	Week 4	n	110	104	108
		Mean	0.10	0.10	0.31
		Median	0.00	0.00	0.00
2	Baseline	n	49	47	66
		Mean	0.43	0.40	0.47
		Median	0.00	0.00	0.00
	Week 4	n	53	48	68
		Mean	0.17	0.06	0.29
		Median	0.00	0.00	0.00

Table 33 shows the results of question 2. Question 2 asked 'How many times yesterday did you change your shirt or other clothes due to the effects of your hyperhidrosis?" The answers were scored as follows: 0='Not at all', 1='Once', 2='Twice' and 3='3 times or more'. For each patient, median scores of the observed data were analyzed for each pre-visit diary. The median score before the first treatment was 2 for the 75 U group and 1 for the 50 U and placebo groups. After the first treatment the active groups had numerically lower median scores than placebo.

Table 33 Subject Daily Diary - Question 2

Treatment Session	Visit		BTA 75U (n=110)	BTA 50U (n=104)	Placebo (n=108)
1	Baseline	n	97	90	95
		Mean	1.5	1.28	1.39
		Median	2.00	1.00	1.00
	Week 4	n	110	104	108
		Mean	0.34	0.32	0.83
		Median	0.00	0.00	1.00
2	Baseline	n	49	47	66
		Mean	0.92	0.89	1.20
		Median	1.00	1.00	1.00
	Week 4	n	53	48	68
		Mean	0.36	0.25	0.71
		Median	0.00	0.00	0.00

Table 34 shows the results of question 3. Question 3 asked 'How many times yesterday did you shower or take a bath?" The answers were scored as follows: 0='Not at all', 1='Once', 2='Twice' and 3='3 times or more'. The mean and median scores did not appear to be affected by the study treatments.

Table 34 Subject Daily Diary - Question 3

Treatment Session	Visit		BTA 75U (n=110)	BTA 50U (n=104)	Placebo (n=108)
1	Baseline	n	97	90	95
		Mean	1.55	1.40	1.40
		Median	2.00	1.00	1.00
	Week 4	n	110	104	108
		Mean	1.20	1.16	1.27
		Median	1.00	1.00	1.00
2	Baseline	n	49	47	66
		Mean	1.27	1.17	1.33
		Median	1.00	1.00	1.00
	Week 4	n	53	48	68
		Mean	1.11	1.08	1.18
		Median	1.00	1.00	1.00

Table 35 shows the results of questions 4 and 5. Question 4 and 5 asked how many hours patients were expected to work and did not work due to their hyperhidrosis. The proportion of missed work was calculated as total number of hours not worked (question 5)/the total number of hours expected to have worked (question 4). The median proportion of missed work at baseline for the first and second treatments was 0 across groups. Mean values showed no change in response to study treatments.

Table 35 Subject Daily Diary - Questions 4 and 5

Treatment Session	Visit		BTA 75U (n=110)	BTA 50U (n=104)	Placebo (n=108)
1	Baseline	n	80	81	79
		Mean	3.0	4.6	5.7
		Median	0.0	0.0	0.0
	Week 4	n	89	94	92
		Mean	2.6	2.0	4.2
		Median	0.0	0.0	0.0
2	Baseline	n	35	41	54
		Mean	10.0	0.6	1.3
		Median	0.0	0.0	0.0
	Week 4	n	39	38	59
		Mean	0.1	0.4	1.8
		Median	0.0	0.0	0.0

Table 36 shows the results of question 6. Question 6 asked 'How much do you think your hyperhidrosis symptoms influenced your effectiveness at work yesterday?' The answers were scored as follows 0='Not at all', 1='A little', 2='Moderately', 3='Quite a bit' and

4='Extremely'. For each patient, median scores of the observed data were analyzed for each pre-visit diary. The median score for all three groups was 1 at baseline and 0 after treatment. The mean scores were similar at baseline in the three groups and were numerically lower after each treatments session in the active groups compared to placebo.

Table 36 Subject Daily Diary - Question 6

Treatment Session	Visit		BTA 75U (n=110)	BTA 50U (n=104)	Placebo (n=108)
1	Baseline	n	80	78	78
		Mean	1.15	1.10	1.13
		Median	1.00	1.00	1.00
	Week 4	n	90	94	92
		Mean	0.18	0.31	0.77
		Median	0.00	0.00	0.00
2	Baseline	n	36	44	57
		Mean	1.11	1.14	1.12
		Median	1.00	1.00	1.00
	Week 4	n	39	43	58
		Mean	0.21	0.12	0.69
		Median	0.00	0.00	0.00

Table 37 shows the results of question 7a based on a five point scale. Question 7a asked "How limited do you feel you were yesterday being in public places due to your hyperhidrosis?". Median and mean scores were approximately 1 at baseline and were lower in the active groups compared to placebo after the first treatment session. Mean scores were also lower after the second treatment session in the active groups compared to placebo.

Table 37 Subject Daily Diary - Question 7a

Treatment Session	Visit		BTA 75U (n=110)	BTA 50U (n=104)	Placebo (n=108)
1	Baseline	n	97	90	95
		Mean	1.23	1.11	1.28
		Median	1.00	1.00	1.00
	Week 4	n	110	103	107
		Mean	0.17	0.22	0.85
		Median	0.00	0.00	1.00
2	Baseline	n	49	47	66
		Mean	1.02	0.98	1.20
		Median	1.00	1.00	1.00
	Week 4	n	51	48	66
		Mean	0.25	0.17	0.79
		Median	0.00	0.00	0.00

Table 38 shows the results of question 7b based on a five point scale. Question 7b asked "How limited do you feel you were yesterday when meeting or being introduced to people for the first time due to your hyperhidrosis?." Mean scores were numerically lower after treatment in the active groups compared to placebo; median scores were similar across groups after treatment.

Table 38 Subject Daily Diary - Question 7b

Treatment Session	Visit		BTA 75U (n=110)	BTA 50U (n=104)	Placebo (n=108)
1	Baseline	n	83	83	83
		Mean	1.35	1.14	1.23
		Median	1.00	1.00	1.00
	Week 4	n	97	99	101
		Mean	0.28	0.23	0.76
		Median	0.00	0.00	0.00
2	Baseline	n	41	41	57
		Mean	1.07	1.07	1.14
		Median	1.00	1.00	1.00
	Week 4	n	48	46	62
		Mean	0.25	0.17	0.76
		Median	0.00	0.00	0.00

Table 39 shows the results of question 7c based on a five point scale. Question 7c asked "How limited do you feel you were yesterday on family occasions or with friends due to your hyperhidrosis?". Mean scores were numerically lower after treatment in the active groups compared to placebo, median scores did not appear to be affected by treatment.

Table 39 Subject Daily Diary - Question 7 c

Treatment Session	Visit		BTA 75U (n=110)	BTA 50U (n=104)	Placebo (n=108)
1	Baseline	n	94	87	92
		Mean	1.11	0.90	0.90
		Median	1.00	1.00	1.00
	Week 4	n	103	100	103
		Mean	0.12	0.19	0.55
		Median	0.00	0.00	0.00
2	Baseline	n	45	47	65
		Mean	0.80	0.79	0.89
		Median	1.00	1.00	0.00
	Week 4	n	53	48	65
		Mean	0.21	0.10	0.52
		Median	0.00	0.00	0.00

Question 7d (**Table 40**) asks "How limited do you feel you were yesterday when shaking hands due to your hyperhidrosis?". Median scores at baseline suggest that there is little impact of hyperhidrosis on this activity. The scores did not appear to be affected by treatment.

Table 40 Subject Daily Diary - Question 7d

Treatment Session	Visit		BTA 75U (n=110)	BTA 50U (n=104)	Placebo (n=108)
1	Baseline	N	82	86	87
		Mean	1.12	0.85	0.79
		Median	1.00	0.00	0.00
	Week 4	N	100	100	101
		Mean	0.47	0.22	0.59
		Median	0.00	0.00	0.00
2	Baseline	N	44	40	59
		Mean	0.98	0.90	0.71
		Median	0.00	0.00	0.00
	Week 4	N	49	47	61
		Mean	0.61	0.30	0.56
		Median	0.00	0.00	0.00

Question 7e (**Table 41**) states 'How limited do you feel you were yesterday in developing personal relationships due to your hyperhidrosis?'. Mean scores were lower in the active groups compared to placebo after each treatment session. Median scores were not affected by treatment.

Table 41 Subject Daily Diary - Question 7e

Treatment Session	Visit		BTA 75U (n=110)	BTA 50U (n=104)	Placebo (n=108)
1	Baseline	n	74	68	68
		Mean	0.99	0.84	0.96
		Median	1.00	1.00	1.00
	Week 4	n	92	94	90
		Mean	0.24	0.15	0.52
		Median	0.00	0.00	0.00
2	Baseline	n	41	38	53
		Mean	0.66	0.68	0.83
		Median	0.00	0.00	1.00
	Week 4	n	45	39	56
		Mean	0.29	0.08	0.57
		Median	0.00	0.00	0.00

Question 7f (**Table 42**) states 'How limited do you feel you were yesterday in sexual activities due to your hyperhidrosis?'. Median scores indicate little impact of hyperhydrosis on this activity. Mean scores are lower after the first treatment session in the active groups compared to placebo.

Table 42 Subject Daily Diary - Question 7 f

Treatment Session	Visit		BTA 75U (n=110)	BTA 50U (n=104)	Placebo (n=108)
1	Baseline	n	54	56	67
		Mean	0.63	0.59	0.57
		Median	0.00	0.00	0.00
	Week 4	n	77	78	79
		Mean	0.13	0.13	0.43
		Median	0.00	0.00	0.00
2	Baseline	n	31	33	42
		Mean	0.48	0.24	0.50
		Median	0.00	0.00	0.00
	Week 4	n	37	39	46
		Mean	0.19	0.05	0.24
		Median	0.00	0.00	0.00

Question 7g (**Table 43**) states "How limited do you feel you were yesterday in sports activities due to your hyperhidrosis?". Hyperhydrosis appears to have little impact on this activity and there is no evidence of an effect from the treatment.

Table 43 Subject Daily Diary – Question 7g

Treatment Session	Visit		BTA 75U (n=110)	BTA 50U (n=104)	Placebo (n=108)
1	Baseline	n	68	60	68
		Mean	0.88	0.83	0.75
		Median	0.00	0.00	0.00
	Week 4	n	76	80	79
		Mean	0.14	0.23	0.34
		Median	0.00	0.00	0.00
2	Baseline	n	34	29	47
		Mean	0.71	0.34	0.53
		Median	0.00	0.00	0.00
	Week 4	n	46	36	54
		Mean	0.28	0.22	0.39
		Median	0.00	0.00	0.00

Table 44 shows the response to question 7h 'How limited do you feel you were yesterday in other situations due to your hyperhidrosis?'. The baseline scores to this more global limitation question are higher than for any of the other mores specific limitation questions. There was no evidence of treatment effect for this question.

Table 44 Subject Daily Diary - Question 7h

Treatment Session	Visit		BTA 75U (n=110)	BTA 50U (n=104)	Placebo (n=108)
1	Baseline	n	27	24	22
		Mean	2.67	2.04	2.32
		Median	3.00	2.00	2.00
	Week 4	n	44	40	35
		Mean	0.43	0.25	0.63
		Median	0.00	0.00	0.00
2	Baseline	n	8	9	5
		Mean	1.75	1.67	1.00
		Median	2.00	2.00	1.00
	Week 4	n	21	15	17
		Mean	0.43	0.00	0.24
		Median	0.00	0.00	0.00

Reviewers' comments
The scores indicated that at baseline the limitations imposed by hyperhidrosis were on average mild and none in some cases. Numerical differences were observed between treatment arms for a number of questions but the magnitude was small and the differences between groups were not consistent. Some of the differences were significant by Wilcoxon rank sums but the multiplicity of the comparisons was not addressed. Finally the validity of the questions has not been demonstrated.

Hyperhidrosis Impact Questionnaire

As previously discussed this questionnaire contains items that are identical or similar to the patient diary and does not appear to provide additional information. The four subscales group items are related to emotional, occupational, physical, and social effects of hyperhidrosis.

The distribution of scores (generally based on a five point scale) for each items in the subscales was examined at baseline and at weekly intervals after each treatment session. The distribution of the scores post-treatment appeared to shift towards milder scores for a number of items in the subscales. The shifts appeared to be more pronounced for the active groups compared to placebo.

The scores were also dichotomized into a mild or better group and moderate or worse group. The percentages of patients in each of the two subgroups were again compared at baseline and post-treatment. The percentages of patients in the mild or better subgroups were numerically higher post-treatment compare to pretreatment and the percentages in the mild or better subgroup tended to be higher in the active groups than in the placebo group.

Reviewers' comments
It is not evident that this scale provides any information different from the information provided by the Patient Daily Diary. The scale has not been validated and the clinical significance of the findings is not clear.

Dermatology Life Quality Index (DLQI)

This is a 10-item scale with items scored with a 4-point scale ranging from "not at all" to "very much". Median baseline scores were < 10 and are consistent with a severity of "a little" for this condition.

Small reductions in overall scores following the first and second treatment were observed in the three study arms. The decreases were numerically higher in the active arms than in placebo (**Table 45**). Decreases in score indicate improvement. Decreases in scores favoring the active groups were also observed in various domains of the scale.

Table 45 Reduction in Mean DLQI Scores from Baseline after Treatments 1 and 2

		BTA 75U (n=110)	BTA 50U (n=104)	Placebo (n=108)
Treatment 1 Baseline	n	102	94	98
	Mean	9.3	7.8	7.8
	SD	5.45	5.30	5.73
	Median	9.0	8.0	6.0
Change at Week 4	n	93	88	86
	Mean	-7.2	-5.6	-1.6
	SD	5.59	4.79	4.53
	Median	-7.0	-5.0	-1.0
Treatment 2 Baseline	N	53	48	68
	Mean	6.7	6.3	7.5
	SD	4.73	5.90	6.33
	Median	6.0	4.5	7.0
Change at Week 4	N	43	38	56
	Mean	-4.3	-5.5	-1.1
	SD	4.65	5.83	3.33
	Median	-4.0	-4.0	-1.0

Reviewer's comments

The DLQI has not been validated for hyperhidrosis. Baseline measurements indicated mild impairment. Decreases in scores post-treatment favored the active groups but were small in magnitude and are of uncertain clinical significance.

Subgroup Analyses

Study Center Effects:

Table 46 shows the treatment response assessed by change in HDSS score in the 50 U and placebo groups by study center. A treatment effect is evident for all study centers except for one (2137, n=7). Also, a generally consistent by-center treatment effect (in 15 of the 18 centers) was observed for the 75 U dose group.

Table 46 Proportion of Responders (Treatment Response HDSS scale) by Study Center

Center	BTA 50U (n=104)	Placebo (n=108)	Difference 50U BTA - Placebo (95% CI)
Overall	57/104 (54.8%)	6/108 (5.6%)	49.3 (38.8, 59.7)
0228	3/7 (42.9%)	0/8 (0.0%)	42.9 (6.2, 79.5)
1901	5/5 (100.0%)	1/5 (20.0%)	80.0 (44.9, 100.0)
2137	0/4 (0.0%)	0/3 (0.0%)	0.0
2925	2/4 (50.0%)	1/5 (20.0%)	30.0 (-30.3, 90.3)
2936	3/4 (75.0%)	1/6 (16.7%)	58.3 (6.5, 100.0)
2941	2/3 (66.7%)	1/5 (20.0%)	46.7 (-17.2, 100.0)
3157	4/9 (44.4%)	0/9 (0.0%)	44.4 (12.0, 76.9)
3158	2/4 (50.0%)	0/6 (0.0%)	50.0 (1.0, 99.0)
3160	2/7 (28.6%)	0/7 (0.0%)	28.6 (-4.9, 62.0)
3164	0/1 (0.0%)	0 (NA)	NA
3166	8/12 (66.7%)	0/11 (0.0%)	66.7 (40.0, 93.3)
3167	7/9 (77.8%)	0/9 (0.0%)	77.8 (50.6, 100.0)
3187	4/8 (50.0%)	0/8 (0.0%)	50.0 (15.4, 84.6)
3270	1/3 (33.3%)	0/3 (0.0%)	33.3 (-20.0, 86.7)
3278	3/6 (50.0%)	0/5 (0.0%)	50.0 (10.0, 90.0)
3644	2/3 (66.7%)	0/3 (0.0%)	66.7 (13.3, 100.0)
3646	5/8 (62.5%)	2/7 (28.6%)	33.9 (-13.5, 81.3)
3681	4/7 (57.1%)	0/8 (0.0%)	57.1 (20.5, 93.8)

A responder is based on the results of treatment sessions 1 and 2, or treatment session 1 if no additional treatment given.

Response by Baseline Disease Severity:

Table 47 shows the treatment response assessed by change in HDSS score in the 50 U and placebo groups by HDSS stratum. The response to treatment was similar irrespective of baseline severity of hyperhidrosis.

Table 47 Treatment Response by HDSS Stratum at Baseline

	BTA 50U	Placebo	Treatment effect
Overall	57/104 (54.8%)	6/108 (5.6%)	49.3 (38.8, 59.7)
3	27/54 (50.0%)	1/58 (1.7%)	48.3 (34.5, 62.0)
4	30/50 (60.0%)	5/50 (10.0%)	50.0 (34.1, 65.9)

Response by Age Group:

Overall, 78% (241/322) of subjects were <40 years old, 24% (78/322) were 40 to 64 years old, and 0.9% (3/322) were ≥65 years old. There were too few subjects > 65 years (n=3) to evaluate efficacy in this age group. As shown in **Table 48** below, analysis of efficacy by age group

showed response rates to be similar for the under 40 and over 40 age group in the active groups. In the placebo group, responder rates were higher in the over 40 than in the under 40-year-old subjects.

Table 48 Responder Rates Based on HDSS by Age Group

Age Group	BTA 75U (n=110)	BTA 50U (n=104)	Placebo (n=108)
< 40 years	53% (42/79)	55% (43/78)	4% (3/84)
40 to 64 years	41% (12/29)	56% (14/25)	13% (3/24)
≥ 65 years	0% (0/2)	0% (0/1)	-- (-/0)

Response by Gender:
Overall, 54% (174/322) of subjects were male and 46% (148/322) were female. As shown in **Table 49** below, analysis of efficacy by gender showed statistically significant differences in the responder rates between both active groups and placebo for both males and females, although the response rates were higher for females receiving BTA than for males.

Table 49 Responder Rates Based on HDSS by Gender

Gender	BTA 75U (n=110)	BTA 50U (n=104)	Placebo (n=108)	BTA 75U vs Placebo[a]	BTA 50U vs Placebo[a]	BTA 75U vs 50U[a]
Male	43% (26/60)	47% (27/57)	7% (4/57)	< 0.001	< 0.001	0.650
Female	56% (28/50)	64% (30/47)	4% (2/51)	< 0.001	< 0.001	0.412

[a] P-value based on Cochran-Mantel-Haenszel test stratified by study baseline HDSS score.

Response by Race:
Overall, 84% (262/322) of subjects were Caucasian and 19% (60/322) of subjects were non-Caucasian. Responder rates based on HDSS by race are shown in **Table 50**. Statistically significant differences in favor of both active groups over placebo were shown for both Caucasians and non-Caucasians.

Table 50 Responder Rates Based on HDSS by Race Group

Race Group	BTA 75U (n=110)	BTA 50U (n=104)	Placebo (n=108)	BTA 75U vs Placebo[a]	BTA 50U vs Placebo[a]	BTA 75U vs 50U[a]
Caucasian	51% (44/86)	56% (49/87)	7% (6/89)	< 0.001	< 0.001	0.469
Non-Caucasian	42% (10/24)	47% (8/17)	0% (0/19)	0.002	< 0.001	0.738

[a] P-value based on Cochran-Mantel-Haenszel test stratified by study baseline HDSS score.

Summary of Efficacy: Study -016

- For the purpose of the primary efficacy analysis responders were subjects in the ITT population who, after each of the first two treatments, had a ≥ 2-grade improvement on HDSS at 4 weeks post-treatment or who responded to the first treatment and completed the 52-week study in remission. Patients who enrolled in the study with an HDSS score of 4,

showed a 2-grade improvement following the first treatment, and were retreated with an HDSS score of 3, needed only a 1-grade improvement at 4 weeks following the second treatment session to be classified as responders.

- The study met its primary endpoint. The proportion of responders to 50U BTA was approximately 50% (ranging from 47% to 55% based on sensitivity analyses). The proportion of responders in the placebo group was 6%.

- The proportions of responders to the 75U and 50U BTA based on HDSS were similar.

- The principal secondary efficacy variable was the measurement of spontaneous resting axillary sweat production using a filter paper weighed before and after placement in the axilla. This measurement was carried out for each axilla at room temperature over 5 minutes. The proportion of responders (defined as subjects who achieved at least a 50% reduction in spontaneous resting axillary sweat production at week 4 postinjection) and the percentage change in spontaneous resting axillary sweat production at week 4 postinjection for the first two treatment sessions were compared between groups. The proportion of responders after the first treatment session was greater in patients receiving 50 U BTA (81%) than in patients receiving placebo (41%). The percentage change from baseline in sweat production also favored the 75 U and 50 U BTA groups over placebo.

- The onset of treatment response was evident by 1 week after treatment. The median duration of response was approximately 6 months. The onset and duration of response were similar in the 50 U and 75 U dose groups.

- Based on placebo-controlled comparisons of patients who were retreated following loss of response, there was no evidence of loss of treatment response upon retreatment.

- The principal patient-reported outcome was assessed based on responses to a daily diary. Patients made entries for 7 days before office visits and for 7 days following a visit at which they were first considered a non-responder. Questions 1-3 assessed the effect of hyperhidrosis on daily activities.(e.g. frequency of showering and clothes changing) on a daily basis. Questions 4-6 related to work productivity (number of days affected and percent of normal work effectiveness). Question 7 contained 8 parts and dealt with limitations on various activities (e.g. social activities and relationships). This tool is not validated and interpretation of the results is difficult. The scores at baseline indicated that the limitations induced by hyperhidrosis were on average mild. Numerical differences were observed between treatment arms for a number of measures but the magnitude was relatively small and multiplicity of comparisons was a factor. The clinical significance of these findings is not clear.

- Hyperhydrosis Impact Questionnaire
  This scale provides information that appears to differ very little from the information provided by the Patient Daily Diary. The scale has not been validated. The scale showed

numerical changes in various domains favoring the active groups over placebo. However, the clinical significance of the findings is not clear.

- Dermatology Life Quality Index
  The Dermatology Life Quality Index is a general scale for assessment of the effect of dermatologic disorders on patient's activities, emotions and relationships. The scale requires responses (scored on a 4 point scale) to 10 questions in 6 domains: Symptoms and Feelings, Daily Activities, Leisure, Work and School, Personal Relationships, and Treatment. This scale has not been validated for hyperhidrosis, the scores at baseline suggested little impairment from hyperhidrosis. Small changes favoring the active groups over placebo were seen.

- Too few non-Caucasians and elderly were in the study to permit an independent assessment of efficacy in various race and elderly sub-groups.

2. Study -505 (Non-IND Study)

Study Title
A Multicenter, Double-Blind, Randomized, Vehicle-Controlled, Parallel Group Study of the Safety and Efficacy of Botulinum Toxin A Purified Neurotoxin Complex for the Treatment of Bilateral Primary Axillary Hyperhidrosis

Study Objectives
To evaluate the safety and efficacy of BTA compared with vehicle for the treatment of bilateral primary axillary hyperhidrosis

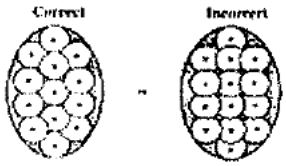
a. Study -505 Protocol

Study Design
This was a multicenter, double-blind, randomized, vehicle-controlled, parallel group study. Subjects were randomly assigned to a single treatment with BTA or vehicle in a ratio of 3:1. At the baseline visit subjects were randomized to receive one treatment administered as multiple (10-15), bilateral intradermal injections evenly distributed in the axilla, for a total dose per axilla of 0 (vehicle) or BTA 50U (total dose BTA 0 or 100 U). Planned enrollment was 300 subjects to give 267 subjects completed (200 in the BTA treatment group and 67 in the vehicle treatment group). A randomization code was generated centrally and allocation was done at each site using consecutively numbered envelopes containing the treatment assignment.

Study Treatment
Single treatment was given on day 0 and follow up consisted of seven scheduled visits over a 17-week period. Each vial of BTA contained 100 units (U) of *Clostridium* BTA, 0.5 mg of albumin (human), and 0.9 mg of sodium chloride in a sterile, vacuum-dried form without preservative. One U corresponds to the calculated median lethal intraperitoneal dose (LD50) in mice. BTA

(formulation 9060X; lots CGD033 and C046) was reconstituted with 4.0 mL of preservative free normal saline (0.9% sodium chloride). Vehicle (formulation 8279X; lot C011) was reconstituted and injected in an identical way to that described for the test product.

Prior to all clinic visits the use of antiperspirants/deodorants was to have been withheld for at least 24 hours prior to the clinic visit being conducted. Also, subjects were instructed to shave each axilla two to three days prior to the treatment visit in preparation for the planned injection. Prior to injection, the hyperhidrotic area was defined using the Minor's iodine starch test. A photograph of each axilla was taken. Immediately prior to injection, the axilla and surrounding areas were treated with anti-microbial solution. Using a sterile 30-guage needle, 2.0 ml of study medication was injected intradermally (10-15 injections), evenly distributed into each axilla within the hyperhidrotic area previously identified by Minor's iodine starch test (see figure below for correct injection distribution). Each axilla was injected with 2.0 mL containing either 0 or 50U of BTA, for a total dose of 0 or 100U.



Number of Injection Sites Per Axilla	Approximate Volume (ml) Per Injection Site
10	0.2
11	0.18
12	0.17
13	0.15
14	0.14
15	0.13

Reviewer's comment
The placebo injection for this study was the vehicle in contrast to the placebo injection in the US study, which consisted of sterile saline.

Key Inclusion Criteria
The following were the principal inclusion criteria.

- Male or female
- 18 to 75 years of age
- persistent bilateral primary axillary hyperhidrosis as judged by the investigator
- sweat production that interfered with activities of daily living by subject history
- baseline gravimetric measurement of at least 50 mg spontaneous sweat production in each axilla measured over 5 minutes at room temperature at rest
- written informed consent had been obtained

- willing and able to complete the entire course of study and to comply with study instructions
- females of child bearing potential must have had a negative pregnancy test on day 0.

Key Exclusion Criteria

The following were the principal exclusion criteria.

- Any medical condition that might have put the subject at increased risk to BTA including diagnosed myasthenia gravis, Eaton-Lambert syndrome, amyotrophic lateral sclerosis, or any other disorder that might have interfered with neuromuscular function
- secondary hyperhidrosis (for example secondary to underlying hyperthyroidism, lymphoma, malaria)
- known allergy or sensitivity to the study medication, its components or iodine
- concurrent use of aminoglycoside antibiotics, curare-like agents, or other agents that might interfere with neuromuscular function
- concurrent use or use within 30 days of enrollment of any herbal medicinal treatments, cholinomimetics, anticholinergic drugs and any other treatments for hyperhidrosis including antiperspirants and deodorants containing aluminum salts
- infection or skin problems at injection sites
- concurrent participation in an investigational drug study or participation within 30 days of such study entry
- previous botulinum toxin treatment within 4 months of study entry
- females of child bearing potential not using reliable methods of contraception.

Concurrent Treatments

Antiperspirants and deodorants (excluding those which contain aluminum salts) were allowed, but were to be withheld for at least 24 hours before study visits.

Primary Efficacy Outcome

The primary efficacy variable was the percentage of responders in each treatment group determined at week 4 post-treatment. Treatment responders were defined as subjects showing at least a 50% reduction from baseline in axillary sweating, measured by gravimetric assessment of spontaneous axillary sweat production for 5 minutes at room temperature and at rest. Secondary evaluations of the primary efficacy outcome included the percentage change from baseline in gravimetric assessment and the duration of response (i.e., elapsed time from injection to end of response).

Reviewer's comment: This endpoint is not an easily clinically interpretable measure of response.

Subjects were instructed to shave both axillae two days before a study visit and to withhold the use of antiperspirants/deodorants for at least 24 hours. Subjects were not to shower within 30 minutes of a study visit. Measurements were performed at least 30 minutes after arrival at the study site. Standard 90mm filter paper was weighed on a standard electronic balance. The filter paper was placed onto the outer surface of a plastic bag (10cm x 10 cm), the axilla dried, and the

filter paper/plastic bag was placed in the axilla secured with strips of tape with good skin contact but avoiding a complete seal. The subject's arm was then lowered so as to be adducted to the body. Sweat was collected over a 5 minute period, the filter paper was removed with forceps, and weighed. The procedure was repeated for the other axilla.

Both axillae were to have produced >50 mg sweat in order for the subject to be included in the study. For eligible subjects the average weight of sweat from both right and left axillae was calculated as the gravimetric assessment for that subject for data analysis.

Secondary Efficacy Outcomes

The following were the study's secondary endpoints:

-Size of sweat-producing area indicated by the Minor's iodine-starch test photography at week 4
-Dynamic Subject's Global Assessment of treatment satisfaction at week 4
-Treatment expectation, satisfaction and limitations as measured by the Impact of Disease Questionnaire at week 4

Minor's iodine-starch test:

Mean changes from baseline area were calculated using Minor's iodine-starch test. The test was performed after the gravimetric assessment to identify the hyperhidrotic area for both axillae. Minor's iodine solution was applied to the skin and after drying, starch powder was applied. Sweat causes a color reaction (blue) to develop after 5 minutes. The borders of the hyperhidrotic area were marked to identify the area for treatment and the axillae were photographed for image analysis of the hyperhidrotic area.

Dynamic Subject's Global Assessment:

The following 9-point scale was used to measure patient's perception of their treatment response. Mean scores were calculated and compared between the treatment groups by the rank-sum test.

+4 Complete abolishment of signs and symptoms (100% improvement)
+3 Marked improvement (some signs and symptoms remain, 75% improvement)
+2 Moderate improvement (fair amount of signs and symptoms remain, 50% improvement)
+1 Slight improvement (substantial signs and symptoms remain, 25% improvement)
0 Unchanged
-1 Slight worsening (about 25% worse)
-2 Moderate worsening (about 50% worse)
-3 Marked worsening (about 75% worse)
-4 Very marked worsening (about 100% worse or greater)

Hyperhidrosis Impact of Disease Questionnaire:

A hyperhidrosis impact questionnaire developed by the sponsor was used to obtain patients' assessment of the following issues. Responses for each of the questions were rated on a five-point scale.

- Effects of previous treatments
- Ability to perform work activities and non-work activities (e.g. social or leisure)

- Limitations at work, public places, when meeting or being introduced to people for the first time, on family occasions or with friends, shaking hands, developing personal relationships, sexual activities, sport, other situations
- Effects on daily life and leisure activities including clothes changes, bathing, employment and work productivity

SF-12 Health Survey:
The SF-12 Health Survey is a general, non-condition specific, health-related, quality of life questionnaire consisting of 12 questions designed to assess patients' views about their general health, physical activity, emotional health, bodily pain and social functioning. Mean scores were calculated and compared between groups by the rank-sum test. The survey is shown below.

SF-12 HEALTH SURVEY

INSTRUCTIONS: This questionnaire asks for your views about your health, how you feel and how well you are able to do your usual activities.

Please answer every question by marking one box. If you are unsure about how to answer, please give the best answer you can.

1. In general, would you say your health is:

☐ Excellent ☐ Very good ☐ Good ☐ Fair ☐ Poor

The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
2. **Moderate activities**, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐	☐	☐
3. Climbing **several** flights of stairs	☐	☐	☐

During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	YES	NO
4. Accomplished less than you would like	☐	☐
5. Were limited in the kind of work or other activities	☐	☐

During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	YES	NO
6. Accomplished less than you would like	☐	☐
7. Didn't do work or other activities as carefully as usual	☐	☐

8. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

☐ Not at all ☐ A little bit ☐ Moderately ☐ Quite a bit ☐ Extremely

These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks...

	All of the Time	Most of the Time	A good bit of the Time	Some of the Time	A Little of the Time	None of the Time
9. Have you felt calm and peaceful?	☐	☐	☐	☐	☐	☐
10. Did you have a lot of energy?	☐	☐	☐	☐	☐	☐
11. Have you felt downhearted and low?	☐	☐	☐	☐	☐	☐

12. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?

☐ All of the time ☐ Most of the time ☐ Some of the time ☐ A little of the time ☐ None of the time

Safety Measures

Safety measures included detection of anti-BTA antibodies in serum samples, the incidence and severity of spontaneously reported adverse events, physical examination, vital signs, and urine pregnancy test results.

Serum Antibody Test:

Blood specimens collected at baseline (prior to treatment) and at week 16 were used to detect the presence of serum antibodies to BTA. Sera were prepared and stored at <-20 degrees C at the site until they were shipped to a central laboratory for serum antibody testing.

Serum samples were evaluated for antibodies to BTA using a mouse protection assay. Mouse mortality rates determined whether the result was positive, negative or inconclusive for the presence of BTA antibodies. If an insufficient volume of serum had been provided to enable the analysis to be performed, the sample was classified as 'Quantity not sufficient'.

Other Clinical Assessments

The visit schedule and the clinical assessments are shown in the **Table 51** below. There were seven scheduled visits over a 17-week period: day –10 to –4 (screening), day 0 (baseline/treatment), and at weeks 1, 4, 8, 12, and 16 (follow-up visits).

Table 51 Schedule of Visits and Measurements

Visit	Screening	Baseline/ treatment	Follow-up Visits				
	Day -10 to -4	Day 0	W 1	W 4	W 8	W 12	W 16
Consent and Medical History	X						
Physical Examination	X						X
Vital Signs	X	X	X	X	X	X	X
Pregnancy Test (urinary)		X					X
Gravimetric Assessment	X	X	X	X	X	X	X
Minor's Iodine-starch test/Photography	X	X	X	X	X	X	X
SF-12 Health Survey™		X					X
Impact of Disease Questionnaire©		X	X	X	X	X	X
Subject's Global Assessment of Treatment Satisfaction			X	X	X	X	X
Inclusion/Exclusion Criteria		X					
Study Injection of BOTOX® or vehicle		X					
Adverse Events and Concurrent Medication		X	X	X	X	X	X
Blood Collection for Serum Antibody Test		X					X

i. Study -505 Statistical Analyses

Sample Size

A minimum of 267 subjects (i.e. 200 BTA and 67 vehicle) were required to detect a 25% point difference in response rate, assuming a 35% vehicle response rate and 60% BTA response rate, a two-tailed type I error of 0.05 and a study power of 93%. A sample size of 300 (225 BTA treated subjects and 75 vehicle treated subjects) was planned for recruitment to account for a drop out rate not expected to exceed 10%.

Efficacy and safety data were analyzed on an intent-to-treat basis with last observation carried forward (LOCF). ITT was considered the primary analysis. A per-protocol analysis of the primary efficacy variable was performed as a secondary analysis. The primary endpoint was assessed at week 4.

Reviewers' comments

This method of imputation of missing data for the efficacy analyses may not be sufficiently conservative. The sponsor agreed to provide in the original BLA supplement submission, as a secondary analysis, an analysis in which patients with missing efficacy data at endpoint were considered treatment failures.

Primary Efficacy Endpoint Analyses

The primary efficacy variable was the percentage of treatment responders in each treatment group. A treatment responder was defined as a subject showing at least 50% reduction from baseline in axillary sweating. Bilateral responses were averaged for each subject at each time point before analysis.

The between-group comparison of responder rates was performed using Fisher's exact test. A p-value of ≤ 0.05 was considered statistically significant.

Reviewers' comment

The original study protocol did not describe the statistical test to be used for the primary efficacy analyses. There were no protocol amendments. It is not documented whether the decision to use Fischer's exact method was made before unblinding the study.

Secondary analyses included the percentage change in gravimetric measurement from baseline and absolute values at each visit were analyzed as secondary variables. These were compared between treatment groups using a one-way analysis of variance. Within-group changes from baseline at each follow-up visit were analyzed using the paired t-test.

Duration of response was defined as elapsed time from injection to end of response. End of response required two consecutive non-responder timepoints. The number of subjects classed as persistent responders (i.e., without 2 consecutive non-responder time points) at week 16 was compared between treatment groups using a Fisher's exact test. Where data showed deviation form normality, a Wilcoxon rank sum test was performed.

Reviewers' comment
A definition of loss of response based on two consecutive visits may over-estimate the durability of the response.

A per protocol analysis of the primary efficacy endpoint included any treated subject with ≥ 1 follow-up visit evaluable with regard to the protocol requirements. Subject visits were excluded if one or more of the criteria below were fulfilled: sweat production at baseline <50mg in one or both axillae; prohibited medication or treatment taken within 30 days of baseline or after baseline; deodorants/antiperspirants used within 24 hours of study visit; visits occurred outside the specified window.

Secondary Efficacy Endpoint Analyses
The principal secondary efficacy variable was the sweat-producing area indicated by the Minor's iodine-starch test. Mean values and changes from baseline were compared between treatment groups using a one-way analysis of variance. Within-group changes from baseline at each follow-up visit were analyzed using the paired t-test. Where data showed deviation from normality, a Wilcoxon rank sum test was performed. Data from the Impact of Disease Questionnaire, from the SF-12 Health Survey (SF-12), and from the Subject's Global Assessment were described by a frequency distribution and between–group differences were tested using the Wilcoxon rank sum test. Antibody data were to be summarized by treatment group in shift tables. Analyses were also performed on the primary efficacy variable for the following subgroups: age, gender, body mass index, investigator and degree of sweat production at baseline.

Safety
Adverse events were summarized with sample size, mean and/or frequency counts and percentages. Continuous variables were summarized using descriptive statistics.

b. Study -505 Results

Study Centers and Study Period
There were 17 participating study centers (7 in Germany, 6 in UK, 2 in Belgium, 2 in Switzerland). The first subject was enrolled on 4/27/99; the last subject completed on 3/6/00.

Study Conduct
A randomization code was generated centrally and allocation was done at each site using consecutively numbered envelopes containing the treatment assignment. Seven subjects were assigned numbers out of sequence (**Table 52**).

Table 52 Mis-Assigned Subjects

Investigator Number	Subject Number	Actual Treatment Assignment	Reason for Mis-Assignment
228	0510	BTA	Site allocated this number to the first randomized subject. All subsequent subjects were randomized in the correct order (i.e. 0501-0509 and 0511-0522)
2763	0101	BTA	Site did not use this number. All subsequent subjects were randomized in the correct order (i.e. 0102-0142)
3148	0803 and 0805	BTA BTA	Site randomized these two numbers to the first two randomized subjects. All subsequent subjects were randomized in the correct order (i.e. 0801-0802, then0804, then 0806-0809)
3222	1304	BTA	Site randomized the first two subjects in the correct order (1301 and 1302). Site then allocated 1304. All further subjects were then randomized in the correct order (i.e. 1303, then 1305-1339)
3146	0426	BTA	Site did not use this number. Subjects 0401-0425 were randomized correctly and then 0427 was randomized correctly.
3233	1504	BTA	Subjects 1501-1503 were randomized correctly. Subject 1504 was then randomized after subjects 1505 and 1506. Subjects 1507-1509 were then randomized correctly.

Reviewers' comment
It is notable that all mis-assignments were BTA assignments. There is no clear overall evidence of bias for or against the allocation of these numbers.

Protocol Violations

Overall, 8% (26/320) of subjects in the ITT population had protocol violations that led to exclusion of the subject form the per protocol population at all time-points. The reasons for exclusion were: use of deodorants/antiperspirants within 24 hours of baseline (3 subjects), baseline gravimetric assessment <50 mg (5 subjects), use of prohibited treatments/therapies for hyperhidrosis within 30 days of baseline (18 subjects) and unauthorized unblinding of one subject. Subject 1601 was un-blinded by the investigator in order to tell the subject the treatment assignment after completion of all the study assessments but before resolution of all queries. In addition, some subjects had violations at a particular visit that led to exclusion of that visit only from the PP analysis. The reasons for exclusion of a visit were: visit falling outside the PP visit window (88 visits excluded), use of deodorants/antiperspirants within 24 hours of a visit other than at screening/baseline (20 visits excluded), use of prohibited treatments for hyperhidrosis other than within 30 days of screening/baseline (9 visits excluded) and gravimetric assessment not performed on both axillae other than at screening/baseline (2 visits excluded). Also, a large proportion of subjects did not complete the Subject's Global Assessment (see **Table 66**).

Reviewer's comments
The amount of missing data for the Subject's Global Assessment, makes this treatment outcome uninterpretable. The other protocol violations in overall number and type were judged to be consistent with an adequately run clinical trial. Relative to the treatment effect size, the number of protocol violations is small and would not be expected to have a major impact on the assessment of efficacy .

Patient Demographics and Disposition

A total of 450 subjects were screened for the study. The main reason for subjects failing at the screening visit was gravimetric assessment <50 mg (100 subjects). A total of 320 subjects were randomized: 242 in the BTA group and 78 in the vehicle group (**Table 53**). There were 172 women and 148 men ranging in age from 17 to 74 years. The mean age was approximately 31 years and about 80% of the patients were <40 years in age. Nearly all patients were Caucasians.

Table 53 Patient Demographics

		BTA (n=242)	Placebo (n=78)
Age (Years)	Mean	31.5	31.2
	Median	28.0	29.0
	< 40	187 (77)	67 (86)
	40-65	49 (20)	11 (14)
	>65	6 (3)	0 (0)
Gender	Men	113 (47)	35 (45)
	Women	129 (53)	43 (55)
Physical Type	Caucasian	237 (98)	77 (99)
	Black	1 (0.4)	0 (0)
	Asian	1 (0.4)	0 (0)
	Other	3 (1)	1 (1)
Height (cm)	Mean	173.12	172.22
	Median	172.0	172.5
Weight (Kg)	Mean	72.82	71.16

Table 54 shows that a high proportion of patients completed the study treatment and follow up periods. A total of 307 subjects completed the study. Treatment Compliance was high because there were very few dropouts and the treatment is not self-administered.

Table 54 Patient Disposition

	BTA (n=242)	Vehicle (n=78)
Completed	234 (96.7%)	73 (93.6%)
Overall Discontinued	8 (3.3%)	5 (6.4%)
Reasons Discontinued:		
Adverse event	1 (0.4%)	0 (0.0%)
Lost to follow-up	4 (1.7%)	1 (1.3%)
Other	3 (1.2%)	4 (5.1%)

Subjects received multiple (10-15), bilateral intradermal injections of BTA or vehicle, evenly distributed in each axilla within the hyperhidrotic area previously identified by the Minor's iodine-starch test. The number of injections in each axilla did not have to be the same, but had to be in the range of 10-15 injections per axilla. Each axillary treatment consisted of a total of 2 mL of study medication containing 0 or 50 U BTA for a total dose of 0 or 100 U BTA. **Table 55** shows that all subjects had treatments applied to both axillae and the average number of injections per axilla was 14.

Table 55 Total Number of Sites Injected (ITT Analysis)

		BTA (n=242)	Vehicle (n=78)	Overall (n=320)
Left Side	N	242	78	320
	Mean	13.53	13.13	13.43
	SD	2.21	2.00	2.16
	Min	7.0	10.0	7.0
	Max	22.0	15.0	22.0
	Median	14.0	14.0	14.0
Right Side	N	242	78	320
	Mean	13.65	13.51	13.62
	SD	2.16	1.94	2.11
	Min	9.0	7.0	7.0
	Max	22.0	16.0	22.0
	Median	15.0	14.0	15.0

Hyperhidrosis Characteristics at Baseline

Table 56 shows that the groups were balanced at screening with respect to previous and current hyperhidrosis medications and procedures for hyperhidrosis.

Table 56 Medication and Treatment History: Number (and Percent) of Subjects Giving Yes Responses

	BTA (n=242)	Vehicle (n=78)
Previous and Current Hyperhidrosis Medication	238 (98)	77 (99)
Previous and Current Hyperhidrosis Procedure	86 (36)	27 (35)
Current non-hyperhidrosis Medication	117 (48)	35 (45)

Table 57 shows that the use of medications and treatments for hyperhidrosis in particular was similar in the two study groups. Approximately 50% of the subjects in the two study groups had previously used anti-hidrotic treatments (prescription drugs classified as antihidrotics consist of topical aluminum chloride in suspension); other commonly used hyperhidrosis treatments used by about 90% of patients were over-the counter deodorants and antiperspirants (classified as non-therapeutic auxiliary products). Use of other therapeutic products (19-24%) was similar in the two groups. The proportion of patients who underwent procedures for hyperhidrosis (e.g., use of iontophoresis) or surgical interventions such as denervation (open thoracic or endoscopic sympathectomy), and sweat gland excision, was also similar in the two study groups.

Table 57 Medication and Treatment History - Number of Subjects with Previously Used Hyperhidrosis Medication and Treatments, by Category of Medication

	BTA (n=242)	Vehicle (n=78)
PREVIOUS AND CURRENT MEDICATION:		
Overall	238 (98%)	77 (99%)
Antihidrotics (prescription)	118 (49%)	38 (49%)
Other (non-prescription) auxiliary products	211 (87%)	75 (96%)
Other (prescription) products	58 (24%)	15 (19%)
Antiandrogens, plain preparations	1 (0.4%)	0 (0%)
Anticholinergic agents	4 (2%)	0 (0%)
Barbiturates, combinations	1 (0.4%)	0 (0%)
Benzothiazepine derivatives	1 (0.4%)	0 (0%)
Beta blocking agents, non-selective	5 (2%)	1 (1%)
Beta blocking agents, selective	0 (0%)	2 (3%)
Boric acid products	1 (0.4%)	0 (0%)
Corticosteroids, moderately potent (group 2)	1 (0.4%)	0 (0%)
Diphenylbutylpiperidine derivatives	0 (0%)	1 (1%)
Other antifungals for topical use	1 (0.4%)	0 (0%)
Other antipruritics	8 (3%)	1 (1%)
Other laxatives	1 (0.4%)	0 (0%)
Other muscle relaxants, peripherally acting	1 (0.4%)	2 (3%)
Progestogens and estrogens, fixed combinations	1 (0.4%)	0 (0%)
Selective serotonin reuptake inhibitors	1 (0.4%)	0 (0%)
Soft paraffin and fat products	2 (1%)	3 (4%)
Tertiary amines	21 (9%)	10 (13%)
Uncodable term	3 (1%)	0 (0%)
Xanthine derivatives	1 (0.4%)	0 (0%)
PREVIOUS PROCEDURES	86 (36%)	27 (35%)

Table 58 shows that emotional factors, physical exertion, and heat were the most commonly cited stimuli inducing hyperhidrosis; each was identified by about 70% of patients. Beverages, spicy foods and cold were each identified as stimuli inducing hyperhidrosis by about a third of the patients. The two study groups were similar with respect to reported hyperhidrosis stimuli.

Table 58 Stimuli for Hyperhidrosis

	BTA (n=242)	Vehicle (n=78)
Emotions (pleasure, fear, anxiety, stress)	188 (77.7%)	65 (83.3%)
Cold	78 (32.2%)	33 (42.3%)
Heat	168 (69.4%)	58 (74.4%)
Physical exertion	174 (71.9%)	61 (78.2%)
Tea, coffee, beverages	92 (38.0%)	30 (38.5%)
Alcoholic beverages	36 (14.9%)	12 (15.4%)
Spicy food	86 (35.5%)	31 (39.7%)
Other	25 (10.3%)	7 (9.0%)

Axillary sweat production at baseline

All subjects were diagnosed as having primary hyperhidrosis. A total of 315 of the 320 randomized subjects met the entry criterion of $\geq$ 50 mg of axillary sweat production at baseline.

Median sweat production was similar in the two study groups, 159 g for BTA and 164 g for vehicle. Mean sweat production at baseline was similar in the two treatments groups (215.8 mg $\pm$ 178.7 mg in the BTA treatment group and 235.7 $\pm$ 213.8 mg in the vehicle treatment group).

Reviewers' comment
The median sweat production was far from the mean sweat production, indicating substantial individual variability in the parameter.

The Minor's iodine-starch test and photographic image analysis defined and quantified the area of sweat production. The median size of the sweat producing area was similar in the two treatment groups (2.5 cm^2 in the BTA treatment group and 3.6 cm^2 in the vehicle treatment group). The mean size of the sweat producing area (mean values) were similar in the two treatment groups (5.3 $\pm$ 7.0 cm^2 in the BTA treatment group and 6.0 $\pm$ 7.0 cm^2 in the vehicle treatment group).

Concomitant Medications

The use of concomitant medications was examined to look for evidence of hiperhidrotics use (not allowed by protocol) and for evidence of imbalance in the two study groups in the use of specific drug classes. Use of concomitant medications was important as it might have confounded the interpretation of the efficacy outcomes. The concomitant medications listings were reclassified into the following subgroups: analgesics, anti-inflammatory, anti-infectives, sedatives, psychotropics, anti-depressants, and application site topical agents.

Table 59 Selected Concomitant Medications by Categories

Selected Grouping	Drug Class	BTA (n=151)	Placebo (n=43)
Overall		151 (100.0%)	43 (100.0%)
Analgesics	Overall	25 (16.6%)	7 (16.3%)
	Anilides	16 (10.6%)	5 (11.6%)
	Salicylic acid and derivatives	5 (3.3%)	1 (2.3%)
	Propionic acid derivatives	2 (1.3%)	1 (2.3%)
	Opium alkaloids and derivatives	1 (0.7%)	1 (2.3%)
	Pyrazolones	1 (0.7%)	1 (2.3%)
Anti-inflammatories	Overall	20 (13.2%)	7 (16.3%)
	Acetic acid derivatives and related substances	7 (4.6%)	0 (0.0%)
	Glucocorticoids	3 (2.0%)	1 (2.3%)
	Other cold combination preparations	3 (2.0%)	0 (0.0%)
	Corticosteroids	2 (1.3%)	0 (0.0%)
	Propionic acid derivatives	1 (0.7%)	3 (7.0%)
	Corticosteroids, plain	1 (0.7%)	1 (2.3%)
	Corticosteroids, moderat. Potent, comb w/antisept.	0 (0.0%)	1 (2.3%)
	Corticosteroids, moderately potent (group ii)	0 (0.0%)	1 (2.3%)
Anti-infectives	Overall	26 (17.2%)	9 (20.9%)
	Tetracyclines	5 (3.3%)	0 (0.0%)
	Penicillins with extended spectrum	3 (2.0%)	2 (4.7%)
	Cephalosporins and related substances	3 (2.0%)	1 (2.3%)
	Beta-lactam antibacterials, penicillins	3 (2.0%)	0 (0.0%)
	Beta-lactamase sensitive penicillins	2 (1.3%)	2 (4.7%)
	Macrolides	2 (1.3%)	1 (2.3%)
	Comb of penicillins, incl. Beta-lactamase inhib.	2 (1.3%)	0 (0.0%)
	Imidazole derivatives	1 (0.7%)	2 (4.7%)
	Antibiotics	1 (0.7%)	1 (2.3%)
	Beta-lactamase resistant penicillins	1 (0.7%)	1 (2.3%)
	Fluoroquinolones	1 (0.7%)	1 (2.3%)
	Other antibiotics for topical use	0	2 (4.7%)
	Other antifungals for topical use	0	1 (2.3%)
Sedatives/Psychotropics/ Anti-Depressants	Overall	4 (2.6%)	0 (0.0%)
	Benzodiazepine derivatives	1 (0.7%)	0 (0.0%)
	Butyrophenone derivatives	1 (0.7%)	0 (0.0%)
	Non selective monoamine reuptake inhibitors	1 (0.7%)	0 (0.0%)
	Other hypnotics and sedatives	1 (0.7%)	0 (0.0%)
	Selective serotonin reuptake inhibitors	1 (0.7%)	0 (0.0%)
	Thioxanthene derivatives	1 (0.7%)	0 (0.0%)

Table 59 Selected Concomitant Medications by Categories (Continued)

Selected Grouping	Drug Class	BTA (n=151)	Placebo (n=43)
Topical agents to axillae		1 (0.7%)	0 (0.0%)
	Zinc products	1 (0.7%)	0 (0.0%)
Other	Overall	132 (87.4%)	40 (93.0%)
	Progestogens and estrogens, fixed combinations	51 (33.8%)	18 (41.9%)
	Antiandrogens and estrogens	11 (7.3%)	4 (9.3%)
	Beta blocking agents, selective	9 (6.0%)	2 (4.7%)
	Iodine therapy	9 (6.0%)	0 (0.0%)
	Pregnen (4) derivatives	7 (4.6%)	1 (2.3%)
	Thyroid hormones	7 (4.6%)	0 (0.0%)
	Other antihistamines for systemic use	5 (3.3%)	3 (7.0%)
	Natural and semisynthetic estrogens, plain	5 (3.3%)	1 (2.3%)
	Mucolytics	4 (2.6%)	2 (4.7%)
	Selective beta-2-adrenoceptor agonists	4 (2.6%)	1 (2.3%)

Reviewers' comment
The rationale for the use of the concomitant medications is not provided. However, there is no evidence of greater use of specific drugs in the active treatment group compared to the vehicle group. Therefore, medication use did not have an impact on efficacy outcomes.

Table 60 shows that the two study groups complied with the requirement that anti-hidrotics be avoided. The use of over the counter antiperspirants and deodorants (allowed by protocol) was not different in the two groups.

Table 60 Summary of Deodorants/Antiperspirants Used During the Study

Drug Class	BTA (n=242)	Vehicle (n=78)
Overall	191 (79%)	66 (85%)
Antihidrotics	1 (0.4%)	1 (1%)
Other non-therapeutic auxiliary products	188 (78%)	66 (85%)
Soft paraffin and fat products	2 (1%)	0 (0.0%)
Uncodable term	1 (0.4%)	0 (0.0%)

Primary Efficacy Outcome

The study met its primary endpoint, namely an increase in the proportion of patients with a $\geq$50% reduction in axillary sweat production at 4 weeks after treatment. Using the ITT population and LOCF, the percentage of responders was 94% in BTA and 37% in vehicle (**Table 61**). By Fisher's exact test the difference in the proportions in the two groups (58%) was significant ($p<0.001$). The LOCF method was used for the gravimetric assessment if there was no visit within the window or the gravimetric assessment was not performed in either axilla. Eight subjects were imputed in the BTA treatment group and none were imputed in the vehicle treatment group. It is noteworthy that evidence of treatment effect is seen at the earliest study visit (week 1).

Table 61 Responder Rates: Percentage of Subjects with a 50% Reduction in Axillary Sweating from Baseline (ITT population using LOCF)

		BTA (n=242)	Vehicle (n=78)	Difference: BTA-Vehicle (95% CI)
Week 1	Responders	230 (95%)	25 (32%)	63% (52.3, 73.7)
Week 4	Responders	227 (94%)	28 (36%)	58% (46.8, 69.0)

Sensitivity analyses included an analysis using observed data only with 241 and 77 patients analyzed at week 1 and 233 and 75 patients analyzed at week 4 for BTA and vehicle, respectively. **Table 62** shows a treatment effect (57%) similar to that of the primary analysis.

Table 62 Responder Rates: Percentage of Subjects with a 50% Reduction in Axillary Sweating from Baseline (Observed Data)

		BTA (n=242)	Vehicle (n=78)	Difference: BTA-Vehicle (95% CI)
Week 1	N	241	77	
	Responders	230 (95%)	25 (33%)	63% (52, 74)
Week 4	N	233	75	
	Responders	219 (94%)	28 (37%)	57% (45, 68)

A per protocol analysis of the primary efficacy endpoint included any treated subject with: ≥ 1 follow-up visit and none of the following protocol deviations: sweat production at baseline <50mg in one or both axillae; prohibited medication or treatment taken within 30 days of baseline or after baseline, deodorants/antiperspirants used within 24 hours of study visit; visits occurred outside the specified window. Responder rates based on per protocol analyses yielded a treatment response (54%) similar to the response with the primary analysis.

In addition, an ITT analysis using treatment failure as the imputation for missing data was also carried out. **Table 63** shows a treatment effect of 55%. The table below also shows evidence of treatment effect for up to the last study visit (week 16).

Table 63 Treatment Responders Based on Gravimetric Measurement (Intent-to-Treat Population, Treatment Failure Imputation for Missing Data)

Visit		BTA 50U (n=242)	Placebo (n=78)	Difference (BTA-Placebo)	95% CI on the Difference	BTA 50U vs. Placebo
Week 4	Responder	219 (91%)	28 (36%)	55%	43%, 66%	<0.001
	Non-Responder	23 (10%)	50 (64%)			
Week 8	Responder	209 (86%)	28 (36%)	50%	39%, 62%	
	Non-Responder	33 (14%)	50 (64%)			
Week 12	Responder	191 (79%)	23 (30%)	49%	38%, 61%	
	Non-Responder	51 (21%)	55 (71%)			
Week 16	Responder	182 (75%)	14 (18%)	57%	47%, 67%	
	Non-Responder	60 (25%)	64 (82%)			

Confidence intervals are based on the normal approximation of the binomial distribution.
P-value for between-group comparison is based on Fisher's exact test.

Reviewers' comment
The data above show that the response to treatment is durable in the majority of patients through week 16.

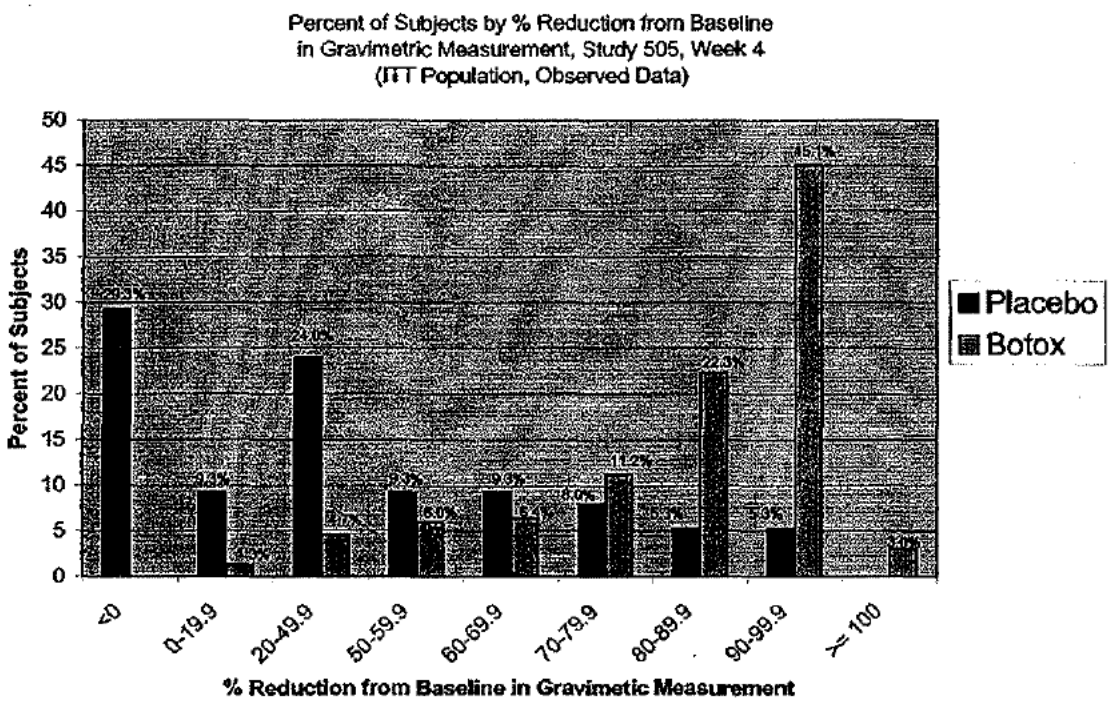
A secondary analysis of the primary efficacy endpoint (gravimetric assessment) was the mean change from baseline in axillary sweating as measured by gravimetric assessment (**Table 64**). This analysis supported the primary endpoint and gave estimates of treatment effect (about 60%) similar to that of the primary analysis.

Table 64 Gravimetric Assessment: Mean Percent Changes from Baseline in Axillary Sweating (Observed Data)

		BTA (n=242)	Vehicle (n=78)	P-value
Week 0	n	242	78	0.739
	Mean	215.8 mg	235.7 mg	
	SD	178.7	213.8	
	Median	158.6 mg	163.7 mg	
Week 4	n	233	75	<0.001
	Mean	-82.9%	-21.3%	
	SD	18.4	55.4	
	Median	-89.5%	-37.6%	

Figure 2 shows the distribution of reduction in sweat production in the BTA and placebo groups. Given the large difference in the number of subjects in the two study groups, the distribution of reduction in sweat production is presented as percentages of patients within study group. It is noteworthy that there is no evidence of worsening of sweating in the BTA group.

Figure 2. Distribution of % Reduction from Baseline in Gravimetric Measurement



Secondary Efficacy Outcomes

Change from baseline in area affected by hyperhidrosis

Table 65 shows the principal secondary endpoint (change from baseline in area affected by hyperhidrosis). There is substantial variability in the measurements and skewed distribution. The median area is numerically higher in the placebo group. There is much missing data at baseline and various other visits for both groups. Taking into consideration these limitations, there appears to be some evidence of treatment effect based on median change in affected area at 4 weeks post-treatment. It is not clear if the assay is sensitive enough to differentiate between abrogation of sweat production in specific areas of axilla and overall reduction in sweat production.

Table 65 Baseline Axillary Area (cm^2) Affected with Hyperhidrosis as Measured by Minor's Iodine Starch Test Photography (Observed Data) and Changes from Baseline

		BTA (n=242)	Vehicle (n=78)	P-value
Week 0	n	216	66	0.495
	Mean	5.34	6.01	
	SD	7.01	7.04	
	Median	2.5	3.6	
Week 1	n	205	64	0.015
	Mean	-5.23	-1.81	
	SD	6.94	7.53	
	Median	-2.2	-1.3	
Week 4	n	198	58	0.001
	Mean	-5.05	-2.12	
	SD	6.99	8.73	
	Median	-2.2	-0.3	

Subject's Global Assessment of Treatment

Table 66 shows subject's assessment of the study treatment. Subjects rated their satisfaction with the treatment on a dynamic scale from –4 to +4 (100% worse to 100% improvement). At endpoint (week 4), the subject's median score was 3 for the BTA treatment group compared to 0 for the placebo. No analyses of validity of the scale are provided.

Reviewers' comment

The subject's global assessment is not interpretable due to the large amount of missing data. A static scale assessing level of satisfaction at baseline and at each visit would have been preferable.

Table 66 Subject's Global Assessment of Treatment

Visit		BTA (n=242)	Vehicle (n=78)
Week 1	N	67	24
	Mean ± SD	3.1 ± 1.1	0.8 ± 1.4
	Median	3.0	0.5
Week 4	N	85	29
	Mean ± SD	3.3 ± 0.9	0.8 ± 1.4
	Median	3.0	0.0
Week 8	N	129	41
	Mean ± SD	3.0 ± 1.4	0.3 ± 1.1
	Median	3.0	0.0
Week 12	N	158	48
	Mean ± SD	2.9 ± 1.2	0.3 ± 1.0
	Median	3.0	0.0
Week 16	N	204	61
	Mean ± SD	2.6 ± 1.6	0.3 ± 1.2
	Median	3.0	0.0

SF-12 Health Survey

According to the sponsor, the SF-12 Health Survey showed a statistically significant improvement in quality of life in the BTA treated group at the last study visit compared to baseline. The validity of this scale in hyperhidrosis has not been assessed.

Reviewers' comments

The sensitivity of the scale in this condition appears to be limited at best. It may be concluded that the SF-12 survey showed no meaningful changes in response to study treatment given the small magnitude of change relative to the dynamic range of the scale. The fact that there was a large amount of missing data also adds to the difficulties in interpretation of the results. The relationship of change in score to change in hyperhidrosis parameters is not known.

Table 67 SF-12 Health Survey – Baseline and Change From Baseline

Visit		BTA (n=242)	Vehicle (n=78)
Physical Component Summary Score			
Baseline	N	229	77
	Mean ± SD	52.2 ± 7.3	52.8 ± 7.2
	Median	54.8	55.6
Exit	N	199	69
	Mean ± SD	0.9 ± 7.6	-1.2 ± 6.7
	Median	0.6	-0.1
Mental Component Summary Score			
Baseline	N	229	77
	Mean ± SD	49.1 ± 9.5	46.4 ± 10.4
	Median	52.5	49.3
Exit	N	199	69
	Mean ± SD	1.7 ± 9.1	0.5 ± 8.8
	Median	1.4	0.0
		0.013	0.890

Subgroup Analyses

Analyses of efficacy by gender showed response rates to be similar in men and in women (**Table 68**).

Table 68 Gravimetric Assessment: Responder Rate by Gender

	Male				Female			
	BTA (n=113)		Vehicle (n=35)		BTA (n=129)		Vehicle (n=43)	
Responders	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Week 1	107	95%	10	29%	123	95%	15	35%
Week 4	99	88%	14	40%	120	93%	14	33%

The numbers of non-Caucasians studied (5 in BTA and 1 in vehicle) were too low to be informative about treatment response by race.

The sponsor assessed treatment response in two subgroups using 35 years of age as cut-point. No reason was given for the choice of age for the cut-point. Treatment responses were similar in these two subgroups (**Table 69**).

Table 69 Gravimetric Assessment: Responder Rate by Age

	Age <35 years				Age >35 years			
	BTA (n=170)		Vehicle (n=54)		BTA (n=72)		Vehicle (n=24)	
Responders	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Week 1	166	98%	18	33%	64	89%	7	30%
Week 4	151	93%	20	38%	68	97%	8	36%

In addition, an ITT analysis using treatment failure as the imputation for missing data was also carried out and 40 years of age was used as the cut-point. Treatment responses were similar in these two groups as well (**Table 70**).

Table 70 Gravimetric Assessment: Responder Rate by Age (ITT)

	Age <40 years				Age >40 years			
	BTA (n=187)		Vehicle (n=67)		BTA (n=49		Vehicle (n=11)	
Responders	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Week 1	183	98%	22	33%	42	86%	3	27%
Week 4	167	89%	24	36%	46	94%	4	36%

Examination of other age subgroups showed treatment responses similar to those of the overall population.

The effect of sweat production at baseline on treatment response was evaluated (**Table 71**). The treatment effect appeared to be similar in the two subgroups defined as above or below the median value (160 mg) for sweat production in each axilla at baseline.

Table 71 Gravimetric Assessment: Responder Rate by Degree of Baseline Sweat Production

	≤160 mg sweat production at baseline				>160 mg sweat production at baseline			
	BTA (n=122)		Vehicle (n=38)		BTA (n=120)		Vehicle (n=40)	
Responders	n	%	n	%	n	%	n	%
Week 1	112	92%	12	32%	118	99%	13	32%
Week 4	109	94%	11	31%	110	94%	17	42%

Analysis by Study Center

For all investigators a similar rate of responders at all the assessment visits was seen in the BTA treatment group. When there is an approximately 90% response with BTA overall, this is not surprising. For most investigators too few subjects were enrolled in the vehicle treatment group to assess differences by center.

Summary of Efficacy: Study -505

- The study met its primary efficacy endpoint.
- Secondary efficacy analyses and secondary efficacy endpoints also show evidence of treatment effect.

- Patient-reported outcomes used scales that are not validated in hyperhidrosis, appeared to be insensitive to change, had missing data that made results uninterpretable.

D. Efficacy Conclusions

Two adequate and well controlled studies showed reproducible evidence of efficacy for primary axillary hyperhidrosis. The non-IND study showed objective evidence of the ability of the product to decrease axillary sweat production. The IND study confirmed that finding and in addition showed that using a global 4-point assessment scale, the severity of hyperhidrosis decreased in response to treatment from "intolerable" or "barely tolerable" to "tolerable" or "never noticeable".

VII. Integrated Review of Safety

A. Brief Statement of Conclusions

- No serious adverse events related to treatment have been observed to date in the patients with hyperhidrosis. The database is small and the potential for rare serious adverse events cannot be judged.

- The most common adverse event was injection site reaction (pain/hemorrhage); it was numerically higher in the BTA groups. Infection and flu syndrome, pharyngitis, fever, pain, headache were all numerically higher in the BTA groups compared to the placebo group. Non-axillary sweating was also higher in the BTA groups.

- There is little information on the safety of repeated treatment cycles with respect to local tolerance and development of anhydrosis. It is not known if intradermal injection will prove to be more sensitizing than intramuscular injection. The sponsor has ongoing open-label studies of repeated treatment cycles and completion and reporting of these studies will be stipulated by PMC.

- Rare but serious immediate hypersensitivity reactions including urticaria, soft tissue edema, and one case of anaphylaxisis resulting in death were observed postmarketing in non-hyperhydrosis indications. The warnings section of the package insert will be updated with this information.

- There is no convincing evidence that clinically important systemic spread of toxin may occur.

- One patient among the 445 hyperhidrosis patients with analyzed specimens showed the presence of neutralizing antibodies.

B. Description of Patient Exposure

In Study -016, a total of 322 adults were randomized 1:1:1 to 50 Units of BTA, 75 U of BTA or placebo and were eligible to receive one or more treatments over the course of one year of study. In Study -505, 320 adults were randomized 3:1 to receive a single treatment of 50Units of BTA or placebo. 346 patients were exposed to 50 Units and 110 patients were exposed to 75 Units of BTA. The participating study centers were located in the US, Canada, and Europe.

Given the off-label use of the product for hyperhidrosis of other anatomic sites, the sponsor conducted a chart review study (Study -059) to ascertain serious adverse events that might be associated with such uses **(see Appendix for review)** and provided literature reports.

C. Methods and Specific Findings of Safety Review

The reviewers examined clinical study reports, case report forms, data listings, patient narratives, MedWatch forms, safety updates including reports of postmarketing experience across all indications, and reprints of articles from the scientific literature.

1. Study -016

Study -016 was a multicenter, double-blind, randomized, placebo-controlled, parallel group study of the safety and efficacy of repeated treatment with either one of 2 dosages of BTA (50U or 75U) compared with placebo (saline) for the treatment of primary axillary hyperhidrosis. Patients were randomized to treatment with either placebo, 50U, or 75U of BTA (ratio of 1:1:1) at the first treatment session. Assignment to treatment group was stratified within investigational site and by disease severity at day 0 as assessed by the Hyperhydrosis Disease Severity Scale (HDSS). Patients were followed for up to 52 weeks after the first treatment. Patients who responded to the first treatment and relapsed were eligible to receive a second treatment. A total of 322 adults were randomized 1:1:1 to 50 Units of BTA, 75 U of BTA or placebo and were eligible to receive one or more treatments over the course of one year of study.

Serious and severe adverse events

All randomized patients received study medication and are included in the safety population. There were no deaths. There were three serious adverse events: patient 3164-3091 (50 U BTA) sustained a fall during a hike with multiple severe/life-threatening injuries (onset 120 days post BTA), patient 3681-3244 (placebo) had degenerative disk disease and had surgical spinal fusion; patient 3166-3159 (placebo) had difficulty swallowing and hoarseness from laryngeal edema due to accidental neck trauma. Patients 3278-3061 (BTA 75 U) and 3646-3038 (placebo) became pregnant during the study. Each woman delivered a healthy baby.

The following were the severe adverse events reported; the events were judged to be unrelated to study treatment.

Table 72 Severe Adverse Events Reported for Study -016

BTA 75 U	flu syndrome (session 2), accidental injury (session 3), bone pain (session 2)
BTA 50 U	back pain (session 1), allergic reaction (antiperspirant allergy, session 1), respiratory infection (session 1), rhinitis (session 1), and in 1 patient, head trauma, traumatic bone fracture, pneumothorax, and skin laceration (session 1)
Placebo	back pain (session 2)

Treatment withdrawals

One patient in the 50 U BTA group discontinued after an accidental injury judged to be unrelated to treatment.

Common adverse events

The overall incidence of adverse events was similar between groups (**Table 73**). The most common adverse event was injection site reaction (pain/hemorrhage); it was numerically higher in the BTA groups. Infection and flu syndrome, pharyngitis, fever, pain, headache were all numerically higher in the BTA groups compared to the placebo group. Non-axillary sweating was also higher in the BTA groups.

The allergic reactions listed were attributed to antiperspirant, cigarette smoke, bacitracin, and seasonal allergy.

Table 73 Number (%) of Patients with Adverse Events, Regardless of Causality, Reported by >3% of Patients in Any Treatment Group During the Entire Study

BODY SYSTEM Preferred Term[a]	BTA 75U (n=110)	BTA 50U (n=104)	Placebo (n=108)
OVERALL	73 (66.4%)	80 (76.9%)	58 (53.7%)
BODY AS A WHOLE			
Injection site pain, stinging, burning, or hypersensitivity	14(12.7%)	15 (14.4%)	10 (9.2%)
Infection	9 (8.2%)	9 (8.7%)	4 (3.7%)
Flu syndrome	7 (6.4%)	5 (4.8%)	0 (0.0%)
injection site hemorrhage	6 (5.5%)	5 (4.8%)	3 (2.8%)
accidental injury	5 (4.5%)	8 (7.7%)	5 (4.6%)
headache	5 (4.5%)	5 (4.8%)	3 (2.8%)
fever	4 (3.6%)	4 (3.8%)	0 (0.0%)
pain	4 (3.6%)	3 (2.9%)	1 (0.9%)
neck pain	4 (3.6%)	2 (1.9%)	0 (0.0%)
body odor	2 (1.8%)	5 (4.8%)	2 (1.9%)
allergic reaction	0 (0.0%)	4 (3.8%)	2 (1.9%)
DIGESTIVE SYSTEM			
nausea	0 (0.0%)	3 (2.9%)	4 (3.7%)
NERVOUS SYSTEM			
anxiety	4 (3.6%)	4 (3.8%)	0 (0.0%)
RESPIRATORY SYSTEM			
infection	10 (9.1%)	13 (12.5%)	6 (5.6%)
rhinitis	8 (7.3%)	8 (7.7%)	8 (7.4%)
pharyngitis	2 (1.8%)	12 (11.5%)	0 (0.0%)
SKIN AND APPENDAGES			
Sweating[a]	6 (5.5%)	12 (11.5%)	4 (3.7%)
pruritus	4 (3.6%)	1 (1.0%)	1 (0.9%)
folliculitis	0 (0.0%)	0 (0.0%)	4 (3.7%)
UROGENITAL SYSTEM			
urinary tract infection	4 (3.6%)	1 (1.0%)	0 (0.0%)

a Additional non-axillary sweating

Adverse events suggestive of neurologic effects of BTA

Patients' listings were surveyed for adverse event terms (including weakness and paresthesia) suggestive of neurologic reactions to BTA

BTA 75U:

3646-4042: muscular weakness mild, probably related, arms heavy feeling, onset day-1, duration 3 days.

0228-3006: numbness left thumb, mild, possibly related, onset day-1, duration 4 days; numbness left forearm onset day-1, duration 1 day.

3167-4111: arm pain right shoulder, discomfort mild probably related, onset day-1, duration 2 days.

3278-4061:asthenia/fatigue mild probably related, onset day-1, duration 1day.

3636-4042: asthenia, arms heavy feeling, mild, probably related, onset day-1, duration 3 days.

BTA 50U:
1901-4275: tingling left axilla, mild, probably related, onset day-1 duration 31 days.
2925-3076: pain down left arm mild, possibly related onset day-1, duration 2 days.
3166-4098: tingling left axilla mild possibly related onset day-3.
3270-4055: skin angioedema bilateral eye swelling; due to allergic reaction, moderate, unrelated.
3646-3116 asthenia, mild, probably related onset day-1, duration 3 days.

Placebo:
3681-4106: weakness of shoulders, mild, possibly related onset day-1, duration 2 days.

Reviewer's comments
Although the numbers of terms suggestive of neurologic reaction (e.g., weakness) were higher in the active groups than placebo, the short duration of the events was not consistent with known neurologic actions of BTA.

The number of adverse events did not appear to increase with multiple treatment sessions (see **Table 74**).

Table 74 Percentage (Number) of Patients with Adverse Events, Regardless of Causality, Overall and Per Treatment Session

	BTA 75 U (n=110)	BTA 50 U (n=104)	Placebo (n=108)
Entire 12-Month Study	66.4% (73/110)	76.9% (80/104)	53.7% (58/108)
Treatment Session 1	59.1% (65/110)	68.3% (71/104)	45.4% (49/108)
Treatment Session 2	39.6% (21/53)	47.9% (23/48)	36.8% (25/68)
Treatment Session 3	28.6% (2/7)	40.0% (2/5)	0% (0/8)
Treatment Session 4	no new adverse events reported	no new adverse events reported	no new adverse events reported

Lab data
One patient in the 75 U group and two patients in the 50 U group had abnormal liver function tests reported as "mild' AE vs. none in the placebo group. To evaluate the potential for BTA to induce liver injury, shifts in AST and ALT values from baseline were examined (**Table 75**). There was no evidence of greater shifts in the BTA groups compared to the placebo group.

Table 75 Shift from Baseline to Exit

	BTA 75U (n=110)					BTA 50U (n=104)					Placebo (n=108)				
Baseline	Low	Norm	High	Miss	Total	Low	Norm	High	Miss	Total	Low	Norm	High	Miss	Total
ALT															
Low	1	0	0	0	1	0	0	0	0	0	0	0	0	0	0
Norm	0	84	4	8	96	0	75	4	16	95	0	71	3	18	92
High	0	3	3	3	9	0	3	1	2	6	0	8	5	2	15
Missing	0	3	0	0	3	0	3	0	0	3	0	1	0	0	1
Total	1	90	7	11	109	0	81	5	18	104	0	80	8	20	108
AST															
Low	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Norm	0	83	5	13	101	0	76	4	18	98	0	71	7	19	97
High	0	2	2	1	5	0	2	0	0	2	0	6	2	1	9
Missing	0	3	0	0	3	0	4	0	0	4	0	2	0	0	2
Total	0	88	7	14	109	0	82	4	18	104	0	79	9	20	108

Note: Baseline value is categorized horizontally and exit value is categorized vertically.

There were no shifts from normal to high in alkaline phosphatase in the three groups. There were three shifts from normal to high bilirubin in the two active groups and two shifts in the placebo group

Reviewers' comment
There is no evidence of treatment-related liver toxicity.

There were no clinically significant changes in laboratory values post treatment compared to baseline. There were no significant changes in blood pressure, heart rate, or body temperature after treatment.

Immunogenicity

Sampling for antibody testing was performed before each injection and at the end of the study. None of the serum samples tested (77/110 in the 75U group, 68/104 in the 50U group, and 78/108 in the placebo group) showed a shift in the presence of neutralizing antibodies to BTA from baseline to exit (**Table 76**). There were many missing results due to insufficient sample collection by the study site (77 samples) or an error in preparing the control serum at a contract laboratory (34 samples).

Table 76 Antibody Assay: Shift from Baseline to Exit

	BTA 75U (n=110)					BTA 50U (n=104)					Placebo (n=108)				
Baseline	Neg	Pos	Inc	Miss	Tot	Neg	Pos	Inc	Miss	Tot	Neg	Pos	Inc	Miss	Tot
Negative (Neg)	77	0	0	15	92	68	0	0	21	89	78	0	0	15	93
Positive (Pos)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Inconclusive (Inc)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Missing (Miss)	15	0	0	3	18	13	0	0	2	15	10	0	0	5	15
Total (Tot)	92	0	0	18	110	81	0	0	23	104	88	0	0	20	108

Note: Baseline value is categorized horizontally and exit value is categorized vertically.
If results were missing at exit, the last post baseline assay result was used.

Summary of Safety: Study -016:

- No serious adverse events judged to be related to study treatment were observed in this study.
- The most common adverse event was injection site pain.

2. Study -505

Study -505 was a multicenter, double-blind, randomized, vehicle-controlled, parallel group study of the safety and efficacy of BTA (50 U) compared with vehicle for the treatment of bilateral primary axillary hyperhidrosis. Patientss were randomly assigned to a single treatment with BTA or vehicle in a ratio of 3:1. At the baseline visit, patients were randomized to receive one treatment administered as multiple (10-15), bilateral intradermal injections evenly distributed in the axilla, for a total dose per axilla of 0 (vehicle) or BTA 50U (total dose BTA 0 or 100 U). A single treatment was given on day 0 and follow up consisted of seven scheduled visits over a 17-week period. A total of 320 adults were randomized 3:1 to receive a single treatment of 50 Units of BTA or placebo.

Serious and severe adverse events

No deaths were reported. The incidence of serious adverse events was similar in BTA and placebo (1.7% and 1.3%). Onset of SAE was 3 weeks post-treatment or longer and the events were judged to be unrelated to study treatment (**Table 77**). One adverse event led to withdrawal from the study; subject 1104 withdrew from the study because of hospitalization for paranoid reaction. One subject became pregnant during the study, no further information is provided.

Table 77 Serious Adverse Events

Group	Subject	Days	Adverse event	AE Description	Causality
BTA	232	37	Bone fracture; cause unknown	Fracture of right foot	Unrelated
	321	159	Anxiety Depression	Hospitalization for anxiety and depression	Unrelated
	337	110	Hyperthyroidism	Hyperthyroidism	Unrelated
	1104	19	Paranoid reaction	Paranoid psychosis	Unrelated
Vehicle	134	81	Pharyngitis	Chronic tonsillitis	Unrelated

The following six severe adverse events (all in the BTA group) were reported: pain (n=2), neck pain (n=1), headache (n=1), sweating in other body sites (forehead and back, n=1), hyperthyroidism (n=1)

The narratives of the SAEs were evaluated and were judged to support the sponsor's assessment of unrelatedness to study treatment.

The narrative for subject 0232 identifies an accident as the cause of the foot fracture (the cause is listed as unknown in the SAE table).

Subject 0337 is said to have developed tachycardia, to have been newly diagnosed as hyperthyroid 3.5 months after BTA treatment. He is said to have been treated with daily levothyroxine with improvement of symptoms. The reported treatment is inconsistent with the diagnosis. The case illustrates the need to exclude patients with underlying medical etiology for hyperhidrosis.

Subject 1104 was abusing multiple illicit drugs including "speed." The paranoid reaction was likely related to drug abuse.

Common adverse events

The unequal treatment allocation makes it difficult to compare across arms adverse events with low reported frequencies. The most common individual AEs (**Table 78**) were infection (occurring in 5.8% of subjects in the BTA treatment group and 12.8% of subjects in the vehicle treatment group), sweating (occurring in 5% of subjects in the BTA treatment group and 1.3% of subjects in the vehicle treatment group) and pharyngitis (occurring in 3.3% of subjects in the BTA treatment group and 5.1% of subjects in the vehicle treatment group).

Table 78 Number (%) of Subjects with Adverse Events, Reported by > 2% of Subjects in Either Treatment Group

Body System	BTA (n=242)	Vehicle (n=78)
Body as a whole		
Infection	14 (5.8%)	10 (12.8%)
Flu syndrome	7 (2.9%)	2 (2.6%)
Headache	7 (2.9%)	0 (0.0%)
Injection site pain	6 (2.5%)	1 (1.3 %)
Pain	6 (2.5%)	1 (1.3%)
Back pain	5 (2.1%)	0 (0.0%)
Skin		
Sweating	12 (5.0%)	1 (1.3%)
Dermatitis	0 (0.0%)	2 (2.6%)
Respiratory		
Pharyngitis	8 (3.3%)	4 (5.1%)
Digestive system		
Gastritis	0 (0.0%)	2 (2.6%)

The report of adverse event of hyperhidrosis in other body locations (**Table 79**) raises the possibility of compensatory reaction.

Table 79 Subjects with Adverse Event of Sweating

Group	Subject	Causality	Frequency	Duration	Onset Day	Severity	Body Sites Affected	Pre-existing
BTA	504 M	probable	intermittent	ongoing	28	severe	forehead, back	N
	509 F	probable	intermittent	ongoing	1	moderate	Palms	Y
	515 M	possible	once	ongoing	<1	mild	Forehead	N
	520 F	possible	once	ongoing	32	moderate	palms, feet	Y
	522 M	possible	once	ongoing	21	mild	forehead ,chest	N
	1003 M	unrelated	intermittent	hours	7	mild	Forehead	N
	1004 M	possible	intermittent	1 month	1	mild	forehead, hands	N
	117 F	possible	intermittent	ongoing	5	mild	Unspecified	unknown
	129 M	possible	intermittent	2 months	23	mild	Face	Y
	701 F	possible	intermittent	2 months	4	moderate	face, trunk	N
	703 F	possible	intermittent	Ongoing	14	moderate	Groin	Y
	705 M	possible	unknown	Unknown	<1 month	unknown	Palms	N
Placebo	316 M	unrelated	once	Minutes	same day	moderate	General	N

Reviewers' comment
Adverse events of hyperhidrosis in other body locations were also reported with higher frequency in the BTA groups in the US study. It is unclear if this is a drug effect.

Antibodies to BTA

Antibodies to BTA were measured at baseline and at week 16 post-treatment. Two patients had antibodies to BTA detected at baseline only. At 16 weeks several subjects had assays that were inconclusive (n=9, n=2) or were marked Quantity Not Sufficient (n=17, n=12) in the BTA and placebo group respectively.

Table 80 Antibody Assay Results: Shift From Baseline to Final Visit

	BTA n = 232	Vehicle n = 75
Negative – Negative	176 (75.9%)	55 (73.3%)
Negative – Inconclusive	6 (2.6%)	2 (2.7%)
Negative – Quantity not sufficient	7 (3.0%)	6 (8.0%)
Positive – Negative	1 (0.4%)	1 (1.3%)
Inconclusive – Negative	9 (3.9%)	1 (1.3%)
Inconclusive – Inconclusive	1 (0.4%)	0
Inconclusive – Quantity not sufficient	2 (0.9%)	1 (1.3%)
Quantity not sufficient – Negative	20 (8.6%)	4 (5.3%)
Quantity not sufficient – Inconclusive	2 (0.9%)	0
Quantity not sufficient – Quantity not sufficient	8 (3.4%)	5 (6.7%)

Reviewers' comment
There was a large number of antibody assay results designated "Inconclusive" and "Quantity not sufficient," indicating the existence of sample collection problems and assay limitations. However, the most important observation is that no subjects had antibodies detected at the final visit.

Safety Summary

- No serious treatment-related adverse events were observed.

- Injection site pain, back pain, headache, and non-axillary sweating were reported at higher frequency in the BTA group. The small number of patients allocated to placebo and low event rates make interpretation of differences in rates uncertain.

3. Study -059

Given the off-label use of the product for hyperhidrosis of other anatomic sites, the sponsor conducted a chart review study (Study -059) to ascertain serious adverse events that might be associated with such uses **(see Appendix for review)** and provided literature reports. The following conclusions were drawn from Study –059:

- There were no deaths or other serious adverse events in this retrospective chart review study. No new adverse events were identified in patients receiving treatment of axillary hyperhidrosis.
- Over all treated body areas and all treatment sessions, 45% (55/122) of patients reported adverse events. The most frequently reported events were muscular weakness, injection site hemorrhage, injection site edema, and injection site pain.
- For the axillae, the most frequently reported events were acne and injection site pain.
- For the palms, the most frequently reported events were muscular weakness, injection site hemorrhage, and injection site edema.
- For the soles, none of the two patients reported adverse events.
- For the face, 1 of 2 patients reported adverse events following treatment session 1 and 0% (0/1) following session 2; the events were vasodilatation, skin disorder and blepharoptosis.

D. Adequacy of Safety Testing

In Study -016, a total of 322 adults were randomized 1:1:1 to 50 Units of BTA, 75 U of BTA or placebo and were eligible to receive one or more treatments over the course of one year of study. In Study -505, 320 adults were randomized 3:1 to receive a single treatment of 50Units of BTA or placebo. 346 patients were exposed to 50 Units and 110 patients were exposed to 75 Units of BTA. This exposure was judged to be sufficient to assess the safety of the product for axillary hyperhidrosis.

E. Summary of Critical Safety Findings and Limitations of Data

The intradermal use of the product is relatively more recent than the intramuscular use and the safety of repeated treatment cycles over the course of years is not known.

VIII. Dosing, Regimen, and Administration Issues

Study -016 demonstrated that treatment response to the 50U and 75U doses applied to the axilla were similar. Given the lack of evidence of dose-dependent toxicity in this dose-range as applied to this anatomic location, additional dose optimization studies do not appear to be warranted.

IX. Use in Special Populations

A. Evaluation of Sponsor's Gender Effects Analyses and Adequacy of Investigation

The assessment of gender effects in the clinical program was judged to be satisfactory.
In Study -016, overall, 54% (174/322) of subjects were male and 46% (148/322) were female. As shown in **Table 81** below, analysis of efficacy by gender showed statistically significant differences in the responder rates between both active groups and placebo for both males and females, although the response rates were higher for females receiving BTA than for males.

Table 81 Study -016. Responder Rates Based on HDSS by Gender

Gender	BTA 75U (n=110)	BTA 50U (n=104)	Placebo (n=108)	BTA 75U vs Placebo[a]	BTA 50U vs Placebo[a]	BTA 75U vs 50U[a]
Male	43% (26/60)	47% (27/57)	7% (4/57)	< 0.001	< 0.001	0.650
Female	56% (28/50)	64% (30/47)	4% (2/51)	< 0.001	< 0.001	0.412

[a] P-value based on Cochran-Mantel-Haenszel test stratified by study baseline HDSS score.

In Study -505, there was no appreciable difference in responder rates based on gender (**Table 82**).

Table 82 Study -505. Responder Rates Based on Gravimetric Assessment by Gender

	Male				Female			
	BTA 50U n=113		Vehicle n=35		BTA 50U n=129		Vehicle n=43	
Responders	n	%	n	%	n	%	n	%
Week 1	107	95.5%	10	29.4%	123	95.3%	15	34.9%
Week 4	99	92.5%	14	42.4%	120	95.2%	14	33.3%

It was concluded that both men and women showed clinically significant treatment responses.

B. Evaluation of Evidence for Age, Race, or Ethnicity Effects on Safety or Efficacy

Response by age

In Study -016, overall, 78% (241/322) of subjects were <40 years old, 24% (78/322) were 40 to 64 years old, and 0.9% (3/322) were ≥65 years old. There were too few subjects > 65 years

(n=3) to evaluate efficacy in this age group. As shown in **Table 83** below, analysis of efficacy by age group showed response rates to be similar for the under 40 and over 40 age group in the active groups. In the placebo group, responder rates were markedly higher in the over 40 than in the under 40-year-old subjects.

Table 83 Responder Rates Based on HDSS by Age Group

Age Group	BTA 75U (n=110)	BTA 50U (n=104)	Placebo (n=108)
< 40 years	53% (42/79)	55% (43/78)	4% (3/84)
40 to 64 years	41% (12/29)	56% (14/25)	13% (3/24)
≥ 65 years	0% (0/2)	0% (0/1)	-- (-/0)

In Study -505 there was no apparent difference in response rates based on age of subjects. In a subgroup analysis comparing patients ≤ 35 years and > 35 years of age treatment responses at 4 weeks post-treatment were 93% and 97%respectively in patients receiving BTA 50 U and 38% and 36% respectively in patients receiving placebo.

Response by Race

In Study -016, overall, 84% (262/322) of subjects were Caucasian and 19% (60/322) of subjects were non-Caucasian. Responder rates based on HDSS by race are shown in **Table 84.** Statistically significant differences in favor of both active groups over placebo were shown for both Caucasians and non-Caucasians.

Table 84 Responder Rates Based on HDSS by Race Group

Race Group	BTA 75U (n=110)	BTA 50U (n=104)	Placebo (n=108)	BTA 75U vs Placebo[a]	BTA 50U vs Placebo[a]	BTA 75U vs 50U[a]
Caucasian	51% (44/86)	56% (49/87)	7% (6/89)	< 0.001	< 0.001	0.469
Non-Caucasian	42% (10/24)	47% (8/17)	0% (0/19)	0.002	< 0.001	0.738

[a] P-value based on Cochran-Mantel-Haenszel test stratified by study baseline HDSS score.

It was concluded that there was no appreciable difference in treatment response based on age. There was very limited data on non-Caucasians; the available data suggested that non-Caucasians also responded to treatment.

C. Evaluation of Pediatric Program

Studies in pediatric patients were deferred. A study of BTA for the treatment of hyperhydrosis in post-pubescence (12-16 years of age) pediatric patients will be conducted in the post-marketing phase.

D. Comments on Data Available or Needed in Other Populations

This product is not systemically distributed and studies of patients with renal or hepatic failure were judged to be not necessary.

X. Conclusions and Recommendations

A. Conclusions

There is substantial and reproducible evidence of effectivenss of the product in primary axillary hyperhidrosis using objective criteria of axillary sweat production and global patient assessments of disease severity. The safety profile of the product is acceptable. There is reason to expect that dosing, manner of administration and response rates may differ in the anatomic location that has the next most common off-label use, namely the hands. The sponsor plans a study to address this issue. A study in adolescents is planned to address safety, tolerability, and activity in that population.

B. Recommendations

The totality of the data show that BTA is safe and effective for the treatment of severe axillary hyperhydrosis that is inadequately managed with topical agents. The reviewers recommend that the supplemental application by Allergan for marketing of BTA in this patient population be approved.

XI. Appendix

A. Other Relevant Materials

Not Applicable.

B. Individual More Detailed Study Reviews (If performed)

In addition to the two major studies that provided the basis for establishing the efficacy and safety of BTA for axillary hyperhidrosis, this license supplement contained reports from uncontrolled studies. These studies were reviewed primarily for safety and are summarized and discussed here in the Appendix.

The agency requested these data from the sponsor to assess the safety of off-label uses of the product in hyperhidrosis. Of particular interest were the dosages, safety, and activity of uses of BTA in other anatomic sites such as face, hands, and feet. It was also of interest to determine if higher doses than were studied in the clinical programs are being used off-label and whether or not these higher doses show evidence of serious adverse events.

The sponsor has also provided reports of two studies to assess validity of the gravimetric measurements of hyperhidrosis. In addition, the sponsor has provided reports of surveys to assess the prevalence of hyperhidrosis in Germany and the US.

1. Study -059

Given the off-label use of the product for hyperhidrosis of other anatomic sites, the sponsor conducted a chart review study (Study 059) to ascertain serious adverse events that might be associated with such uses.

Title of Study
A Multi-Center, Retrospective Study to Evaluate the Safety of Botulinum Toxin A Purified Neurotoxin Complex for the Treatment of Primary Hyperhidrosis Based on a Review of Subject Charts

Study Objectives
To evaluate the safety of BTA by reviewing charts of patients treated for primary hyperhidrosis at participating investigative sites. It was expected that only major safety events were likely to have good ascertainment

a. Study -059 Protocol

Study Design
Study –059 was a multicenter, retrospective chart review study.

Inclusion Criteria
Male and female patients ≥ 18 years old at the time of their first treatment with BTA for primary hyperhidrosis who had at least one BTA treatment administered for primary hyperhidrosis after 01 January 1998 and prior to 15 March 2003

Exclusion Criteria
Participation in any clinical study of an investigational therapy during the study review period; known treatment with any botulinum toxin other than BTA for any indication; known treatment with BTA for any indication other than primary hyperhidrosis or for primary hyperhidrosis prior to 01 January 1998; surgical procedure(s) for the treatment of primary hyperhidrosis performed prior to the first BTA treatment for primary hyperhidrosis (patients who had such a procedure performed after one or more treatments with BTA may have had their data included for treatments received prior to the procedure); previous inclusion of data relating to BTA treatment administered for primary hyperhidrosis in a published manuscript or abstract; known to have secondary Hyperhidrosis. Patients known to have received Lot 79-11 of BTA were excluded from this study.

Study Methods and Procedures

Overview of Entry Procedures:
Prospective subjects as defined by the inclusion/exclusion criteria were considered by chart review for entry into the study.

Method for Subject Selection:
Each investigative site should have documented in detail the method(s) used to identify patient charts for inclusion in the study. Each site was to have provided a list of all subjects form their subject population who were treated with BTA for primary hyperhidrosis after January 1, 1998 and prior to March 15, 2003. The list of subjects consisted of only a site-specific identifier unique to each subject and sufficient to link to their medical record, e.g., medical record number. Site staff reviewed the charts for all subjects on the list to determine eligibility relative to the inclusion/exclusion criteria. For charts that did not meet inclusion/exclusion criteria, only the reason for ineligibility was recorded. An Allergan representative audited these lists on site to ensure that eligible patients' charts had not been inadvertently omitted from the review. For charts that met the inclusion/exclusion criteria the data specified under Procedures to be Performed was recorded for the Review Period. The "Review Period" is subject-specific and is defined as the time between the first BTA treatment for primary hyperhidrosis (which must occur between January 1, 1998 and March 15, 2003) and *either* 12 months following the final BTA treatment for primary hyperhidrosis *or* until June 15, 2003, whichever occurs first.

Prohibited Medications/Treatments:
Subjects could not be included in the retrospective analysis of data if they ever received:

- Any other form of botulinum toxin (all serotypes) other than BTA for any indication
- BTA for any indication other than primary hyperhidrosis
- BTA for the treatment of primary hyperhidrosis prior to January 1, 1998 (these subjects may have received the previously available BTA lot 79-11).

Only subjects treated with BTA after January 1, 1998 for primary hyperhidrosis were to be included in this study.

Examination Procedures

Overall Introduction:
Charts from subjects who first received BTA as a treatment for primary hyperhidrosis after January 1, 1998 and prior to March 15, 2003 were reviewed. If the chart met the inclusion/exclusion criteria, data from the chart was transferred to the case report form. However, if the chart did not meet the inclusion/exclusion criteria, the reason for screen failure was recorded on a single CRF for the subject; no other CRFs were collected for these subjects.

Each investigative site should have documented in detail the method(s) used to identify patient charts for inclusion in the study.

Procedures to be Performed:
Each investigative site reviewed the charts of all subjects who met inclusion/exclusion criteria for the Review Period.

The following elements (if available) were recorded on case report forms provided to the investigative sites by Allergan:

- Any reported or known medical history including primary hyperhidrosis.
- Demographic information (sex, race, and age) at time of first treatment with BTA for primary hyperhidrosis.
- Any previous treatments for primary hyperhidrosis.
- Concurrent medications taken by subjects in the week prior to their BTA treatment and any concurrent medications taken up to the final post-treatment follow-up contact.
- Any concurrent procedures that were completed between the time of initial BTA treatment for primary hyperhidrosis and up to the final post-treatment follow-up contract.
- The date and type of all follow-up contacts with the subject.
- For each BTA injection visit, for each body site treated:
    - date of treatment
    - total dose administered
    - total volume administered
    - number of injection sites
    - anesthesia used
- Information on whether any adverse events were reported during treatment with BTA during any post-treatment follow-up visits. Ideally, adverse events would have a description/diagnosis, dates started and stopped (if applicable), an evaluation of the seriousness of the event, severity, relationship to BTA treatment given and any treatment that was given for the event.

Adverse Events:
Within the relevant chart entry period, any adverse event was to be recorded on the CRF, including whether it was serious and the severity of the adverse event.

Statistical Procedures:
Database lock was to follow completion of data entry, data verification and validation, database audit and data clarification resolution. An analysis plan was to be developed and finalized prior to the database lock.

Analysis Populations:
All data collected from charts for subjects who met the inclusion and exclusion criteria were included in the analysis.

Collection and Derivation of Primary Assessments:
The primary assessment was the collection of adverse event data from subject charts. Subjects who had no specific follow-up information documented in the chart following a treatment were identified by the recording of 'unknown' in response to the query 'Were there any new Adverse Events following this treatment?' on the CRF. 'Unknown' was classified as "missing" data

instead of "no adverse events." Allergan's modified COSTART nomenclature was used to code adverse events.

Hypothesis and Method of Analysis

Safety Analyses:
The primary focus was the incidence of adverse events reported by treatment session. A "BTA treatment" was defined as the original dose of a treatment session plus any dose given within six weeks (up to 50% of the original dose) for unsatisfactory response. If a single adverse event continued from one treatment session into a consecutive treatment session, the event was to be counted in the session in which it began. For each adverse event reported, the number and percent of subjects was to be tabulated by treatment session. Percentages were to be determined by the number of subjects treated in that session, and not missing adverse event information.

Analyses were for descriptive purposes; no statistical hypothesis testing was performed.

Other Analyses:
Summary statistics (n, mean, standard deviation, minimum and maximum) and/or counts and percents, were provided for the following additional variables by body site treated:

- Number of treatment sessions
- Total dose administered
- total volume administered
- Number of injection sites
- Anesthesia used

Reasons for charts not qualifying for inclusion in the study would be tabulated.

Subgroup Analyses:
Demographic and adverse event incidences were provided by investigational site.

Documentation

Source Documents:
Source documents included a subject's medical records, hospital charts, clinic charts, the investigator's subject study files, as well as the results of diagnostic tests such as X-rays, laboratory tests, and electrocardiograms. The investigator's copy of the case report form served as part of the investigator's record of a subject's study-related data.

Monitoring by the Sponsor:
The sponsor was to review the method(s) used at each investigational site to identify patient charts for inclusion in the study and conduct an audit of the investigator's patient list to ensure that eligible patient charts were not inadvertently omitted. Additionally, a third party contractor was to complete CRF entry at the investigative site. Two representatives of the contractor would conduct data entry, one to enter the data from the source document onto the CRF and one to monitor the data capture through source data verification. A representative of the sponsor was also to monitor the study at a specified time point following IRB approval and finalization of all

contracts and agreements. Following all verification and clarification of data, all case report forms were to be collected and submitted to the sponsor.

Changes in the Conduct of the Study or Planned Analyses
The original protocol dated 17 July, 2003 was amended August 25 ,2003.

Reviewers' comments
There is an inconsistency in the final study report dated December 05 2003, which states that the original protocol was amended on October 25 2003. This inconsistency was clarified with the sponsor. The reference to a protocol amendment on October 25 2003 was incorrect. There was only one protocol amendment, which was dated August 25, 2003.

The main changes were as follows:

- clarification that the sites would document the method(s) used to identify patient charts for inclusion in the study
- clarification as to how the sponsor would review the method(s) used to identify patient charts and that the sponsor would conduct an audit of the investigator's patient list to ensure that eligible patient charts were not inadvertently omitted from the review
- BTA treatment defined to include second injections given within 6 weeks
- reason for screen failure to be captured on CRF
- clarification that the collection of adverse events was the primary assessment for this study
- clarification of how to classify "missing" data as opposed to "no adverse events"

b. Study -059 Results

Study Centers
Two centers in Canada, one center in Germany, and two centers in the United States participated in the study.

Study Period
Date of First Enrollment: 01 January 1998
Date of Last Completion: 15 June 2003

Number of Patients
There were 353 patients screened, 216 enrolled, and 122 evaluable for the analysis of adverse events.

Disposition of Patients
Overall, 353 charts were screened for inclusion in the study at 5 centers of which 216 were deemed eligible for review. The most frequently reported reasons for screen failures were "other" (34%, 46/137), participation in clinical study during review period (33%), and treatment with a botulinum toxin other than BTA (22%). "Other" reasons included patient less than 18 years old at time of first injection (n= 26), first injection outside protocol review period (n= 12), date of first injection could not be confirmed (n = 8).

Demographics and Other Baseline Characteristics

The mean age of the study population was 32.8 years, ranging from 18 to 81 years ,and 39% (85/216) were men. Of the 73 patients with race reported, the majority were Caucasian, 86.3% (63/73).

The mean time since onset of disease to the first BTA treatment for primary hyperhidrosis was 121 months (range ≤ 12 to 408 months) for axillae, 211 months (range 36 to 519) for palms, 102 months (range 84 to 120) for soles (plantar), and 82 months (range 12 to 228) for face.

The body areas affected prior to the first BTA treatment were axillae for 71% (153/216) of patients, palms for 61%, soles for 45%, face for 12%, and other body areas for 11%. The most frequently reported sites or combination of sites affected prior to the first BTA treatment were axillae only for 30% (64/216) of patients, axillae and palms and soles for 22%, palms and soles for 12%, and palms only for 11%.

The most frequently reported medications used to treat hyperhidrosis that were discontinued prior to the first BTA treatment were Drysol (antihidrotic) for 25% (54/216) of patients, and aluminum chloride for 19%.

The most frequently reported concomitant medications taken during BTA treatment were oral contraceptives 15% (33/216) of patients, ethyl chloride (local anesthetic) for 9% , Drysol (antihidrotic) for 7%, benzocaine (local anesthetic) for 7%, EMLA (amide) for 6%, and ibuprofen for 5%.

i. Safety Evaluation

Extent of Exposure

Duration:

Duration of BTA exposure was defined as the number of days + 1 between the first BTA treatment (regardless of body area) and the last follow-up contact in the patient-specific review period. The mean duration of BTA exposure was 254 days, ranging from 1 to 1729 days.

There were 216 unique patients, who received from 1 to 9 treatment sessions in one or more sites as indicated in the "all treated body areas" column of **Table 85**.

Table 85 Number (Percent) of Patients by Total Number of Treatment Sessions Received During the Patient-Specific Review Period

Total Number of Sessions	All Treated Body Areas (n=216)	Axillae (n=112)	Palms (n=98)	Soles (n=8)	Face (n=10)
1	133 (61.6%)	58 (51.8%)	73 (74.5%)	5 (62.5%)	7 (70.0%)
2	38 (17.6%)	24 (21.4%)	15 (15.3%)	2 (25.0%)	3 (30.0%)
3	20 (9.3%)	14 (12.5%)	2 (2.0%)	1 (12.5%)	0 (0%)
4	15 (6.9%)	8 (7.1%)	5 (5.1%)	0 (0%)	0 (0%)
5	4 (1.9%)	2 (1.8%)	2 (2.0%)	0 (0%)	0 (0%)
6	1 (0.5%)	1 (0.9%)	1 (1.0%)	0 (0%)	0 (0%)
7	2 (0.9%)	2 (1.8%)	0 (0%)	0 (0%)	0 (0%)
8	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
9	3 (1.4%)	3 (2.7%)	0 (0%)	0 (0%)	0 (0%)

The 3 patients who received 9 treatment sessions were as follows: Patient 1976-3015 injections in the axillae (100 U, 60 U, 150 U, 150 U, 100 U, 100 U, 150 U, 150 U, and 150 U) over 32 months; Patient 1976-3034 injections in the axillae (300 U, 60 U, 200 U, 200 U, 200 U, 200 U, 200 U, 100 U, and 200 U) over 32 months; and Patient 3644-5002 injections in the axillae (56 U, 53 U, 55 U, 40 U, 50 U, 55 U, 50 U, 45 U and 60 U) over 53 months.

BTA Exposure by Treatment Session:
Dosing information was only available for a subset of patients, and therefore sample sizes are noted for a number of the summary statistics as the number of patients with data over number of patients injected. Total dose includes both unilateral and bilateral treatments. Data for "booster" injections was analyzed as part of the original injection data within a treatment session.

Over all treated body areas, the mean total dose was 123U (208/216), 117U (80/83), 133 U (45/45), and 145 U (24/25) in treatment sessions 1, 2, 3, and 4, respectively.

For the axillae, the mean total dose was 108 U (107/112), 94U (53/54), 110 U (30/30), and 102 U (16/16) in treatment sessions 1, 2, 3, and 4, respectively. The mean total volume was approximately 2.5 mL.

For the palms, the mean total dose was 130 U (95/98), 152 U (23/25), 142 U (10/10), and 140 U (7/8) in treatment sessions 1, 2, 3 and 4, respectively. The mean total volume was 3.86 mL (62/98), 5.40 mL (12/25), 6.82 mL (5/10), and 4.45 mL (4/8) in sessions 1, 2, 3, and 4, respectively. The number of injection sites ranged from 2 to 100.

For the soles, the mean total dose was 138 U and the mean total volume was 5 mL.

For the face, the mean total dose was 68.5 U (10/10) and 50.3 U (3/3) in treatment sessions 1 and 2, respectively. The mean total volume was 2.55 mL (2/10) and 0.70 mL (1/3) in sessions 1 and 2, respectively. The number of injection sites ranged from 8 to 30 (4/10) and 12 to 12 (1/3) in sessions 1 and 2, respectively.

BTA exposure by treatment session was also summarized for the subgroup of evaluable patients, i.e., patients with yes/no responses to the query for adverse event information. In general, the overall exposure was similar for evaluable patients as for all patients with dosing information.

Anesthesia Use:
For the axillae, anesthesia was used in 17% (10/60) of patients in treatment session 1, 27% (9/33) in session 2, 31% (5/16) in session 3, and 46% (5/11) in session 4. For the palms, anesthesia was used in 53% (48/90) of patients in treatment session 1, 65% (13/20) in session 2, 75% (6/8) in session 3, and 71% (5/7) in session 4. For the soles, anesthesia was used in 86% (6/7) of patients in treatment session 1, and 100% (2/2) in session 2. For the face, anesthesia was used in 12% (1/8) of patients in treatment session 1, and 50% (1/2) in session 2.

Reviewer's comments
The proportion of patients receiving anesthesia is higher for those with palmar and plantar hyperhidrosis than for those with axillary hyperhidrosis. This experience is consistent with literature reports that pain is a very common adverse event in patients receiving BTA injections in the palms and soles.

Change in Total Dose across Treatment Sessions:
For the axillae, the mean change in total dose of BTA between treatment sessions 1 and 2 was -5 (n = 49), between sessions 2 and 3 the mean change was +20 U (n= 29), and between sessions 3 and 4 the mean change was -1 U (n = 16). For the palms, the mean change in total dose of BTA between treatment sessions 1 and 2 was +32 U (n= 22), between sessions 2 and 3 the change was -6U (n = 8), and between sessions 3 and 4 the change was +6 U (n = 7). For the soles, the mean change in total dose of BTA between treatment sessions 1 and 2 was 0 U (n = 3). For the face, the mean change in total dose of BTA between treatment sessions 1 and 2 was +9 U (n= 3).

Summary of Adverse Events:
The number of evaluable patients was determined for each treatment session. Patients with specific chart information to indicate the presence or absence of adverse events post-treatment had a "yes" or "no" response to the query for adverse event information on the treatment CRF. Patients with insufficient documentation to determine whether or not an adverse event had occurred had "unknown" response on the CRF. In the primary analysis, yes/no responses were counted as evaluable, and unknown responses (with or without follow-up contact) were counted as missing. In a secondary analysis, yes/no responses were again counted as evaluable, but unknown responses were counted as evaluable if follow-up contact existed, and as missing if follow-up contact was missing. Adverse event incidence rates are based on the number of evaluable patients in both analyses.

Over all treated body areas and over all sessions, 45% (55/122) of patients reported adverse events at one or more treatment sessions. Of all the events charted, the most frequent events were muscular weakness (19% [23/122]), injection site hemorrhage (15%), injection site edema (7%), and injection site pain (4%).

Over all treated body areas by session, 42% (44/104) of patients reported adverse events following treatment session 1, 34% (10/29) following session 2, 56% (5/9) following session 3, and 25% (2/8) following session 4. Note for the calculation of percents, the denominator is the number of evaluable patients, i.e., patients treated in the session and not missing adverse event information.

For the axillae, 16% (7/45) of patients reported adverse events following treatment session 1, 7% (1/15) following session 2, 40% (2/5) following session 3, and 17% (1/6) following session 4. For the palms, 69% (42/61) of patients reported adverse events following treatment session 1, 73% (8/11) following session 2, 67% (2/3) following session 3, and 50% (1/2) following session 4. For the soles, 0% (0/2) of patients reported adverse events following treatment session 1. For the face, 50% (1/2) of patients reported adverse events following treatment session 1, and 0% (0/1) following session 2.

Adverse events reported by greater than 3% of patients over all treated body areas are summarized by treatment session in **Table 86**.

Table 86 Number (%) of Patients Over All Treated Body Areas with Adverse Events, Reported by Greater Than 3% of Patients in Any Session

BODY SYSTEM Preferred Term	Treatment Session 1 (n=104)	Treatment Session 2 (n=29)	Treatment Session 3 (n=9)	Treatment Session 4 (n=8)
BODY AS A WHOLE				
injection site hemorrhage	14 (14%)	3 (10%)	1 (11%)	0
injection site edema	7 (7%)	2 (7%)	0	0
injection site pain	4 (4%)	0	1 (11%)	0
flu syndrome	1 (1%)	1 (3%)	0	0
accidental injury	0	1 (3%)	0	0
arm pain	0	0	1 (11%)	0
CARDIOVASCULAR				
Vasodilatation	0	1 (3%)	0	0
MUSCULOSKELETAL				
muscular weakness	19 (18%)	4 (14%)	2 (22%)	1 (12%)
NERVOUS				
Paresthesia	0	1 (3%)	0	0
SKIN AND APPENDAGES				
Acne	2 (2%)	1 (3%)	1 (11%)	0
skin disorder	2 (2%)	1 (3%)	0	0
irritation skin	0	0	1 (11%)	0
skin hypertrophy	0	0	0	1 (12%)
SPECIAL SENSES				
Blepharoptosis	1 (1%)	1 (3%)	0	0

The denominator represents the number of evaluable patients, i.e., patients treated in the session and not missing adverse event information.

Individual adverse events of interest are discussed following the site-specific summaries.

Adverse events reported by patients treated in the axillae and palms are summarized by treatment session in **Tables 87 and 88.**

Table 87 Number (%) of Patients Treated in the Axillae with Adverse Events, in Each Session

BODY SYSTEM Preferred Term	Treatment Session 1 (n=45)	Treatment Session 2 (n=15)	Treatment Session 3 (n=5)	Treatment Session 4 (n=6)
BODY AS A WHOLE				
injection site pain	1 (2%)	0	1 (20%)	0
METABOLIC & NUTRITIONAL				
Edema	1 (2%)	0	0	0
MUSCULOSKELETAL				
muscular weakness[a]	1 (2%)	0	0	0
NERVOUS				
Hypesthesia[a]	1 (2%)	0	0	0
SKIN AND APPENDAGES				
Acne	1 (2%)	1 (7%)	1 (20%)	0
skin disorder	1 (2%)	0	0	0
irritation skin	0	0	1 (20%)	0
skin hypertrophy	0	0	0	1 (17%)
SPECIAL SENSES				
Blepharoptosis[b]	1 (2%)	0	0	0

The denominator represents the number of evaluable patients, i.e., patients treated in the session and not missing adverse event information.

[a]patient received injections to the axillae and palms

[b]patient received injections to the axillae and face

Adverse events reported by greater than 3% of patients treated in the palms are summarized by treatment session in **Table 88.**

Table 88 Number (%) of Patients Treated in the Palms with Adverse Events, Reported by Greater Than 3% of Patients in Any Session

BODY SYSTEM Preferred Term	Treatment Session 1 (n=61)	Treatment Session 2 (n=11)	Treatment Session 3 (n=3)	Treatment Session 4 (n=2)
BODY AS A WHOLE				
injection site hemorrhage	15 (25%)	3 (27%)	0	0
injection site edema	7 (12%)	2 (18%)	0	0
injection site pain	4 (7%)	0	0	0
chest pain	2 (3%)	0	0	0
Headache	2 (3%)	0	0	0
Pain	2 (3%)	0	0	0
flu syndrome	1 (2%)	1 (9%)	0	0
Accidental injury	0	1 (9%)	0	0
arm pain	0	0	1	0
CARDIOVASCULAR				
hemorrhage	3 (5%)	0	0	0
HEMIC & LYMPHATIC				
ecchymosis	2 (3%)	0	0	0
MUSCULOSKELETAL				
muscular weakness	20 (33%)	3 (27%)	2	1
NERVOUS				
hypesthesia	3 (5%)	0	0	0
hypertonia	2 (3%)	0	0	0
paresthesia	0	1 (9%)	0	0

The denominator represents the number of evaluable patients, i.e., patients treated in the session and not missing adverse event information.

The patient with the term hypertonia complained of tension in hands and back spasms. For the soles, none of the two patients reported adverse events. For the face, 1 of 2 patients reported adverse events following treatment session 1 and none following treatment session 2.

Patient Summaries:
Patients reporting selected adverse events of muscle weakness and injection reactions are further detailed below.

Patient 1901-2003 noted loss of dexterity and decreased strength in right hand during treatment session 3. The patient had received a total of 4 treatment sessions: injections in the palm (100 U); injections in the palm (10 U); injections in the axillae (150 U) and palm (150 U) with a booster in the axillae (20 U); and injections in the axillae (200 U). The patient had received axillary and palmar treatment at the time of this adverse event, muscular weakness is much more likely to have been related to the palmar treatment.

Patient 1976-3012 developed blepharoptosis during treatment sessions 1 and 2, and "feel[ing] hotter inside" and shiny forehead during treatment session 2 "booster". The patient had received a total of 3 treatment sessions: injections in the palm (100 U) and above the hairline (12 U) with a booster in the palm (25 U); injections in the axillae (150 U) and face (30 U) with boosters in the face (10 U and 5 U); and injections in the axillae (100 U) and face (20 U). As the patient had

received treatment in the palms, above the forehead, and face at the times of these adverse events, they are much more likely to have been related to the facial treatments.

Patient 1976-3029 noted cramping of hands - pain when using a pen or holding something in hands, red rash on right hand, back spasms, and chest pain during treatment session 1 in which he received 200 U in the palms.

Patient 3644-5001 noted decreased sensation and decrease in strength of right thumb during treatment session 1, decrease in strength of left thumb during treatment session 2, and pain in right forearm plus weakness in right palm and arm during treatment session 3. The patient had received a total of 4 treatment sessions: injections in the palms (100 U, dose not specified, 100 U, and 100 U).

Patient 3644-5007 noted benign irritated sebhorreic keratosis during treatment session 4. The patient had received a total of 5 treatment sessions over a period of 4 years: injections in the axillae (55 U, 70 U, 70 U, 70 U and 70 U).

Patient 3644-5049 noted chest pain, shortness of breath, bruising, swelling, and redness at injection sites, muscle weakness, blisters on palmar fingers, and increase in sweating in other areas treatment session 1 in which the patient received120U in the palms.

Patient 3644-5069 noted numbness of thumbs, bruising and redness of the palms, and flu symptoms during treatment session 1 in which the patient received 120 U in the palms.

Patient 4144-1041 noted numbness and minimal weakness during treatment session 2. The patient had received a total of 4 treatment sessions: injections in the palms (200 U), injections in the palms (300 U), injections in the palms plus digits and fingertips (300 U), and injections in the palms (300 U).

Patient 4144-1061 noted mild numbness in her hands from the nerve blocks (hypesthesia) during treatment session 1. The patient had received a total of 1 treatment session: injections in the axillae (100 U) and palms (200 U).

Patient 4152-4100 noted tension in hands during treatment session 1. The patient had received a total of 1 treatment session: injections in the palms (192 U).

Three patients had hematoma listed as an adverse event in the first session in which they received injections in the palms: Patient 4152-4105, -4120, and -4127.

Reviewers' comments
From the cases described above, there is suggestion of significant muscle weakness as an adverse event in patients receiving injections of BTA for hyperhidrosis in the hands and face.

Deaths, Other Serious Adverse Events, and Other Significant Adverse Events:
There were no deaths or other serious adverse events in this retrospective chart review study.

Conclusions

- There were no deaths or other serious adverse events in this retrospective chart review study. No new adverse events were identified in patients receiving treatment of axillary hyperhidrosis.
- Over all treated body areas and all treatment sessions, 45% (55/122) of patients reported adverse events. The most frequently reported events were muscular weakness, injection site hemorrhage, injection site edema, and injection site pain.
- For the axillae, the most frequently reported events were acne and injection site pain.
- For the palms, the most frequently reported events were muscular weakness, injection site hemorrhage, and injection site edema.
- For the soles, none of the two patients reported adverse events.
- For the face,1 of 2 patients reported adverse events following treatment session 1 and 0% (0/1) following session 2; the events were vasodilatation, skin disorder and blepharoptosis.

ii. Additional Data Review

FDA was informed (b) (4) that a missing treatment date for a patient (4143) in this retrospective chart review study -059 may have been falsely entered. The (b) (4) also questioned the utility of the data from this chart review study given the amount of missing data and the likelihood that there was bias in the selection of study sites. The reviewers examined the datasets for the data variable called TXDT containing the raw treatment date variables and the data variable called ITXDT, which had imputed treatment dates. Treatment dates for two subjects 4108 and 4113 were imputed.

To verify the data the reviewers requested the following information for study 059 from the sponsor.

- All the data sets and variable definitions
- All the case report forms for screened subjects
- A description of the process for handling missing data.
- Verification that the treatment dates for subjects 4108 and 4113 and verification whether these two subjects were the only two for which treatment dates were imputed.
- Verification of the dates for the following eligible subjects (chosen to include the subject with the alleged made-up treatment date): Subjects 4108, 4113, 4127, 4141, and 4143.
- Copies of the original protocol for study 059 and the amended protocol 059-01
- Process for screening and selection of study sites.

The sponsor verified that subjects 4108 and 4113 were the only two subjects with treatment dates that had to be imputed. They referenced the rules used to impute the dates that were submitted in the December 03, 2003 submission. The rules indicate that when the month and year are provided, the treatment date should be imputed as the first day of that month. This response is acceptable and their approach seems reasonable.

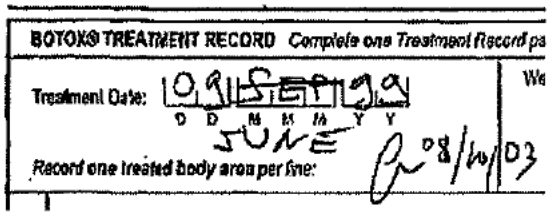
The sponsor provided the scanned Case Report forms (CRFs) for each subject screened in the study, including a "Comments" page with a listing of missing data and Data Clarification Forms sent by the sponsor to the investigator site with queries about discrepancies or missing data. This standard data clarification process was used for the subjects listed below (**Table 89**) to confirm missing treatment dates. For example, a Data Clarification Form was used to obtain the missing treatment date for subject 4152-4143. The Data Clarification Form was faxed to the study site investigator on 10/27/03 to clear up the missing treatment date in the CRF dated 10/8/03. A treatment date of 9/22/99 was inserted based on information from the source document and the data correction information was approved on 11/3/03. It was verified that the BTA treatment date entered into the CRT for subject 4143 was correct. For a total of 20 subjects including the five subjects listed in the Table 00 as well as fifteen additional subjects arbitrarily selected from four out of the five study sites (subjects 2003, 2012, 2033 from site 1901; subjects 3003, 3013, 3025, and 3049 from site 1976; subjects 5001, 5005, 5030, and 5046 from site 3644; and subjects 1005, 1020, 1029, and 1053 from site 4144), it was confirmed by reviewing the CRFs versus the SAS data sets that the correct treatment date and adverse event information were entered into the SAS data sets.

Table 89 Entries in the CRF and CRT for Selected Patients

Patient #	CRF Chart Review	BT[a] #	CRF Treatment Date	CRT Treatment date TXDT[b]	TXDTEN[c]	ITXDT[d]	CRF "Data Clarification Form"
4108	06OCT03	1	08OCT01	10/08/2001	20011008	10/08/2001	Missing BT treatment day confirmed in source document
		2	--MAR02	Missing	200203	03/01/2002	
4113	06OCT03	1	--JUN99 (partial date) changed to NKJUNE99	Missing	199906	06/01/1999	Missing BT treatment day confirmed in source document
4127	08OCT03	1	09SEPT99 changed 09JUN99	06/09/1999	19990609	06/09/1999	NA
4141	07OCT03	1	29JAN02	01/29/2002	20020229	01/29/2002	NA
		2	05JUNE02	06/05/2002	20020605	06/05/2002	
		3	04DEC02	12/04/2002	20021204	12/04/2002	
4143	08OCT03	1	-/--/- changed to 22SEPT99	09/22/1999	19990922	09/22/1999	Requested Missing BT treatment date on 27OCT03 Approved correction 03NOV03

[a] BTA treatment
[b] from Bxtx file: variable TXDT (treatment date)
[c] from Bxtx file: variable TXDTEN (treatment date as entered)
[d] from Bxtx file: variable ITXDT (imputed treatment date)

Patient 4127:
Treatment date 09SEP99 changed on the same day as the original entry as shown below. No explanation was provided in the "comments" or data clarification section of CRF. This is assumed to have been a transcription error.


BOTOX® TREATMENT RECORD Complete one Treatment Record pa

Treatment Date: 09SEP99 (D D M M M Y Y)

JUNE 08/14/03

Record one treated body area per line:

Reviewers' Comment: A standard process for data entry and quality control was in place and was followed for the tabulation of the missing treatment date for patient 4143. As far as we can tell, the statistician entering the data was not involved in the change of the date.

The sponsor provided a description of the criteria and process used to screen and select the sites. The sponsor screened 10 potential sites over the phone, of which 7 met the criteria in that they had sufficient patients and could accurately identify the patients they had treated. Only 5 sites ultimately participated. The others did not participate either because they had no paper log, electronic spreadsheet or electronic database of potential patients (and were not considered further by the sponsor) or they withdrew because of concerns about patient privacy during the chart review study.

Reviewers' Comment: The criteria for the selection of study sites appear reasonable.

Conclusions
The reviewers verified the process of entry of treatment dates from CRF into CRT and for imputing missing treatment dates. No evidence of falsification of data was found.

The studies summarized below were reviewed with the primary purpose of assessing safety.

2. Study Number -505; Health Economics Report

Study Title
A Multicenter Double-blind, Randomised, Vehicle-controlled, Parallel Group Study of the Safety and Efficacy of Botulinum Toxin A Purified Neurotoxin Complex for the Treatment of Bilateral Axillary Hyperhidrosis

Summary
This report is designated "Health Economics Report" and contains analyses of the following outcomes: Subject's Global Assessment of Treatment Satisfaction, SF-12 Health Survey, and Impact of Disease Questionnaire. The sponsor provides a report of safety and efficacy for this

study elsewhere in the sBLA submission (see review of **Study -505**). The results presented in this report show numerical differences in favor of the active treatment compared to placebo in the three patient reported outcomes. The tools used have not been validated for hyperhidrosis and the clinical significance of the results is not clear. No safety data are presented in this report. The appended literature references to non-IND studies of BTA for hyperhidrosis were reviewed. The adverse events reported for axillary hyperhidrosis are injection site reactions, (bleeding, hematoma, pain). For palmar hyperhidrosis treatments weakness of hand muscles is reported.

Reviewers' comments
No new findings are identified in this report that are relevant to axillary hyperhidrosis. The reports of weakness of hand muscles after injection of BTA in the palms are noted.

3. Study Number -506; Health Economics Report

Study Title
A Multicenter, Open Label Study of the Impact of Botulinum Toxin A Purified Neurotoxin Complex for the Quality of Life of Patients with Bilateral Primary Axillary Hyperhidrosis

Summary
This report is designated health economics report. The report is based on data obtained in Study -506. Study -506 was an open label extension study for patients who had completed Study -505. Patients received BTA when they requested it, providing the patients met the eligibility criteria and they had not received another BTA treatment within the preceding 16 weeks. Patients could receive up to a total of three BTA treatments in this study. The objective of this sub-study was to assess the following patient reported outcomes: Hyperhidrosis Impact Questionnaire and the Medical Outcomes Trust SF-12 Health Survey (SF-12).

A total of 207 patients enrolled in Study -506; 158 patients had received BTA in Study -505 and 49 had received vehicle. A total of 84 % of patients completed the one-year study period. Of the 33 patients discontinuing, one withdrew due to an adverse event and subsequently died due to myocardial ischemia; one became pregnant, another withdrew due to a protocol violation and a fourth patient withdrew due to lack of efficacy. Of the remaining patients, 12 were lost to follow-up and 17 withdrew due to 'other' reasons. A total of 15 SAEs were reported in 9 subjects.

Reviewers' comments
The Health Survey is a general tool whose validity for hyperhidrosis is questionable. The Hyperhidrosis questionnaire attempts to address hyperhidrosis-specific issues; the validity of the tool is not established. The open-label, uncontrolled design further limits the ability to interpret the findings of the study. The results will not be considered further.

*With regard to safety findings, no further information on the adverse events is provided in this report. These adverse events are reported and reviewed elsewhere (see review of **Study -506**).*

4. Study Number -506

Study Title
A Multicenter, Open Label Study of the Safety of BTA (Botulinum Toxin, Type A) Purified Neurotoxin Complex for the Treatment of Bilateral Primary Axillary Hyperhidrosis

Study Initiation Date
12 August 1999; Study Completion Date: 31 January 2001

Study Objective
To evaluate the safety of BTA for the treatment of bilateral primary axillary hyperhidrosis. Drug activity parameters were also assessed in this study.

Study Centers
Six centers each for Germany and UK; two centers in Belgium.

a. Study -506 Protocol

Single-arm multi-center, open-label extension study of safety and activity of BTA in approximately 200 subjects who completed Study -505.

Inclusion Criteria
Patients were required to have successfully completed Study -505; signed informed consent obtained; women of childbearing potential had to have a negative urinary pregnancy test before treatment.

Exclusion Criteria
The following were grounds for exclusion: medical condition that could put the subject at increased risk with exposure to BTA, allergy or sensitivity to study medication, concurrent use of other treatments for hyperhidrosis.

Study Treatment
Up to three treatments were allowed in this study, with a minimum time interval of 16 weeks between each treatment. No treatments were permitted after week 32 to ensure a minimum of 16 weeks follow-up for all subjects.

Visit Schedule
All subjects were scheduled to have an enrollment visit at week 0 and an exit visit at week 52. Intervening visits were dependent on the subject's request for treatment and verification of eligibility criteria. Following each treatment, subjects were assessed in the clinic at weeks 4 and 16, with telephone contact in the intervening periods of week 8 and week 12. Subjects not requesting further treatment received monthly telephone contacts.

Outcome Measures

Drug activity: The primary activity variable was the percentage of treatment responders at week 4 post-treatment defined as patients showing a 50% reduction from baseline (time-point before the most recent treatment) in axillary sweating measured by gravimetric assessment of spontaneous axillary sweat production at room temperature, at rest. Other activity assessments included percentage change from baseline in sweat production, size of sweat-producing area as shown by the Minor's iodine starch test, subject's global assessment of treatment satisfaction, SF-12 Health Survey, and Impact of Disease Questionnaire.

Safety

Safety measures were the incidence of adverse events, vital signs, anti- BTA antibodies. Other than pregnancy testing, no laboratory assessments were performed in this study.

Statistical Methods

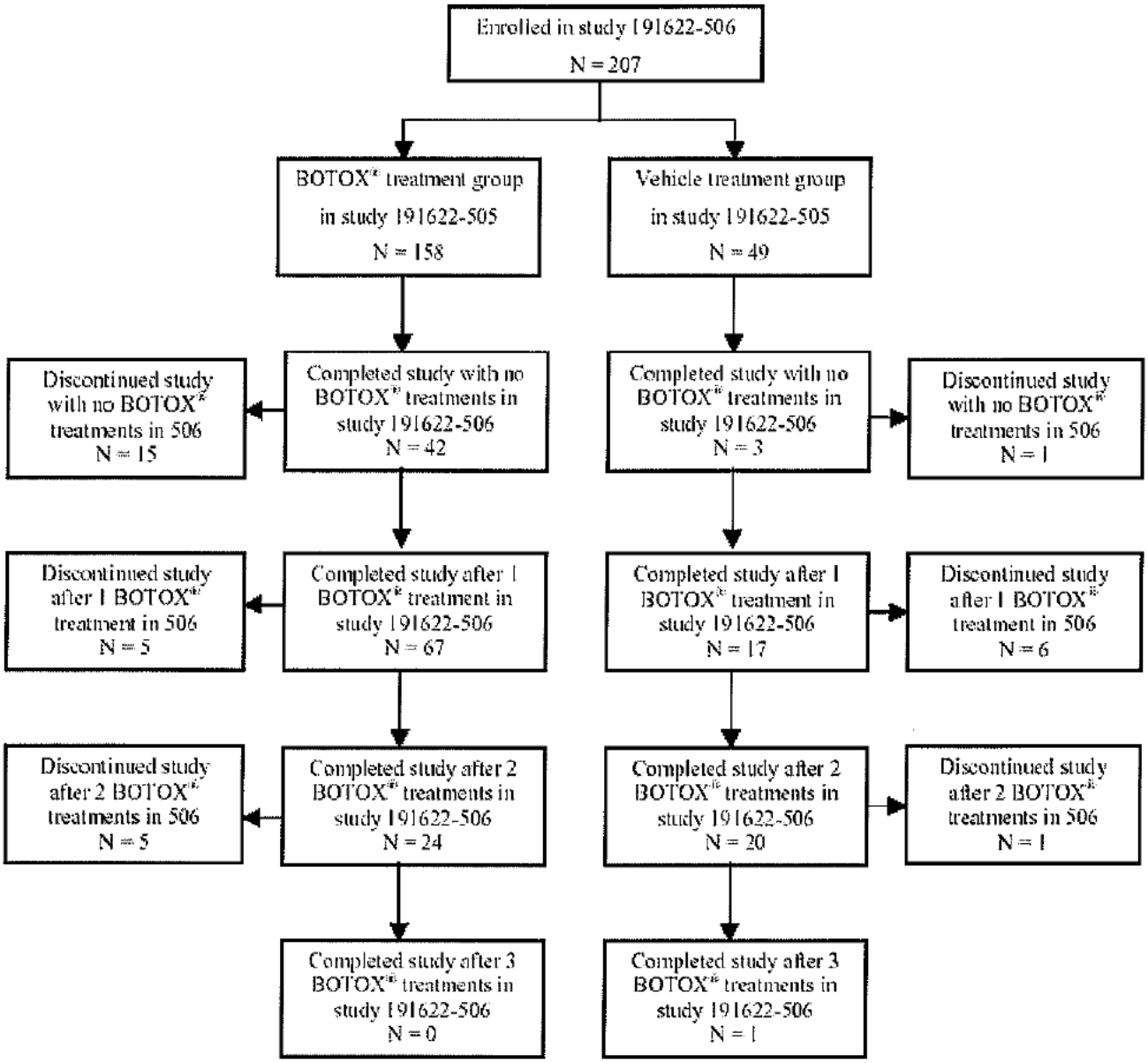
For the primary measure of drug activity, data were analyzed on an intent-to-treat basis with last observation carried forward for missing values within a treatment cycle. For the remaining variables, data were analyzed without replacement of missing values.

b. Study -506 Results

Patient Disposition

A total of 207 patients entered the study; 46% (96/207) were men; the mean age was 31 years and ranged from 17 to 74 years. Overall 84% of subjects (174/207) completed the study. Of the 174 subjects who completed the study 48% (84/174) received 1 treatment, 25% (44/174) received 2 treatments and one patient received 3 treatments. Forty-five subjects received no treatments (**Figure 3**).

Figure 3 Patient Disposition



Withdrawals

One patient died on study, death was attributed to myocardial ischemia (Patient # 804, see Safety: Serious adverse events).

Protocol deviations

A total of 42% (87/207) of subjects had protocol deviations. The main deviations were missing office visits during a treatment cycle (23%), minor's iodine-starch photography not performed on either axilla (9%) and use of prohibited medications at baseline (7%).

i. Safety Evaluation

Vital signs (systolic and diastolic BP, temperature, HR) showed no clinically significant changes following BTA treatment.

Common adverse events

Below is a listing of the most common adverse events and of events judged by the reviewers to be possibly treatment-related; the patient's study number is included.

- Paresthesia (tingling in the axilla) mild and lasting 1 day (patient #904).

- Muscular weakness (arm weakness), mild related, (#1010, 1325).
  A 39-year-old woman developed mild weakness of both arms with difficulty driving and lifting 30 min after the first and only BTA treatment. The weakness lasted four days and was accompanied by soreness at the injection site.
  A 27-year-old man complained of mild weakness of both arms starting 4 days after the second BTA treatment not affecting hands or restricting activities. Clinical assessment was not done. The patient reported a gradual improvement over a 2-month period.

  Reviewers' comment: the two events are not likely to be related to study treatment.

- Skin discoloration: mild related (#703). No further information provided.

- Urticaria: severe unrelated (#422), mild unrelated (#127), mild unrelated (#602); allergic reaction, mild unrelated, (#1107). No further information provided.

- Sweating: severe, related, (#1010).

- Increased non-axillary sweating: (#117, 504, 703, 907, 1003, 1010,1013,1014). Three of the events were rated as severe; the sites included forehead, back, hand, feet, and groin.

Table 90 summarizes the adverse events reported by $\geq$ 2% of study subjects.

Table 90 Number (%) of Patients with Adverse Events Reported by >2% of Subjects

	n	(n=207) %
At least 1 AE reported	78	37.7
Body as a whole		
Infection	17	8.2
Flu syndrome	11	5.3
Back pain	6	2.9
Headache	5	2.4
Neck pain	3	1.4
Nervous System		
Depression	5	2.4
Respiratory		
Cough increased	6	2.9
Pharyngitis	6	2.9
Sinusitis	7	3.4
Infection	4	1.9
Rhinitis	2	1.0
Skin		
Sweating	8	3.9
Special Senses		
Otitis externa	2	1.0

Serious adverse events

A total of 15 SAEs were reported in 9 subjects (4%). None of the SAEs were considered related to study treatment. An abbreviated summary of the events follows.

- Perforated ear drum (#1305), due to trauma and required myringoplasty; the event resolved.
- Cholecystitis (#130). A 23 year-old woman with colelithiasis underwent chloecystectomy for cholecystitis 3 weeks after second BTA treatment; the event resolved.
- Uterine disorder (uterine adenomyosis) (#1107). A 43 year-old woman 10 months after receiving vehicle underwent hysterectomy for abnormal uterine bleeding and recovered.
- Back pain (#1106). A 36 year-old man with history of lumbar disk herniation at 4 months after BTA was hospitalized for pain management and the pain resolved.
- Appendicitis (#808). A 39 year-old man six months after BTA underwent appendectomy for acute appendicitis.
- Depression: (#138). A 40 year-old woman with previous history of depression, was hospitalized for depression five months after BTA treatment and recovered.
- Adenocarcinoma of colon, pulmonary embolism (#106). A 46 year old woman with symptoms and signs of malignancy two months after BTA treatment ultimately underwent colectomy and chemotherapy and was continued on study.
- Pulmonary edema, myocardial ischemia, bronchitis, death (#804). A 55 year old man with HBP, DM, diabetic retinopathy was found dead at home five weeks after the second BTA treatment. Postmortem examination revealed CAD, pulmonary edema, and purulent bronchitis. The cause of death was listed as ischemic heart disease.

- Pregnancy. A 29 year-old woman had a negative pregnancy test after the first and only BTA treatment in Study -505. The patient received no BTA in Study -506; ten months after the BTA treatment she gave birth to a full-term, healthy infant.

Anti-botulinum toxin antibodies
One subject had a positive antibody result at the end of the study (subject had negative results in preceding 191622-505 study).

Reviewers' comment
No safety signal is seen.

ii. Activity

The incidence of response at week 4 post-treatment was 92% (134/146) following the first treatment and 88% (45/51) following the second treatment. Mean sweat production was reduced by 82% at week 4 following the first treatment and by 80% following the second treatment. The subject's global assessment of treatment satisfaction, the SF-12 Health Survey and Impact of Disease Questionnaire showed numerically positive responses.

Reviewers' comment
The activity measures are not interpretable due to the design and conduct of the study.

5. Study HH/003

Study Title
Report on the Burden of Disease of Hyperhidrosis in Germany (EHEU/BTA-HH/003)

Study Objective

The objective of this study was to evaluate the impact of disease on hyperhidrosis patients in Germany. The study began in April 1999 and was completed in November 2000.

Study Design
Single-center survey. The Hyperhidrosis Impact Questionnaire, Dermatology Life Quality Index, and SF-12 Health Survey were administered to all patients asking for care at the study center from March 1999 to February 2000. In addition, the questionnaires were administered to a sample of non-hyperhidrotic subjects matched for age, gender and body mass index. No safety data were obtained.

Results Relevant to Assessment of Safety
Of the 345 patients who participated in the study, 165 patients identified axillary as their primary, but not necessarily exclusive, site of involvement, while 116 patients indicated primarily palmar involvement. The remaining 64 patients identified other sites as primarily involved or had no one primarily involved site. A total of 154 comparative subjects completed questionnaires. The majority of patients reported the onset of hyperhidrosis to be adolescence or

earlier (**Table 91**). The sponsor concludes that hyperhydrosis is a serious clinical disease with detrimental emotional and social consequences.

Table 91 Age of Onset of Hyperhidrosis

Age at Onset	Hyperhidrosis Patients Overall (n=345)	Axillary (n=165)	Palmar (n=116)
< 6 years (%)	11.6	2.4	25.0
6 to 11 years (%)	14.8	4.2	31.9
12 to 17 years (%)	40.9	49.1	35.3
> 17 years (%)	31.0	43.6	5.2

Reviewers' comments
This study is a survey and the methodology used does not allow valid inferences about the impact of this condition on patient's reported outcomes. There are no safety data.

6. German Chart Review Study

Study Title
BTA (BTA) in the Treatment of Hyperhidrosis: An Observational Study Conducted in Germany

Study Design
This was a retrospective chart review survey of patients who received treatment with BTA for hyperhidrosis at a single center.

a. German Chart Review Study Protocol

Study Treatment
The number of treatments ranged from a single treatment to four treatments over 21 months. Multiple intradermal injections were given into the anatomic site affected by hyperhidrosis. If response to treatment was unsatisfactory patients could receive a second BTA injection given within six weeks that was not more than half of the initial dose.

Inclusion Criteria
Hyperhidrosis

Exclusion Criteria
Known contraindication to the use of BTA.

Activity Measures
The investigator assessed the efficacy of treatment using a scale ranging from 1 = excellent, to 4 = no effect.

Safety Measures
Safety was not consistently documented in the medical records; there was no requirement for post-injection follow up.

Statistical methods
All available data were summarized.

b. German Chart Review Study Results

Treatment Dates
The first patient was treated in the clinic on 5 December 1996 and the last patient was treated on 29 January 1999.

A total of 29 patients (72% were women) ranging in age from 18 to 47 years (mean 32 years) were reviewed. The most common anatomic sites receiving study treatment were the palms (79%), axillae (62%) and plantar aspect of the feet (62%). One patient was treated for facial hyperhidrosis.

The mean doses were approximately 36 U (20-40U), 44 U (28-58U) and 42 U (40-48 U) respectively for each axilla, each palm, and each foot. The one patient treated for facial hyperhidrosis received 46U. There is only one report of adverse events. Patient KB had light paresis of both hands after the first treatment, (about 40 U into each hand).

Reviewers' comments
This report provides no new information about safety and activity of BTA

7. Swedish Chart Review Study

Study Title
BTA (BTA) in the Treatment of Hyperhidrosis: An Observational Study Conducted in Sweden.

Study Design
Structure This was a retrospective chart review survey of patients who received treatment with BTA for Hyperhidrosis at a single center.

a. Swedish Chart Review Study Protocol

Study Treatment
Treatment duration ranged from a single treatment to five treatments over 15 months. Patients were given a range of numbers of treatments, from single treatment to five treatments per site, over a period of up to 15 months. If response to BTA was unsatisfactory patients might receive a second dose given within six weeks that was not more than half of the initial dose.

Inclusion Criteria
Patients with hyperhidrosis.

Exclusion Criteria
Known contraindication to the use of BTA.

Activity Measures
The investigator assessed the efficacy of treatment using a scale ranging from 1 = excellent, to 4 = no effect.

Safety Measures
Safety was not consistently documented in the medical records; there was no post-injection follow up.

Statistical methods
All available data were summarized.

b. Swedish Chart Review Study Results

The first patient was treated on 10 March 1997 and the last patient was treated on 12 February 1999.

A total of 157 patients (62% were women) were reviewed. Age ranged from 15-70 years (mean 32 years). The most common anatomic sites receiving treatment were the palms (68 %), axillae (44%), feet (8%), or other (including facial and genital, <5%). The mean initial doses were approximately 56U (17-130U) for axillae, 150U (30-240U) for palms, 220U (120-460U) for feet, 80 U (50-150) for face.

Record keeping was of poor quality. Examples of missing activity data are 40 of 67 treated axillae have missing data; 32 of 106 left hand 21 of 102 of right hand have missing data.

Forty three patients (27%) reported a total of 46 adverse events. The most common adverse event was transient muscle weakness (35 reports). The weakness, except for one case, occurred in the hands, was classified as severe in two cases and mild in the others and was associated with doses ranging between 140 and 200U to each palm. The one non-palmar case is described as "problems with wrinkling of forehead", was described as mild and normal function returned after a few weeks. Six patients reported transient pain. Three patients reported transient paraesthesia. One patient had a bacterial infection at three injection sites, which required treatment with flucloxacillin. One patient was fearful of the injections and treatment was interrupted.

Reviewers' comment
This experience is notable for the large doses of BTA administered. The occurrence of weakness, pain and paresthesia in the hands is noted.

8. Study -015

Study Title
Randomized Inter-Rater and Intra-Rater Reliability Study of Gravimetric Measurement of Spontaneous Resting Axillary Sweat Production Both in Patients With and Without Primary Axillary Hyperhidrosis.

No safety or efficacy data were collected in this study. The study will not be considered further.

9. Normal Volunteer Study

Summary
Single center study investigating bilateral axillary sweat production in 46 normal healthy adult volunteers at rest, measured non-invasively using gravimetric assessment. No study treatments administered. No safety or efficacy data were collected in this study. The study will not be considered further.

C. Literature Review

The sponsor searched the literature (STN International files;Medline 1960-present Embase 1974-present; Biosis 1969-present; SciSearch 1974-present; JISCT; Pascal; Chemical abstracts 1967-present) for the terms hyperhidrosis and botulinum toxin and provided copies of the articles.

The articles were reviewed and the following issues are noted.

Safety
There are a number of reports of decreased muscle strength (weakness of hand), pain and paresthesia after injection of palms and digits. There are two reports of decreased muscle strength in the face following injections for gustatory sweating.

- Decreased muscle strength in hands was reported in 2 of 4 patients treated for palmar Hyperhidrosis. Alavarez Fernadez et al. Acta Dermo-Sifiliogr 90:599,1999.

- Weakness of upper lip was reported in 1 of 7 patients treated for gustatory sweating (Frey's syndrome). Arad-Cohen et al., Otolaryngol Head Neck Surg 122:237,2000.

- A review paper cites pain on application to palms and soles, weakness of small muscles of the hands following treatment of palmar hyperhydrosis. Atkins JL, Plast Recontr Surg 10:22, 2002.

- A total of 19 evaluable patients were treated for palmar and digital hyperhidrosis; all had pain on application, four had weakness of abductor pollicis brevis, all had weakness (scored 4 on a 5 point scale with 5=normal) of the thenar eminence. Solomon and Hayman , J Am Acad Dermatol 42:1026, 2000.

- A total of 20 evaluable patients experienced pain, 15 cited mild hand weakness, mean decreases in strength of intrinsic muscles of hand (finger pinch measured by hydraulic dynamometer) of 30-50% at 50-100 U BTA per palm. Saadia et al., Neurology 57:2095, 2001.

- Decreased mean compound muscle action potential for abductor pollicis brevis (60%) and abductor digiti minimi (30%) following a mean of 160 U (102-240U) injected in each hand for palmar hypehydrosis in 37 patients. Recovery to normal by 37 weeks. Swartling et al., Eur J Neurol 8:451,2001.

No new adverse events are identified in patients treated for axillary hyperhydrosis from the literature reports. The reporting frequency for adverse events in the anectodal reports and one multicenter study does not appear to be higher than the actual observed incidence of the same adverse reported in the clinical trials for this sBLA.

- Intra-patient controlled study of BTA 100 and 200 U per axilla in 145 patients with axillary hyperhidrosis. No serious adverse events reported. Decreased sweat production observed. No difference between 100 and 200 mg dose in decreased sweat production. Heckman et al., NEJM 344:488, 2001.

There is suggestive evidence of muscle weakness induced by BTA at sites distant from the injection site.

- Case report of one patient treated for palmar hyperhidrosis with Botulinum type A and B who developed dry mouth and eyes, dysphagia, and blurred vision in addition to weakness of the hand muscles. Baumann LS, Arch Dermatol 139:226,2003.
- Suggestion of subclinical neurologic effects measured by single fiber electromyography in limb muscles in patients injected with BTA in neck muscles for torticollis. Lange et al., Muscle and Nerve 14:672,1991.

Activity

There are a few anecdotal reports suggesting that duration of treatment effect in axillary hyperhydrosis is dose dependent. These reports are not supported by data from the controlled trial.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 103000/S-5050

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

BLA/Serial Number:	STN BL 103000/5050
Drug Name:	BOTOX (Botulinum Toxin Type A) Purified Neurontin Complex
Indication(s):	Primary Bilateral Axillary Hyperhidrosis
Applicant:	Allergan
Date(s):	Submission Date: July 11, 2003
Review Priority:	Standard
Biometrics Division:	DBII (Stat Reviewer), BTSS (Stat Team Leader)
Statistical Reviewer:	A G Mucci, DBII (HFD-715)
Concurring Reviewers:	Zhen, Boguang, BTSS
Medical Division:	DTBIMP
Clinical Team:	Louis Marzella (Medical Reviewer)
Project Manager:	Jim Reese, OND/ODEVI/DRMP

Keywords: Clinical Studies, BLA Review, Hyperhidrosis, Placebo Controlled Superiority Trials

Table of Contents

1 EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

The Sponsor provided two randomized, placebo controlled, parallel group studies for the evaluation of Botox Injection for the treatment of Primary Bilateral Axillary Hyperhidrosis. Study#505 compared Botox to Placebo for the endpoint of significant reduction in axillary sweating as measured by gravimetric assessment; Study#16 compared Botox to Placebo for the endpoint of patient assessment of significant reduction in perceived hyperhidrosis severity. Study#505 and Study#16 each clearly demonstrated the Efficacy of Botox for the treatment of Primary Bilateral Axillary Hyperhidrosis. No significant Safety problems were found.

For the primary efficacy variable of Responder Rate in Study#505, the 50U Botox group achieved a 91% Responder rate, while the Placebo group scored a 36% Responder rate. The p-value for this difference under the hypothesis of equality of rates was less than .001.

For the primary efficacy variable of Responder Rate in Study#16, the Placebo group, 50U Botox group, and 75U Botox group had rates 6%, 47%, and 42%, respectively. The p-values for the two pair-wise comparisons, 75U Botox vs. Placebo and 50U Botox vs. Placebo, were each less than .001 under the hypothesis of equality of rates.

The efficacy results from the two Phase III trials support the new claim of using Botox axillary injections for the treatment of primary bilateral axillary hyperhidrosis.

1.2 Brief Overview of Clinical Studies

1.2.1 Overview of Study#16 Design

Study Title: A Multicenter, Double-Blind, Placebo-Controlled, Parallel Study of the Safety and Efficacy of Repeated Treatment with One of Two Dosages of BOTOX (Botulinum Toxin Type A) Purified Neurotoxin Complex for the Treatment of Primary Axillary Hyperhidrosis.

Study Objective: The objective of this study was the assessment of the Safety and Efficacy of repeated Botox injections for the treatment of primary bilateral axillary hyperhidrosis.

Study Design: Patients in Study#16 were randomized to one of three arms – Placebo, 50U Botox, or 75U Botox, and were followed for up to 52 weeks subsequent to the initial injection, with visits to the investigator alternating with telephone communications at approximately 4 week intervals.

Inclusion Criteria: The principal inclusion criteria were the patient's report of a significant level of persistent primary bilateral axillary hyperhidrosis and a baseline gravimetric read of 50mg or more in spontaneous sweat production in each axilla.

Primary Efficacy Variable: The primary efficacy variable was the patient's assessment of degree of axillary sweating, denoted as HDSS. This variable was evaluated at specified times during the trial to determine if a patient was a *Responder* or a *Non-Responder*. (See Section 2.1 for the definition of Responder.)

Primary Efficacy Endpoint: The Primary Efficacy Endpoint was the Responder Rate. A principal secondary endpoint investigated in this review was the Median Duration of Response, defined as the median time a patient with an Initial Response to treatment remained responsive.

Primary Statistical Objective: The Primary Statistical Objective was to demonstrate that the difference between the Botox Responder Rates and the Placebo Responder Rates was at least 25% for both the 50U Botox vs. Placebo comparison and for the 75U Botox vs. Placebo comparison. The 322 patients included in the ITT analysis Study provided enough patients to validate this difference for each of the two comparisons with power at least .95, given a significance level of .025 for each comparison under a Null Hypothesis of Equality of Rates.

Investigational Sites: 17 US centers; 1 Canadian center.

Remarks Concerning the 75U BOTOX Treatment: The companion Study#505 provided substantial evidence for the Efficacy and Safety of 50U BOTOX (see relevant sections below.) The 75U BOTOX treatment was included in Study#16 to obtain a more complete safety profile.

1.2.2 Principal Efficacy Results for Study#16:

Primary Endpoint HDSS Responder Rate: The ITT analysis determined:

A 42% Responder Rate for 75U Botox vs. a 6% Responder Rate for Placebo

A 47% Responder Rate for 50U Botox vs. a 6% Responder Rate for Placebo

P-values: The p-values for both these results was effectively zero (less than $(10)^{-9}$). No considerations of adjustments for multiple comparisons were necessary, given these p-values.

95% CI: The confidence intervals for the group rate differences were:

The two-sided 95% CI for the 36% rate difference in 75U Botox vs. Placebo was (26% , 47%)

The two-sided 95% CI for the 41% rate difference in 50U Botox vs. Placebo was (31% , 52%)

The two-sided 95% CI for the 5% rate difference in 50U Botox vs. 75U Botox was (- 8% , +18%)

These CI's are interpreted here as evidence that both the Botox Responder rates were at least 25% better than the Placebo Responder rate, and that the two Botox treatments were equally effective.

Secondary Endpoint Median Duration of Response: For patients who were WK#4 Responders:

The 75U Botox group had median duration of response of 168 days

The 50U Botox group had median duration of response of 173 days

The Placebo group had a median duration of response of 63 days

Note: The duration of response was calculated as the time beginning at the WK#4 office visit and ending 30 days before the first subsequent office visit where an HDSS ≥ 3 was reported.

1.2.3 Overview of Study#505 Design

Study Title: A Multi-center, Double-Blind, Vehicle-Controlled, Parallel Group Study of the Safety and Efficacy of Repeated Treatment with One of Two Dosages of BOTOX (Botulinum Toxin Type A) Purified Neurotoxin Complex for the Treatment of Primary Axillary Hyperhidrosis.

Study Objective: The objective of this study was the evaluation of the Safety and Efficacy of a single Botox injection for the treatment of primary bilateral axillary hyperhidrosis.

Study Design: Patients in Study#505 were randomized to receive a single 50U dose of Botox or Placebo, and were followed for 16 weeks, with visits to the investigator scheduled for every four weeks.

Principal Inclusion Criteria: The principal inclusion criteria were the investigator determination of the presence of primary bilateral axillary hyperhidrosis , and a baseline gravimetric read of 50mg or more in spontaneous sweat production in each axilla.

Primary Efficacy Variable: The primary efficacy variable was the percentage reduction over baseline in gravimetric reads registered at each scheduled visit. Patients were classified as *Responders* at the various visits if the percentage reduction in gravimetrics was at least 50% below baseline at the time of those visits.

Primary Efficacy Endpoint: The primary efficacy endpoint was the *Responder Rate* (as a percentage) at Week#4 after the baseline visit. The principal secondary endpoint investigated in this review was the *Persistent Responder Rate*, that is, the percentage of patients who remained Responders at every scheduled visit.

Primary Statistical Objective: The primary statistical objective was to demonstrate that the difference between Botox Responder rates and Placebo Responder rates at WK#4 was at least

25%. The 320 patients included in the ITT analysis provided at least 90% power to validate this difference.

Investigational Sites: 7 centers in Germany; 6 centers in UK ; 2 centers in Belgium ; 2 centers in Switzerland.

1.2.4 Principal Results for Study#505:

Primary Endpoint of Responder Rate: The ITT analysis determined:

A 91% Responder Rate for Botox vs. a 36% Responder Rate for Placebo.

P-value: The p-value for these results, under a Null Hypothesis of Equality of rates, was effectively zero ($(10)^{-20}$).

95% CI: The confidence intervals for the Botox vs. Placebo rate differences was: (44% , 66%).

This is interpreted here as evidence that the 50U Botox rates are at least 25% better than the Placebo rates.

Secondary Endpoint of Persistent Responder Rate: The ITT analysis determined:

A 69% Persistent Responder Rate for Botox vs. a 10% Persistent Responder Rate for Placebo Once again the p-value for these results, under a Null Hypothesis of Equality of Rates, was effectively zero.

95% CI: The 95% CI for the 59% difference in Botox Persistent Rate vs. Placebo Persistent Rate was (50% , 68%).

1.3 Statistical Issues and Findings

Study#505 and Study#16 did not share primary endpoints; therefore comparisons of the principal results were not possible. However, both studies imposed the Inclusion Criterion that the screening Gravimetrics were at least 50mg in each axilla, and the studies shared several secondary endpoints:

(1): Rates for WK#4 Gravimetric Reductions of 50% or more

(2): Rates for WK#4 Gravimetric Reads <50mg

Thus, there is some rationale for investigating similarity between the two studies for the statistics listed above. These statistics are presented in the table below. Note that the comments subsequent to the table are directed not toward Botox vs. Placebo performance similarities

between the trials, but rather toward Botox vs. Botox and Placebo vs. Placebo performance similarities.

Table (1.3.1)
Table of Comparisons of Common WK#4 Endpoints: Study#505 vs. Study#16

	STUDY#505			STUDY#16	
	Placebo	50U Botox		Placebo	50U Botox
# Patients	78	242		108	104
WK#4 Grav drops at least 50%	36%	91%		42%	82%
WK$#4 Grav <50mg	19%	81%		29%	81%

Listed below are the 95% CI's for the Botox vs. Botox and Placebo vs. Placebo differences in Responder rates between the studies:

For the WK#4 Endpoint of a 50% or more drop in Gravimetrics:

95% CI for Study#16 Placebo Rate – Study#505 Placebo Rate = (-.08 , +.20)

95% CI for Study#16 Treatment Rate – Study#505 Treatment Rate = (-.17, -.01)

***For the WK#4 Endpoint of a reduction to a Gravimetric< 50mg*:**

95% CI for Study#16 Placebo Rate – Study#505 Placebo Rate = (-.02 , +.22)

95% CI for Study#16 Treatment Rate – Study#505 Treatment Rate = (-.09 , +.09)

These CI's are taken to be evidence for similarity of response (Placebo vs. Placebo and Treatment vs. Treatment) between the two trials.

2. INTRODUCTION

2.1 Overview

2.1.0.1: Drug Class and Existing and Proposed New Indications: BOTOX (Botulinum Toxin Type A Purified Neurotoxin Complex) is a purified BTA which blocks neuromuscular transmission by binding to acceptor sites on motor or sympathetic nerve terminals, inhibiting the release of acetylcholine. The drug product is produced from fermentation of Hall strain Clostridium botulinum type A. The product is intended, under the currently proposed indication, for intracutaneous administration in the sweat producing area of the axillae in adults with primary axillary hyperhidrosis that is severe and inadequately managed with topical agents. BOTOX is currently licensed in the US for treatment of cervical dystonia, blepharospasm, and glabellar lines, and is also licensed in over 70 other countries for these indications and for several other indications including axillary hyperhidrosis.

2.1.0.2: Milestones In Product Development: The submitted BLA presents results from two independent phase III trials: Study#505 and Study#16. Study#505 provided an objectively measured primary endpoint - the gravimetric read of axillary sweat production. Study#16 incorporated a global disease severity scale primary efficacy endpoint (HDSS) agreed upon between the FDA and the Sponsor prior to trial initiation. This endpoint, consisting of the patient's assessment of severity of axillary hyperhidrosis before and at prescribed times after treatment, was intended to provide more clinically relevant information than the primary endpoint of gravimetric assessment provided in Study#505.

2.1.1 Overview of Study#16 Design

Study Title: A Multicenter, Double-Blind, Placebo-Controlled, Parallel Study of the Safety and Efficacy of Repeated Treatment with One of Two Dosages of BOTOX (Botulinum Toxin Type A) Purified Neurotoxin Complex for the Treatment of Primary Axillary Hyperhidrosis.

Study Objective: The objective of this study was the assessment of the Safety and Efficacy of repeated Botox injections for the treatment of primary bilateral axillary hyperhidrosis.

Study Design: Patients in Study#16 were randomized to one of three arms – Placebo, 50U Botox, or 75U Botox, and were followed for up to 52 weeks subsequent to the initial injection, with visits to the investigator alternating with telephone communications at approximately 4 week intervals.

Inclusion Criteria: The principal inclusion criteria were the patient's report of a significant level of persistent primary bilateral axillary hyperhidrosis and a baseline gravimetric read of 50mg or more in spontaneous sweat production in each axilla. The patient's report was score from a four level subjective measure, denoted as HDSS, ranging from level 1(sweating not noticeable) through level 4(sweating persistent and intolerable), and patients with the requisite baseline gravimetric reads were included in the if the baseline HDSS was at least at level 3.

Primary Efficacy Variable:: The primary efficacy variable was the HDSS reported by the patients throughout the trial. This variable was used to determine if a patient was a *Responder* or a *Non-Responder*. A patient was classified as a Responder by means of a complex algorithm approximately described as follows: A patient was a Responder if his/her HDSS dropped by 2 units at the Week#4 visit after first injection and thereafter remained below a 3 until trial termination, or, if having met the condition that his/her HDSS dropped by at least two units at the Week#4 visit after first injection, but having at some subsequent official visit registered an HDSS of at least level 3, returned to an HDSS of at most 2 four weeks after re-injection.

Primary Efficacy Endpoint: The Primary Efficacy Endpoint was the Responder Rate. The principal secondary endpoints investigated in this review were the Initial Response Rate, also denoted as the WK#4 Response Rate, and defined as the percentage of patients who experienced at least a 2 point drop in HDSS at Week#4 after the first injection, and the Median Duration of

Response, defined as the median time a patient with an Initial Response remained with an HDSS of at most 2.

Primary Statistical Objective: The Primary Statistical Objective was to demonstrate that the difference between the Botox Responder Rates and the Placebo Responder Rates was at least 25% for both the 50U Botox Treatment vs. Placebo comparison and for the 75U Botox Treatment vs. Placebo comparison.

Power and Sample Size: The 322 patients included in the ITT analysis Study (108 in Placebo ; 104 in 50U Botox ; 110 in 75U Botox) provided more than enough patients to validate the proposed 25% difference in Botox vs. placebo rates under the assumption that the Botox Rate =.50 and the Placebo Rate =.25 for each of the two comparisons separately with power at least .95, given a significance level of .025 for each comparison under a Null Hypothesis of Equality of Rates. Thus, the sample sizes were sufficient to ensure simultaneous validation of the differences with power at least .90, given a significance level of .025 for each comparison under a Null Hypothesis of Equality of Rates. The statistical procedure employed for this prospectively defined sample size calculation was the Fisher Exact Test for binomial proportions.

2.1.2 Principal Results for Study#16:

Primary endpoint HDSS Responder Rate: The ITT analysis determined:

A 42% Responder Rate for 75U Botox vs. a 6% Responder Rate for Placebo

A 47% Responder Rate for 50U Botox vs. a 6% Responder Rate for Placebo

P-values: The p-values for these results, under a Null Hypothesis of Equality of rates for Botox vs. Placebo, was effectively zero (less than $(10)^{-9}$) for both the 75U Botox vs. Placebo and the 50U vs. Placebo comparisons. No considerations of adjustments for multiple comparisons were necessary, given these p-values.

95% CI: The confidence intervals for the rate differences were as follows:

The two-sided 95% CI for the 36% rate difference in 75U Botox vs. Placebo was (26% , 47%)

The two-sided 95% CI for the 41% rate difference in 50U Botox vs. Placebo was (31% , 52%)

The two-sided 95% CI for the 5% rate difference in 50U Botox vs. 75U Botox was (- 8% , +18%)

These CI's are interpreted here as evidence that both the Botox Responder rates were at least 25% better than the Placebo Responder rate, and that the two Botox treatments were equally effective.

Secondary Endpoint WK#4 HDSS Responder Rate: The ITT analysis determined:

A 73% Responder Rate for 75U Botox vs. a 19% Responder Rate for Placebo

A 72% Responder Rate for 50U Botox vs. a 19% Responder Rate for Placebo.

Secondary endpoint of Median Duration of Response: *For patients who were WK#4 Responders*:

The 75U Botox group had median duration of response of 168 days

The 50U Botox group had median duration of response of 173 days

The Placebo group had a median duration of response of 63 days

Note: The duration of response was calculated as the time beginning at the WK#4 office visit and ending 30 days before the first subsequent office visit where an HDSS≥3 was reported.

2.1.3 Overview of Study#505 Design

Study Title: A Multi-center, Double-Blind, Vehicle-Controlled, Parallel Group Study of the Safety and Efficacy of Repeated Treatment with One of Two Dosages of BOTOX (Botulinum Toxin Type A) Purified Neurotoxin Complex for the Treatment of Primary Axillary Hyperhidrosis.

Study Objective: The objective of this study was the evaluation of the Safety and Efficacy of a single Botox injection for the treatment of primary bilateral axillary hyperhidrosis.

Study Design: Patients in Study#505 were randomized to receive a single 50U dose of Botox or Placebo, and were followed for 16 weeks, with visits to the investigator scheduled for every four weeks.

Principal Inclusion Criteria: The principal inclusion criteria were the investigator determination of the presence of primary bilateral axillary hyperhidrosis , and a baseline gravimetric read of 50mg or more in spontaneous sweat production in each axilla. The baseline gravimetric read was the value against which post-injection values were compared in order to assess efficacy.

Primary Efficacy Variable: The primary efficacy variable was the percentage reduction over baseline in gravimetric reads registered at each scheduled visit. Patients were classified as *Responders* at the various visits if the percentage reduction in gravimetrics was at least 50% below baseline at the time of those visits.

Primary Efficacy Endpoint: The primary efficacy endpoint was the *Responder Rate* (as a percentage) at Week#4 after the baseline visit. This rate was denoted as the WK#4 Responder Rate. The principal secondary endpoint investigated in this review was the *Persistent Responder Rate*, that is, the percentage of patients who remained Responders at every scheduled visit.

Primary Statistical Objective: The primary statistical objective was to demonstrate that the difference between Botox Responder rates and Placebo Responder rates at WK#4 was at least 25%.

Power and Sample Size: The 320 patients included in the ITT analysis (242 to Botox ; 78 to Placebo) provided at least 90% power to validate the proposed 25% difference in Botox vs. Placebo rates, when the Botox Responder Rate was assumed to be 60% , and the Placebo Responder Rate was assumed to be 35%, and when a significance level of .05 was imposed for the Null Hypothesis of Equality of Rates. The statistical procedure employed for this prospectively defined sample size calculation was the Fisher Exact Test for binomial proportions.

2.1.4 Principal Results for Study#505:

Primary Endpoint of WK#4 Gravimetric Responder Rate: The ITT analysis determined:

A 91% WK#4 Responder Rate for Botox vs. a 36% WK#4 Responder Rate for Placebo.

P-value: The p-value for these results, under a Null Hypothesis of Equality of rates, was effectively zero ($(10)^{-20}$).

95% CI: The confidence intervals for the Botox vs. Placebo rate differences was: (44%, 66%).

This is interpreted here as evidence that the 50U Botox WK#4 rates are at least 25% better than the Placebo WK#4 rates.

Secondary Endpoint of Persistent Gravimetric Responder Rate: The ITT analysis determined:

A 69% Persistent Responder Rate for Botox vs. a 10% Persistent Responder Rate for Placebo

Once again the p-value for these results, under a Null Hypothesis of Equality of Rates, was effectively zero.

95% CI: The 95% CI for the 59% difference in Botox Persistent Rate vs. Placebo Persistent Rate was (50%, 68%).

2.2 Data Sources

The data source for all analyses was the EDR document:

STN 103000\5050

The particular data sets within this source on which the analyses and validations of the two principal Phase III clinical trials were based were:

For Study#16:
BLAMAIN/STATISTICAL/DATASETS/016/ANALYSIS/EFF1.xpt; EFF2.xpt; HDSSTR.xpt

For Study#505:
BLAMAIN/STATISTICAL/DATASETS/505/ANALYSIS/EFF2.xpt

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Detailed Description of the Protocol for Study#16.

Title of Study: A Multicenter, Double Blind, Randomized, placebo Controlled, Parallel Group Study of the Safety and efficacy of Repeated treatment with One or Two doses of BOTOX for the Treatment of Primary Axillary Hyperhidrosis.

Clinical Trial 191622-016 was a 53 week, multi-center(17 US centers; one Canadian center) , double blind, placebo controlled, parallel group study of the safety and efficacy of repeated BOTOX injections for the treatment of bilateral primary axillary hyperhidrosis (excessive underarm sweating).

The key patient Inclusion criterion was the patient's personal report of high levels of axillary sweating, along with a baseline gravimetric read of at least 50mg of spontaneous resting sweat production in each axilla. Patients who qualified for trial inclusion were randomly assigned in an approximate 1:1:1 ratio to one of three groups:

BOTOX 75 U Arm (110 Patients)

BOTOX 50 U Arm (104 Patients)

Placebo Arm (108 Patients)

The Primary Efficacy Variable was the binary classification of patients into Responders and Non-Responders. The primary statistical efficacy evaluations were the two between- group comparisons of Responder Rates of BOTOX Treatment vs. Placebo:

BOTOX 75 U Arm Responder Rate vs. Placebo Arm Responder Rate

BOTOX 50 U Arm Responder Rate vs. Placebo Arm Responder Rate

The classification of a patient as a Responder or Non-Responder was determined by an algorithm involving office visits, injections, and measurements. The details are presented directly below.

The primary efficacy variable was determined through the patient's assessment of hyperhidrosis severity; this assessment was denoted HDSS. This measure took the following four values:

1 = No noticeable underarm sweating

2 = Tolerable underarm sweating which sometimes interferes with daily activities

3 = Barely tolerable underarm sweating which frequently interferes with daily activities

4 = Intolerable underarm sweating which always interferes with daily activities

The principal secondary efficacy variable under investigation was a Gravimetric measure, G, of spontaneous resting axillary sweating (measured in milligrams.) This continuous measure was reduced, for purposes critical to the trial, to two states: $G \geq 50$ mg and $G<50$ mg .

These two variables were used to define trial inclusion criteria, injection/ re-injection criteria, and Responder criteria. These various criteria were defined as follows:

(1): Patients were entered into the trial if they reported an $HDSS \geq 3$ and registered a Gravimetric $G \geq 50$ mg in each axilla at the time of the first office visit. This visit was denoted as the First Day Zero visit. At this time patients were randomized to Study Arm. Thereafter patients were scheduled for a sequence of alternating office visits and telephone communications, at approximately four week intervals, some of which could involve further Botox injections, provided certain HDSS and Gravimetric criteria were met. If a second injection was given at one of these visits, that visit was denoted the Second Day Zero visit. Injections beyond the second injection did not enter into Efficacy analyses for the Study. There were two classes of patients who were classified as Responders – those requiring only one injection and those requiring two injections.

First Class of Responders – Patients who received no Second Injection
These are the patients with an initial $HDSS \geq 3$ and Gravimetric ≥ 50mg (each axilla) whose HDSS dropped by two units as measured at Week#4 after the first injection, and who, thereafter, at all scheduled office visits, had HDSS scores ≤ 2.

Second Class of Responders– Patients who received at least two Injections
These are the patients who satisfied the initial conditions - Initial Baseline HDSS ≥ 3 and G ≥ 50 (both axilla) and who, at Week#4, reported at least a two point drop in HDSS, but who, before end of Study, (at Week8, Week12, etc), returned to an HDSS ≥ 3, along with a G>50mg in at least one axilla, were re-injected, and at Week#4 after this second injection, reported an HDSS at least two points below the first Baseline HDSS.

3.1.2 Detailed Results for Study#16

Study#16 enrolled 322 patients (174 males; 142 females; 262 Caucasians), all of whom were included in the Intent-To-Treat (ITT) Analysis. The mean age for the patients was 33 years, and the mean age for onset of disease was 17 years. A total of 252 patients (78%) completed the Study. A patient was a Completer if he/she stayed with the Study throughout the prescribed 52 weeks, or stayed long enough to be classified as a Non-Responder. Patient disposition is provided in the table below.

Table(3.1.2.1)
Demographics

		Placebo (N=108)	50U Botox (N=104)	75U Botox (N =110)
Age (Years)	Mean	31 yrs	32 yrs	
Age Category	<40	84 (78%)	78 (75%)	79 (72%)
Gender	Male	57 (53%)	57 (55%)	60 (55%)
	Female	51 (47%)	47 (45%)	50 (45%)
Race	Caucasian	89(82%)	87(84%)	86 (78%)
	Non-Caucasian	19 (18%)	17 (16%)	24 (22%)

Table(3.1.2.2)
Disposition of Patients

	Placebo	50U Botox	75U Botox
Total Number Enrolled	108	104	110
Study Completers	73 (68%)	83 (80%)	96 (87%)
Drop-Outs Due to Dissatisfaction	11 (10%)	0	1 (1%)

The reviewer's analyses and validations of the Sponsor's results will focus on the statistics involving the following classes of patients:

(1): **Responders** (Also denoted Trial Responders or Study Responders)

(2): **Initial Responders** (Also denoted WK#4 Responders): These are the patients who registered at least a two-point drop in HDSS at Week#4. Median Duration Times will be provided for this class of Responders.

(3): **G<50U Responders**: These are the patients who registered average gravimetrics<50U at Week#4

(4): **G<50% Responders**: These are the patients who registered more than a 50% reduction in average gravimetrics at Week#4

The three tables presented below, and the accompanying statistics, constitute the statistical analysis for Study#16. Table (3.1.2.3) below presents the tallies for patients who fall into the various categories determined by their disposition (Completers or Non-Completers), the number of Treatments (Injections) received, and their status as Initial Responders and/or Study Responders. Thus, for instance, for the 50U Botox group, there were 23 patients who completed the trial with one injection and were both Initial Responders and Study Responders.

Table(3.1.2.3)
Profile of Patient Responses

Category				Number of Patients		
Completer	Treatments	Initial Responder	Study Responder	Placebo	Low Dose	High Dose
Yes	One	No	No	11	11	11
Yes	One	Yes	No	0	11	15
Yes	One	Yes	Yes	2	23	20
Yes	Two	No	No	49	11	13
Yes	Two	Yes	No	7	3	11
Yes	Two	Yes	Yes	4	24	26
No	One	No	No	20	5	5
No	One	Yes	No	7	6	6
No	Two	No	No	7	3	1
No	Two	Yes	No	1	5	2
No	Two	Yes	Yes	0	2*	0
Totals				108	104	110

* Two patients – Patient#3161 and Patient#3228 – met the Responder criteria, but exited the trial shortly before 52 weeks, without an exit visit. They were classified as both Responders and Non-Completers. Each patient had two injections and reported an HDSS less than 3 at the WK#4 visit thereafter.

Remarks on the classification of patients as Responders both in the above table and in the statistical analyses provided below:

The reviewer assigned "worst outcome" values to all missing data. *This assignment reflects the statistics currently presented in the proposed Labeling.* A less conservative approach, with data restricted to Completers, raises the Responder rates slightly, but not enough to impact the statistics. For instance, in the table below, the "worst outcome" Responder Rates for Placebo, 50U Botox, and 75U Botox are 6%, 47% and 42% , respectively; the corresponding statistics for the Completer class (not included in Table(3.1.2.4), but derivable from Table(3.1.2.3)) are 8%, 56% , and 48% respectively.

Table(3.1.2.4)
Responder Rates

	Placebo (N=108)		Low Dose (N=104)		High Dose (N=110)		Low-Placebo 95% CI	High-Placebo 95% CI
	R	%	R	%	R	%		
WK#4 Grv <50% Responders	45	42%	85	82%	96	87%	(28% , 52%)	(34% , 56%)
WK#4 Grav<50mg Responders	31	29%	84	81%	92	84%	(40% , 64%)	(44% , 66%)
WK#4 Responders	21	19%	74	72%	80	72%	(41% , 65%)	(42% , 66%)
Study Responders	6	6%	49	47%	46	42%	(31% , 52%)	(26% , 47%)

Remarks:
(1): The Sponsor used Fisher's Exact Test to determine p-values for the test of the Null Hypothesis of Equality of Rates for Botox vs. Placebo for the Category of Study Responders. The reviewer verified the Sponsor's Fisher Test results for these comparisons, and then recalculated p-values for all four categories above using the approximately normal two sample statistic Z listed below. The results were the same as were obtained using Fisher's test.

$Z = (P_1 - P_2)/\sqrt{P(1-P)(1/N + 1/M)}$ where

P_1 = Dose Responder Rate; N = Dose Sample Size

P_2 = Placebo Responder Rate; M = Placebo Sample Size

$P = (N/(N+M))\ P_1 + (M/(N+M))\ P_2$

(2): The CI's were calculated as

$(P_1 - P_2)$ +/- $1.96\sqrt{S}$; $S = P_1(1-P_1)/N + P_2(1-P_2)/M$

The p – values for the Null Hypotheses of Equality of Responder Rates for Low Dose vs. Placebo and for High Dose vs. Placebo are less than .001 in all cases.

(3): The Worst Outcome statistics classified the following as Non Responders: Patients with a Response to the original dose who subsequently returned to HDSS ≥ 3, but who were ineligible for re-injection because of low gravimetrics.

(4): Note the 95% CI's for Low Dose – High Dose:

Original CI = (-.08 , .20) ; Worst Case CI = (-.08 , .19)

(5): A "Worst Case" assignment of Responder values would move 8 Placebo Non Responders over into the class of Responders; these patients were those who were Initial Responders, but subsequently dropped out. This reclassification would raise the Placebo Study Responder Rate from 6% to 13%. The "Worst Case" difference between Botox rates and Placebo rates would then be 29%, with a two-sided 95% CI for the difference of (18% , 40%).

Table(3.1.2.5) below presents Median Duration time statistics for patients who were WK# 4 HDSS Responders.

Table(3.1.2.5)
Duration Times for Week#4 Responders
Study Completers vs. All Patients (ITT)

	Study Completers			All Patients		
	Placebo	Low Dose	High Dose	Placebo	Low Dose	High Dose
Total N	73	83	96	108	104	110
Responder N	13(18%)	61(73%)	72(75%)	21 (19%)	74 (71%)	80 (73%)
Median Time	127 days	254 days	198 days	96 days	205 days	197 days
First And Third Quantiles	85 days to 199 days	141 days to 362 days	122 days to 350 days	71days to 169 days	141 days to 356 days	119 days to 321days

Remarks:

There were 252 Completers (Out of 322 ITT Patients). Of these, 156 were WK#4 Responders. Among the 242 ITT patients, 175 were WK#4 Responders. The First Dose Duration Times for the patients among the ITT group who did not drop out were the same as the First Duration Times for the Completers group, namely , the times until a return to an HDSS of 3 or 4 , or times until end of trial; the First Dose Duration Times for the patients among the ITT group who dropped out were time of drop-out. Thus, these times represent Worst Outcome Durations rather than censored survival times. This approach was chosen by the reviewer because there was little reason to believe that the censoring times were independent of treatment effects, and because the Responder Rate analyses were Worst Value analyses. The Sponsor's Survival Analysis Median Responder Times were 93 days, 203 days, and 198 days for Placebo, 50U Botox, and 75U Botox respectively, which agree closely with the ITT Worst Outcome analysis above. The proposed median times for Labeling are (b) (4) for Placebo, 50U Botox, and 75U Botox respectively, since the Agency preferred to set the onset of a bad HDSS at, on the average, 30 days prior to the official recording in order to account for the time lag between an informal communication of a change in HDSS and an official (office visit) recording.

Remarks on Subset Analyses:
Subset analyses have not been a significant element in this review since a perusal of the standard subset analyses – age , gender, etc - did not reveal any significant trends. However, it could be of some interest that the WK#4 HDSS Responder Rate did show signs of a trend, namely that patients with Baseline HDSS = 4 had a statistically significant higher WK#4 Responder Rate than did patients with Baseline HDSS=3. This trend did not carry over to the category of Study Responders.

3.1.3 Detailed Description of the Protocol for Study#505.

Title of Study: A Muticenter, Double-Blind, Randomized, Vehicle-Controlled , Parallel Group Study of the Safety and Efficacy of Botox Purified Neurotoxin Complex for the Treatment of Bilateral Primary Axillary Hyperhidrosis.

Study#505 was a European study which enrolled 320 patients, all of whom were included in the ITT analysis for Efficacy; 242 were assigned to the Botox arm, 78 to the placebo arm. The key inclusion criteria were persistent bilateral axillary hyperhidrosis as judged by the investigator, a history of sweat production that interfered with the daily activities of the subject, and a screening gravimetric measurement of at least 50 mg of spontaneous sweat production in each axilla.

The protocol consisted of six post-screening visits over a 17 week period. The first visit was dedicated to a baseline gravimetric read and a Botox treatment of 50U per axilla; at all the subsequent visits (at weeks 1, 4, 8, 12 and 16) gravimetric measurements were taken for the comparison of patient response to the baseline read. A patient was defined to be a *Responder* at any scheduled visit if he/she registered at least a 50% reduction over baseline in gravimetic read during that visit; otherwise, the patient was considered a *Non-Responder* for that visit. The gravimetric value used for all comparisons was the average value over the two axilla. A patient was defined to be a *Primary Endpoint Responder* if he/she was a Responder at Week#4. In the

interest of simplification in this review, a *Primary Endpoint Responder* will be denoted as a *Wk#4 Responders.* The Sponsor further defined patients to be *Persistent Responders* if they were Responders at Week#4 and were not Non-Responders for any two consecutive scheduled visits thereafter This definition will be modified to reflect the somewhat more stringent criteria used in this review; details are presented below.

Primary and Secondary Endpoints:

One Primary Efficacy variable and three Secondary Efficacy variables are analyzed in this review. The Primary Efficacy variable is the percentage of Wk#4 Responders. The Secondary Efficacy variables are:

(a): Percentage of Persistent Responders

(b): Percentage of Patients whose Wk#4 gravimetric $\leq$ 50mg

(c): Percentage of Patients whose gravimetrics $\leq$ 50mg throughout the trial

3.1.4 Detailed Results for Study#505

Gravimetric Value Assignments for Missing Data: The ITT analyses required specification of responder status for patients with missing gravimetric reads at the various scheduled visits. The Sponsor's approach was to impute median gravimetric values for the missing values, where the median gravimetric was calculated over the population of compliant patients for the scheduled visit. The Agency proposed a "worst case" imputation as a substitute at Wk#4. The Reviewer has taken the following approach: If a gravimetric read is missing at Wk#4, or at Wk#16, the imputed value will be the baseline gravimetric. If a gravimetric read is missing at Wk#8 or Wk#12, and if it is flanked by gravimetric reads from compliant visits, then the gravimetric assigned will be the larger of these two reads. Otherwise the assigned value is the baseline value. This assignment preserves the Agency's proposed "worst case" imputation at Wk#4, and otherwise imposes a "worst case" read except for circumstances where a patient misses a visit between two compliant visits; in this circumstance the patient is not penalized with an imputed value any worse than the larger of the achieved flanking values.

Analyses by the Reviewer revealed that, for the several methods of value imputation described above, and, additionally, for analyses restricted to the per-protocol reduction of the sample to patients with no missing values, all of the primary and secondary endpoint statistics presented only negligible differences from one another.

The first two tables below present the essential information on patient demographics and patient disposition.

Table(3.1.4.1)
Demographics

		Placebo (N=78)	50U Botox (N=242)
Age (Years)	Mean	31 yrs	32 yrs
Age Category	<40	67 (86%)	187 (77%)
Gender	Male	35 (45%)	113 (47%)
	Female	43 (55%)	129 (53%)
Race	Caucasian	77 (99%)	237 (98%)

Table(3.1.4.2)
Patient Disposition

	Placebo (N=78)	50U Botox (N=242
Completed	73 (94%)	234 (97%)
Total Discontinued	5 (6%)	8 (3%)
Discontinued for adverse event	0	1
Discontinued for other reasons	5	7

The two tables presented below provide the essential results for this Study. Table(3.1.4.3) lists the response rate statistics for the aforementioned Efficacy variables; Tables (3.1.4.4) lists these statistics over two strata of Baseline Gravimetrics.

Table(3.1.4.3)
WK#4 Responder Rates & Persistent Responder Rates

Category	Placebo Rate & 95% CI (N=78)	Treatment Rate & 95% CI (N =242)	Trt – Placebo (95% CI)
WK#4 Responders (G decrease> 50%)	.36 (.25 , .47)	.91 (.87 , .95)	.55 (.44 , .66)
WK#4 Responders (G <50mg)	.19 (.10 , .28)	.81 (.76 , .86)	.62 (.52 , .72)
Persistent Responders (G decrease>50%)	.10 (.03 , .17)	.69 (.63 , .75)	.59 (.50 , .68)
Persistent Responders (G <50mg)	.04 (0.0 , .08)	. 51 (.45 , .57)	.47 (.39 , .55)

Table(3.1.4.4)
Responder Rates Stratified by Baseline Gravimetric

PLACEBO						TREATMENT				
Stratum	N	WK4 RSP	WK4 G<50	Trial RSP	Trial G<50	N	WK4 RSP	WK4 G<50	Trial RSP	Trial* G<50
G<160	38	29%	29%	11%	5%	122	89%	89%	62%	66%
G>=160	40	43%	10%	10%	3%	120	92%	73%	77%	36%

Remarks:
All tests of Null Hypotheses of Equality of Responder Rates between Botox Groups and Placebo Groups yield p-values < .001 (using either Fisher's Exact Test or normal approximations.)

** The Test of the Null Hypothesis of Equality of Persistent Responder Rates between the Low Stratum 50U Botox Group and the High Stratum 50U Botox Group (66% vs. 36%) also yields a p-value <.001 when Persistent Response is defined as a gravimetric measure<50mg throughout the trial.*

The normal approximation test statistic used is described below.

(2): The Null Hypothesis of Equality of Rates in all categories above was tested using the approximately normal two sample statistic:

$$Z = (P_1 - P_2)/\sqrt{P(1-P)(1/N + 1/M)}$$

where

P_1 = Dose Responder Rate ; N = Dose Sample Size

P_2 = Placebo Responder Rate ; M = Placebo Sample Size

$P = (N/(N+M))\,P_1 + (M/(N+M))\,P_2$

(2): The CI's were calculated as

$$(P_1 - P_2) \text{ +/- } 1.96\sqrt{S} \quad ; \quad S = P_1(1-P_1)/N + P_2(1-P_2)/M$$

3.2 Evaluation of Safety

There were no significant Safety issues. See medical review.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race and Age

4.1.1 Study#16

The three tables directly below present Responder Rates by Gender, Age , and Race respectively. There is no strong evidence of significant statistical trends.

Table(4.1.1.1)
Responder Rates by Gender

	Placebo		50U Botox		75U Botox	
	N	% of Responders	N	% of Responders	N	% of Responders
Male	57	7% (4/57)	57	47% (27/57)	60	43% (26/60)
Female	51	4% (2/51)	47	64% (30/47)	50	56% (28/50)

Table(4.1.1.2)
Responder Rates by Age

	Placebo		50U Botox		75U Botox	
	N	% of Responders	N	% of Responders	N	% of Responders
<40	84	4% (3/84)	78	55% (43/78)	79	53% (42/79)
≥40	24	13% (3/24)	26	54% (14/26)	31	39% (12/31)

Table(4.1.1.3)
Responder Rates by Race

	Placebo		50U Botox		75U Botox	
	N	% of Responders	N	% of Responders	N	% of Responders
Caucasian	89	7% (6/89)	87	56% (49/87)	86	51% (44/86)
Non-Caucasian	19	0% (0/19)	17	47% (8/17)	24	42% (10/24)

4.1.2 Study#505

The two tables directly below present Responder Rates by Gender and Age. Non-Caucasian subjects were underrepresented (six subjects), so no statistics are provided. There is no evidence of significant statistical trends.

Table(4.1.2.1)
Responder Rates by Gender

	Placebo		50U Botox	
	N	% Responders	N	% Responders
Male	35	40% (14/35)	113	88% (99/113)
Female	43	33% (14/43)	129	93% (120/129)

Table(4.1.2.2)
Responder Rates by Age

	Placebo		50U Botox	
	N	% Responders	N	% Responders
≤35	54	37% (20/54))	170	89% (151/170)
>35	24	33% (8/24)	72	94% (68/72)

4.2 Other Special/Subgroup Populations

None.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

No significant statistical issues.

5.2 Conclusions and Recommendations

Efficacy:
The Sponsor provided two randomized, placebo controlled, parallel group studies for the evaluation of Botox Injection for the treatment of Primary Bilateral Axillary Hyperhidrosis. Study#505 compared Botox to Placebo for the endpoint of significant reduction in axillary sweating as measured by gravimetric assessment; Study#16 compared Botox to Placebo for the endpoint of patient assessment of significant reduction in perceived hyperhidrosis severity.

Study#505 and Study#16 each clearly demonstrated the Efficacy of Botox for the treatment of Primary Bilateral Axillary Hyperhidrosis.

For the primary efficacy variable of Responder Rate in Study#505, the 50U Botox group achieved a 91% Responder rate, while the Placebo group scored a 36% Responder rate. The p-value for this difference under the hypothesis of equality of rates was less than .001.

For the primary efficacy variable of Responder Rate in Study#16, the Placebo group, 50U Botox group, and 75U Botox group had rates 6%, 47%, and 42%, respectively. The p-values for the two pair-wise comparisons, 75U Botox vs. Placebo and 50U Botox vs. Placebo, were each less than .001 under the hypothesis of equality of rates.

Safety:
Study#505 and Study#16 revealed no significant Safety problems. (See Medical Review.)

The efficacy results from the two Phase III trials support the new claim of using Botox axillary injections for the treatment of primary bilateral axillary hyperhidrosis.

SIGNATURES/DISTRIBUTION LIST

A G Mucci

6/15/04

A G Mucci , Ph.D.
Primary Statistical Reviewer

Date

Concur:

Bog Zhen

6/15/04

Boguang Zhen, Ph.D.
Team Leader, BTSS

Date

Alaka Chakravarty

6/15/04

Aloka Chakravarty, Ph.D.
BTSS Director

Date

cc:
HFM-585/Mr. James Reese
HFM-576/Dr. Libero Marzella
HFM-711/Dr. Boguang Zhen
HFM- 711 /Dr. Aloka Chakravarty
HFD-710/Dr. Satya Dubey
HFD-700/Dr. Chuck Anello
HFD- 711 /Chron
HFM-99/DCC

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 103000/S-5050

OTHER REVIEW(S)

Review Memorandum Addendum

Therapeutics Facilities Review Branch, HFD-328

Division of Manufacturing and Product Quality, Office of Compliance
Center for Drug Evaluation and Research, Food and Drug Administration

Date: Initial: June 3, 2004
Final: June 14, 2004

To: James Reese, OND/ODEVI/DRMP, HFM-585
Libero Marzella, Chairperson, OND/ODEVI/DTBIMP, HFD-582

From: Jianming Li, OC/DMPQ/TFRB, HFD-328 JL 6/25/04

Through: Michael D. Smedley (Branch Chief), OC/DMPQ/TFRB, HFD-328 6/25/04

Applicant: Allergan, Inc.

Application: BLA Supplement, STN 103000/5050 (b) (4)

Product: BOTOX (Botulinum toxin type A)

Subject: This BLA supplement seeks an approval of BOTOX for a new indication.

Recommendation: An approval letter should be issued to the sponsor.

Background: The original compliance check on April 29, 2004 found that the GMP status of the facility was unacceptable based on the facility inspection conducted on March 1-11, 2004. Thus, a complete review (CR) letter was issued to the sponsor on May 6, 2004. After reviewing the sponsor's written response to the FDA-483, Office of Compliance, CDER, FDA concluded on May 11, 2004, that Allergan's facility at Westport, Ireland was acceptable for the manufacturing of BOTOX®.

GMP Status: Based on the review of Allergan's response dated April 15, 2004 to the facility inspection, Office of Compliance determined that Allergan's facility at Westport, Ireland is acceptable. Since deficient GMP status was the single reason for disapproval of the original application, we recommend approval of the amended application.

Conclusion: Based on the current status of compliance, we recommend approval of this

application

Revision history
Comment: Michael Smedley on 6/8/04
Revised: 6/14/04

cc:
HFD-328: Smedley
HFD-320: Hoyt (Westport, Mayo County, Ireland)
HFD-328: Blue Files (STN103000/5050)
HFD-328: Facility Files (Westport, Mayo County, Ireland)

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

OFFICE OF NEW DRUGS

OFFICE OF DRUG EVALUATION VI

DIVISION OF REVIEW MANAGEMENT AND POLICY

Woodmont Office Complex, 380N
1401 Rockville Pike
Rockville, Maryland 20852-1448
FAX # (301)827-5397

FACSIMILE TRANSMISSION RECORD

TOTAL NUMBER OF PAGES: 2 **(Including Cover Page)**

FAX TO: Adelbert Stagg. Ph.D. / Allergan

Facsimile Telephone No. 714-246-4272 **Voice Telephone No.** 714-246-6931

FROM: James H. Reese, Ph.D.

Facsimile Telephone No. 301-827-5397 **Voice Telephone No.** 301-827-4358

DATE: 6/2/04 **TIME:**

MESSAGE: Proposed label changes (hologram) 103000/5050

Label Proposal 6/2/04
103000/5050

Allergan Wording:

(b) (4)

(FDA Proposal)

Vials of Botox have a holographic film on the vial label that contains the name "Allergan" within horizontal lines of rainbow color. In order to see the hologram, rotate the vial back and forth between your fingers under a desk lamp or fluorescent light source. (Note: the holographic film on the label is absent in the date/batch area.) If you do not see the lines of rainbow color or the name "Allergan", do not use the product and contact Allergan for additional information at (800) 890-4345 from 8:00 a.m. to 4:00 p.m. Pacific time.

Review Memorandum

Therapeutics Facilities Review Branch, HFD-328

Division of Manufacturing and Product Quality, Office of Compliance
Center for Drug Evaluation and Research, Food and Drug Administration

Date: Initial: April 1, 2004
Final: April 29, 2004

To: James Reese, OND/ODEVI/DRMP, HFM-585
Libero Marzella, Chairperson, OND/ODEVI/DTBIMP, HFD-582

From: Jianming Li, OC/DMPQ/TFRB, HFD-328 JLi 5/6/04

Through: Michael D. Smedley (Branch Chief), OC/DMPQ/TFRB, HFD-328 5/6/04

Applicant: Allergan, Inc.

Application: Biologic License Application (BLA) Supplement, STN 103000/5050

Product: BOTOX (Botulinum toxin type A)

Subject: This BLA supplement seeks an approval of BOTOX for a new indication. A review of categorical exclusion and compliance check are needed

Action Due Date: May 9, 2004

Sections Reviewed: Item 20, Environmental Assessment

Recommendation: A complete review letter should be issued to the sponsor based on outstanding inspectional issues. The sponsor should correct the deficiencies that are cited on the Form FDA 483 issued to the sponsor before FDA issues an approval.

Summary: This supplement requests the Agency approval of the existing BOTOX product for a new clinical indication, primary axillary hyperhidrosis. A compliance check reveals a series of GMP violations at the Westport, Ireland site. These violations have direct impact on the quality of the product. The sponsor should correct these violations before the Agency issues an approval letter.

The claim of categorical exclusion from the requirement of submission of

an environmental assessment (EA) is justified.

Background

BOTOX (Botulinum toxin type A), manufactured by Allergan, is an approved product by FDA and is currently marketed in the United States and other countries for cervical dystonia, blepharospasm, strabismus, and glabellar lines. This supplement requests the Agency approval of the existing BOTOX product for a new clinical indication, primary axillary hyperhidrosis.

The two sites that are used for the manufacturing of BOTOX are:

Establishment Location	**Function**
Allergan Bioscience Laboratories 506-E Vandell Way Campbell, CA 95008-6967	Manufacture of bulk toxin. Quality control release/stability. Labeling for bulk toxin
Allergan Pharmaceutics (Ireland) Ltd Castlebar Rd Westport, County Mayo, Ireland	Manufacture of finished product, Quality control release/stability. Labeling

This review memo will evaluate the request of categorical exclusion from the requirement of submission of an EA and determine the compliance status of the sponsor through a compliance check.

Part I: Categorical exclusion

In the Environmental Assessment section of this application (Item 20), Allergan, Inc. claims, as specified in 21 CFR 25.15(d), that this BLA Supplement qualifies for a categorical exclusion from the requirement of submission of an EA. The proposed action does not alter significantly the concentration or distribution of the substance, its metabolites, or degradation products in the environment. Additionally, Allergan states that no extraordinary circumstances exist that would significantly affect the quality of the human environment as a result of the proposed action. We reviewed the pertinent section and found the applicant's request is justified under 21 CFR 25.31(c) and the FDA guidelines provided in Section III.B. of Guidance for Industry—Environmental Assessment of Human Drug and Biologics Applications (Revision 1, July 1998).

Part II: Compliance check

Allergan uses two sites to produce Botulinum toxin type A. The Campbell, CA site makes bulk toxin, while the site at Westport, County Mayo, Ireland produces the finished product. A compliance check is conducted by the Investigations and Preapproval Compliance Branch, Office of Compliance, Center for Drug Evaluation and Research to determine the compliance status of the manufacturing sites. The results show that there is

a pending compliance action against the company as a result of a recent Team Biologics inspection conducted at the site of Westport, County Mayo, Ireland. This inspection is classified as OAI.

The inspection was conducted in early March 2004 at the Westport, County Mayo, Ireland, facility, used to produce finished product. In this inspection, Team Biologics cited 16 observations and the results are shown in the attached Form FDA 483. According to the compliance check, significant violations were noted during the inspection and the firm's responses to the observations have been deemed inadequate by the Team Biologics investigator. For specific observations that have direct product impact, see attached email from Colleen Hoyt, Investigations and Preapproval Compliance Branch, CDER/OC/DMPQ.

Conclusion:

I. Based on the inspectional observations and the pending enforcement action, we recommend withholding approval of this STN and sending a CR letter to Allergan Inc. The violations need to be corrected before the approval of this application.

II. This review covers only the "Environmental Assessment" section. Other parts of this application are deferred to product review divisions

III. During next inspection of Allergan Inc. in Westport, County Mayo, Ireland, the inspector should verify that the observations cited in the Form FDA 483 have been corrected.

Revision history
Comments: Renshaw on 4/29/04; Smedley on 5/4/04
Revised: Li on 4/29/04, 5/4/04

cc:
HFD-328: Renshaw
HFD-328: Smedley
HFD-320: Hoyt (Westport, Mayo County, Ireland)
HFD-328: Blue Files (STN103000/5050)
HFD-328: Facility Files (Westport, Mayo County, Ireland)

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: April 20, 2004

TO: James Reese, Ph.D., Regulatory Project Manager
Louis Marzella, M.D., Medical Team Leader, Chair & Clinical Reviewer
Elizabeth Sutkowski, Ph.D., Clinical Reviewer
Immunology and Infectious Disease Branch
Division of Internal Medicine Branch, HFM-570

THROUGH: Leslie Ball, M.D., Branch Chief, Good Clinical Practice Branch II (HFD-47)
Division of Scientific Investigations

FROM: J. Lloyd Johnson, Pharm.D., Good Clinical Practice Branch II (HFD-47)
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

BLA: STN 103000/5050

APPLICANT: Allergan, Inc.

DRUG: Botox® (Botulinum Toxin Type A)

CHEMICAL CLASSIFICATION: Type 6

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATION: Treatment of Primary Axillary Hyperhidrosis

CONSULTATION REQUEST DATE: September 23, 2003

GOAL DATE TO PROVIDE CLINICAL INSPECTION SUMMARY: April 23, 2004

ACTION GOAL DATE: May 9, 2004

I. BACKGROUND

Botox® (Botulinum Toxin Type A) is a commercially available purified Neurotoxin Complex product licensed for cervical dystonia, strabismus, and blepharospasm associated with dystonia. Allergan, Inc. submitted a Biologic License Application supplement (sBLA) and is now seeking an expanded indication to treat primary axillary hyperhidrosis (excessive perspiration) that interferes with daily activities.

Botox® is produced by fermentation of *Clostridium Botulinum* Type A, purified from cell culture solution and precipitated to a complex of neurotoxin and several accessory proteins. Each vial of Botox® contains 100 units (U) of *Clostridium Botulinum* Type A neurotoxin complex, 0.5 milligrams of Albumin (Human), and 0.9 milligrams of sodium chloride in sterile, vacuum-dried form with no preservative. The sponsor submitted data from several

controlled studies to demonstrate safety and efficacy for the expanded indication. Data from two pivotal, randomized, double blind, placebo-controlled, multi-centered, Phase III studies (Study 191622-016 and 191622-505) were submitted in support of efficacy. The primary focus of the clinical investigator inspections was Study 191622-016.

II. RESULTS (by site):

NAME	CITY, STATE	COUNTRY	PROTOCOL	INSPECTN DATE	EIR-REC'VD	CLASSN.
Howard Donsky, M.D.	Rochester, NY	USA	*191622-016*	Oct. 30 – Nov. 5, 2003	Dec. 1, 2004	VAI
Alastair Carruthers, M.D.	Vancouver	Canada	*191622-016*	December 8 -12, 2004	Jan. 23, 2004	NAI
Leslie Bauman, M.D.	Miami, FL	USA	*191622-016*	Sept. 19-25, 2002	Oct. 30, 2002	NAI
William Coleman, M.D.	Metairie, LA	USA	*191622-016*	July 30 – Aug.. 7, 2002	Oct. 3, 2002	NAI
William Werschler, M.D.	Spokane, WA	USA	*191622-016*	Nov. 13-19, 2002	Dec. 17, 2002	NAI

Key to Classifications
NAI = No deviation from regulations. Data acceptable
VAI = Minor deviations(s) from regulations. Data acceptable
VAIr= Deviation(s) form regulations, response requested. Data acceptable
OAI = Significant deviations for regulations. Data unreliable
Pending = Inspection/Report not completed

Study Protocol:

Protocol 191622-016: A Multicenter, Double–Blind, Randomized, Placebo-Controlled, Parallel Study Of The Safety and Efficacy of Repeated Treatment With One of Two Dosage Of Botox® (Botulinum Toxin Type A) Purified Neurotoxin Complex For The Treatment of Primary Axillary Hyperhidrosis.

The inspection audited Study Protocol 191622-016. This study compared a single treatment of Botox® 50 U versus placebo in the treatment of primary axillary hyperhidrosis over a period of 16 weeks. Protocol 191622-016 is a multicentered, double-blind, randomized, placebo-controlled, parallel group study in subjects with primary axillary hyperhidrois. Subjects were randomized to treatment with either placebo, 50 U, or 75 U Botox® (ratio of 1:1:1) at the first treatment session. Subjects received 10 – 15 intradermal injections of study medication into each axilla during each treatment session. Each subject received up to 6 treatment sessions, depending upon the response to treatment and duration of response. Randomization was stratified by study center and by the study baseline (day 0) Hyperhidrosis Disease Severity Scale (HDSS) score. Visit schedule included screening, office visit on day 0 (initial treatment), telephone assessment on day 7, office visit at week 4, alternating office visits and telephone assessments every 4 weeks until re-treatment. Following re-treatment, subjects followed the same visiting schedule.

Subjects were followed for up to 52 weeks after their initial treatment session, and up to 8 weeks after their final study treatment. A total of 322 subjects were enrolled with 110 randomized to Botox® 75 U, 104 to Botox® 50, and 108 to placebo. Eligible subjects are 18 – 75 years old, with persistent bilateral primary axillary hyperhidrosis as measured by HDSS score of 3 or 4, and baseline gravimetric measurement of spontaneous resting sweat production of ≥ 50mg in each axilla measured over 5 minutes at room temperature.

The primary efficacy variable is the subject's assessment of hyperhidrosis severity using a 4-point Hyperhidrosis Disease Severity Scale (HDSS). Secondary efficacy variables includes gravimetric measurements of spontaneous resting axillary sweat production at room temperature over 5 minutes, Subject Daily Diary (SDD), Minor's Iodine-Starch Test with photodocumentation, Hyperhidrosis Impact Questionnaire (HHIQ), and Dermatology Life Quality Index (DLQI).

Safety assessments include adverse events, laboratory tests (hematology and blood chemistry), physical examination, vital signs, and serum test for neutralizing antibodies to Botulinum Toxin Type A.

The inspections audited five clinical investigators. The inspections were conducted under the Bioresearch Monitoring Program (CP 7348.811). Three of the clinical investigator inspections were performed under CBER's Surveillance Inspections Program to determine compliance with current regulations under the BIMO program and the remaining two clinical investigator audits were issued by CDER's DSI in consultation with the BLA Review Committee.

Basis for site selection: The following sites were selected for inspection because of their high enrollment, geographic location and response rates.

(1) **Howard Donsky, M.D. (Site 3167) (Number enrolled: 28 subjects) (FACTS # 464732)**
Dermatology & Cosmetic Center of Rochester
1338 East Ridge Road
Rochester, New York 14621 USA
Inspection dates: October 10 - November 5, 2003.

Methodology: Inspection assignments were issued to the field office.

a. What was inspected?
28 subjects were enrolled, one dropped out. The field investigator reviewed nine study subject records during the inspection.

b. Limitations of inspection: None

c. General observations/commentary:

Two deficiencies were noted on the FDA 483. The inspection revealed that Minor's Iodine Starch Test photo identifier for the left and right axillae for Subject 3110 were incorrectly labeled as Subject 3069 (FDA 483, Item 1). The inspection also disclosed that the investigator did not provide a final report to the sponsor in a timely manner as required by the protocol (FDA 483, Item 2). In response to this observation, Allergan was contacted and indicated to the clinical investigator during the inspection that a summary report was not required since Allergan conducted a close-out monitoring visit on 3/13-14/03. The 483 observations and other minor observations were discussed at the end of the inspection. The clinical investigator promised corrective action in future studies.

All 28 subjects had informed consent forms on file. Subject records were legible and neatly organized. Source records, laboratory records and exam records (gravimeteric exams and Minor's Iodine Starch Test photography were reviewed and compared with the CRFs. The records were found complete with medical history data, and test article treatment observations, results of lab tests, completed Hyperhidrosis Impact Questionnaires, completed Dermatology Life Quality Index Questionnaires, and completed Subject Daily Diaries. Adequate documentation was found indicating subjects did exist and were available during their stated participation in the study. Review of source records indicated that adverse events, concomitant meds, and required study procedures were reported accurately in the CRFs. No unreported adverse events were noted and no deviations were noted with respect to the data listing/efficacy endpoints.

Recommendation: Data from this site are acceptable.

(2) **Alastair Carruthers M.D. (Site 1901) (Number enrolled: 16 subjects)**
Carruthers Dermatology Center, Inc
943 West Broadway, Suite 630
Vancouver, British Columbia V5Z
4E1
Canada

Inspection Dates: December 8 - 12, 2003.

Methodology: Inspection assignments were issued to the field office.

a. What was inspected?

16 subjects were randomized and 15 subjects completed the study. Complete study records for five of enrolled subjects were audited. Source document data were compared with the sponsor's data listings.

b. Limitations of inspection: None.

c. General observations/commentary:

In general, Allergan's data listings were found to accurately reflect the study specific source documents and CRFs. Review of subject records disclosed that one subject receiving one late injection. Some study subjects were found to have completed the Subject Daily Diaries (SDDs) and Dermatology Life Quality Indices (DLQIs) prior to the IRB approval of one of the study protocols. The use of DLQIs prior to IRB approval was reported to the IRB but not the use SDDs. Other minor deviations found were reported in the Allegan's protocol Deviations/Violations listing. Overall, study records were found to be legible, well organized, and contain adequate information.

AEs were accurately reported on the CRFs. Allergan's data listing were found to be an accurate reflection of the study-specific source documents and CRFs. Drug accountability records were adequately documented and all informed consents were found to be complete.

No FDA 483 was issued.

Recommendation: Data from this site are acceptable.

(3) Leslie Bauman, M.D. (Site 3166) (Number enrolled: 34 subjects) (FACTS # 319869)

2195 NW 14th Street,
South Building, Suite K
Miami, FL 33125

Inspection Dates: Sept. 19 - 25, 2002.

Methodology: Inspection assignments were issued to the field office.

a. What was inspected?

The inspection covered the study protocol, IRB submissions and approvals, subject selection criteria, informed consent, test article control, source data, case report evaluation, sponsor monitoring activities, and source data of laboratory reports. There were no deficiencies found during the review of those aspects of the study and no deficiencies were noted during the review of adverse events and concomitant therapy. No deviations were found during the review of the test article records and storage conditions. 34 subjects were enrolled, six dropped out of the study (four subjects were lost to follow-up and two dropped out due to personal reasons).

b. Limitations of inspection: None. The audit was performed during CBER's routine surveillance inspections to determine compliance with current regulations under the BIMO program.

c. General observations/commentary:

This is the initial inspection of Dr. Baumann. The site was monitored by the sponsor every four to six weeks during the course of the study. The inspection revealed no deviations from the clinical investigator bioresearch monitoring regulations. No significant issues were identified.

No FDA Form 483 was issued.

Recommendation: Data from site are acceptable.

(4) William Coleman III, M.D. (Site 3157) (Number enrolled: 27 subjects) (FACTS # 319880)
4425 Conlin St
Metairie, LA 70006
Inspection Dates: July 30 – Aug. 7, 2002

Methodology: Inspection assignments were issued to the field office.

a. What was inspected?

27 subjects were enrolled, five of these subjects dropped due to " lost to follow-up", and unwillingness to follow protocol mandated office/telephone visit schedules or the subject moved. Complete study records of four subjects enrolled were audited. Data recorded in case report forms were compared with on site source document records.

b. Limitations of the Inspection: None. The audit was performed during CBER's routine surveillance inspections to determine compliance with current regulations under the BIMO program.

c. General observations/commentary:

The inspection did not disclose any significant deviations from FDA regulations or other objectionable conditions. All subject records audited had signed consent forms on file. All subjects enrolled were found to be eligible, protocol parameters including scheduled office visits, telephone interviews, assessments, and test article administration was sufficiently followed. Drug accountability records were found to be sufficiently complete and test article usage, storage and controls were properly maintained. The only minor deviation discussed with Dr. Coleman involved approximately 5 subjects that had office visit/telephone interviews that occurred outside of the protocol-mandated scheduling window. During the inspection close out discussion, Dr. Coleman made assurances that in future studies all office visits and telephone interviews will occur within the scheduling window as specified in the protocol.

No FDA 483 was issued at the conclusion of the inspection.

Recommendation: Data from this site are acceptable.

(5) William P. Werschler, M.D. (Site 2941) (Number enrolled: 13 subjects) (FACTS # 320066)
Spokane Dermatology Clinic
104 West Fith, Suite 330
Spokane, WA 99204

Inspection Dates: Nov. 11 - 19, 2002.

Methodology: Inspection assignments were issued to the field office.

a. What was inspected?

20 subjects were originally screened, a mis-randomization problem occurred at the beginning of the study and enrollment was subsequently suspended by the sponsor. 13 subjects were enrolled when the study resumed, 11 subjects completed the study, 2 dropped out due to pain on injection sites. The complete records of five subjects were audited. The study closed on 11/12/02

b. Limitations of inspection: None. The audit was performed during CBER's routine surveillance inspections to determine compliance with current regulations under the BIMO program

c. General observations/commentary:

All subjects participating signed informed consents. Data in the case report forms, source document records, and lab report testing data were compared and verified. The sponsor conducted monitoring visits on a regular basis during the conduct of the study. Drug accountability records were found to be complete and in good order. At the end of the inspection, some minor discrepancies were discussed with the

investigator concerning the retrospective conversion of standard time to military time in recording time of gravimetric measurements, drug reconstitution time and times of injection. Study personnel attempted later in some instances to convert times recorded in standard time to military time. In one subject, the number of injections recorded was changed three weeks later without supportive documentation. Dr. Werschler stated that corrective action and procedures were instituted to avoid these types of data errors in future studies. The issue of documenting changes to the CRFs was also discussed at the conclusion of the inspection.

No Form FDA 483 was issued.

Recommendation: Data from site are acceptable.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

In general, for the sites inspected, there was sufficient documentation to assure that all study subjects audited did exist, study eligibility criteria were fulfilled, participants received assigned study medications, adverse events were adequately reported. Primary endpoints and secondary endpoints were captured in accordance with protocol requirements. The data submitted in support of this BLA appear acceptable.

Follow-up action: none

J. Lloyd Johnson, Pharm.D.,
Good Clinical Practice Branch II, HFD-47
Division of Scientific Investigations

CONCURRENCE:

Supervisory comments:

Leslie Ball, M.D.
Branch Chief, Good Clinical Practice Branch II, HFD-47
Division of Scientific Investigations

DISTRIBUTION:
HFM-99: BLA: STN 103000/5050
HFM-99: BB-IND 9006
HFM-582: MO (Louis Marzella, M.D., Chair, STN 103000/5050)
HFM-481/Elizabeth Sutkowski, Ph.D.
HFM-589: RPM (James H. Reese, Ph.D.)
HFD-47/Johnson
HFD-45/Division File
HFD-45/Reading File
HFD-45/Program Management Staff (electronic copy)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 103000/S-5050

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

BLA/NDA/PMA
Review Committee Assignment Memorandum

☐ Initial Assignment
■ Change

STN: 103000/5050

Applicant: Allergan, Incorporated

Product: Botulinum Toxin Type A

Addition of committee members

Name	Reviewer Type*	Job Type	Assigned by	Date
	Reg. Coordinator	Admin/Regulatory		
		Admin/Regulatory		
	Reviewer	Product		
		Product		
		Product		
	Chairperson	Clinical		
Elizabeth Sutkowski	Reviewer	Clinical	Louis Marzella	8/13/03
		Clinical Pharmacology		
		Pharm/Tox		
	Reviewer	Biostatistics		
	Reviewer	BiMo		
		Epidemiology		
		Facility		
		Inspector		
Catherine Miller	Reviewer	Labeling	Marci Kiester	6/9/04
		Other		

Deletion of Committee Member

Name	Reviewer Type*	Job Type	Changed by	Date
Eva Barrion	Reviewer	Labeling	Marci Kiester	6/9/04

***reviewer types**: chairperson, consultant reviewer, regulatory coordinator, reviewer, and reg. project mgr (RPM)

Submitted by RPM:

James Reese
Name Printed

James Reese
Signature

6/9/04
Date

Memo entered in RMS by: _____ Date: _____ QC by: LB Date: 8/11/04

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20852

Our STN: BL 103000/5050

JUN 10 2004

Allergan, Incorporated
Attention: Adelbert L. Stagg, Ph.D.
Senior Director, Worldwide Regulatory Affairs
2525 Dupont Drive
Irvine, CA 92623-9534

Dear Dr. Stagg:

We have received your May 28, 2004, resubmission to your supplement to your biologics license application for BOTOX® on June 1, 2004.

The resubmission contains compliance information that you submitted in response to our May 6, 2004, complete response letter.

We consider this a complete, class 1 response to our action letter. Therefore, the user fee goal date is August 1, 2004.

The regulatory responsibility for review and continuing oversight for this product transferred from the Center for Biologics Evaluation and Research to the Center for Drug Evaluation and Research effective June 30, 2003. For further information about the transfer, please see http://www.fda.gov/cder/biologics/default.htm. Until further notice, however, all correspondence should continue to be addressed to:

CBER Document Control Center
Attn: Office of Therapeutics Research and Review
Suite 200N (HFM-99)
1401 Rockville Pike
Rockville, Maryland 20852-1448

If you have any questions, please contact the Regulatory Project Manager, James H. Reese, Ph.D., at (301) 827-4358.

Sincerely,

Earl S. Dye, Ph.D.
Director
Division of Review Management and Policy
Office of Drug Evaluation VI
Center for Drug Evaluation and Research

CONCURRENCE PAGE

Letter Type: Resubmission Acknowledgment Letter (RAC)
Summary Text: [Class 1 Resubmission]

SS & RIS Data Check:
- **Communication**
- **Milestone: Receipt Date In Ltr. & Milestone (Response To CR) Should Match**

RIS Data Check:
- **Confirm New Action Due Date**

cc: Division BLA Files
HFM-582\L. Marzella
HFD-42\Catherine Miller
HFD-46\J. L. Johnson
HFD-42\M. Kiester
HFM-558\E. Guan
HFM-599\Jianming Li
HFD-715\A. Mucci
HFM-589\J. Reese

History: J. Reese 6/9/04, 6/10/04: K. Townsend: 6.9.2004

File Name: S:Reese\BLA\Current BLAs\103000\5050\Resubmission Acknowledgement Letter

Division	Name/Signature	Date
DRMP	J. Reese	6/10/04
DRMP	Schneider	6-10-04
DRMP	Dep	6-10-04
DRMP	Kelly Townsend	6-14-04

Reese, James

From: Rivera Martinez, Edwin
Sent: Friday, May 14, 2004 9:50 AM
To: Jones, Glen D (CDER/ODEVI); Schneider, Kay; Reese, James
Cc: Walton, Marc; Marzella, Libero; Smedley, Michael; Hoyt, Colleen; Charity, Anthony; Li, Jianming
Subject: RE: Compliance review for BoTox - Allergan

Importance: High

Glen:

After reviewing the Team Bioloigcs inspection of Allergan Pharmaceuticals Ireland, Westport, Ireland, we have reclassified the EIR from OAI to VAI, thus releasing the firm from an unacceptable compliance status. The compliance check issued by the Investigations and Preapproval Compliance Branch on 4/29/04, is now updated to reflect the reclassification to VAI. While there remain concerns with respect to stability data for storage conditions during shipment, there are no pending or ongoing compliance actions that would prevent approval of STN 103000/5050. The firm's corrective actions will be verified upon the next Team Biologics inspection.

Please call me if you have questions or need additional information. I apologize for not sending this earlier. I've been out of the office on supervisory training for the last three days.

Edwin Rivera Martinez
Chief
Investigations and Preapproval Compliance Branch, HFD-322
Division of Manufacturing and Product Quality
CDER's Office of Compliance

-----Original Message-----
From: Jones, Glen D (CDER/ODEVI)
Sent: Friday, May 14, 2004 9:41 AM
To: Schneider, Kay; Reese, James
Cc: Walton, Marc; Marzella, Libero; Smedley, Michael; Hoyt, Colleen; Charity, Anthony; Rivera Martinez, Edwin; Li, Jianming
Subject: RE: Compliance review for BoTox - Allergan

Kay and Jim,

Have we received the necessary documentation from OC (compliance check, new review) to support approval of the supplement?

-----Original Message-----
From: Li, Jianming
Sent: Tuesday, May 11, 2004 2:42 PM
To: Schneider, Kay
Cc: Walton, Marc; Reese, James; Dye, Earl; Jones, Glen D (CDER/ODEVI); Marzella, Libero; Smedley, Michael
Subject: RE: Compliance review for BoTox - Allergan

Kay,

I finished my review and sent it to Jim Reese last Thursday. Nobody tell me anything about an updated compliance review. Yesterday, Mike Smedley forwarded an email from Anthony Charity (addressed to Glen D. Jones) for my information. I have copied and pasted it here for you. I guess this may be the updated compliance review you are talking about.

Let me know if you need more information.

Jim Li

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20852

Our STN: BL 103000/5050

MAY 0 6 2004

Allergan, Incorporated
Attention: Adelbert Stagg, Ph.D.
Senior Director, Global Regulatory Affairs
2525 Dupont Drive
P.O. Box 19534
Irvine, CA 92623-9534

Dear Dr. Stagg:

This letter is in regard to the supplement to your biologics license application (BLA) for Botulinum Toxin Type A to treat primary axillary hyperhidrosis, submitted under section 351 of the Public Health Service Act. We acknowledge your facsimile transmissions dated May 6, 2004, regarding post-marketing commitments and labeling; please officially submit these to your BLA.

The Center for Drug Evaluation and Research (CDER) has completed the review of all submissions made through May 6, 2004, relating to this supplement to your license application. Our review finds that the information and data submitted are inadequate for final approval action at this time based on the deficiencies outlined below.

> We cannot approve your supplement to your application until FDA reviews your responses to the inspection deficiencies recently conveyed to you in Form 483, dated March 11, 2004, and finds that you have taken satisfactory corrective action.

You may request a meeting with CDER to discuss the above steps for approval. Please request the meeting at least 15 days prior to the proposed meeting date. Alternatively, you may choose to discuss this matter via a telephone call. Should you wish this meeting or a telephone discussion please contact the Regulatory Project Manager, James H. Reese, in the Division of Review Management and Policy at 301-827-4358.

Within 10 days after the date of this letter, you are requested to take one of the following actions: (1) amend the supplement; (2) notify us of your intent to file an amendment; (3) withdraw the supplement; or, (4) request an opportunity for a hearing on the question of whether there are grounds for denying approval of the supplement. In the absence of any of the above responses, CDER may initiate action to deny the supplement.

Please note our review clock has been suspended with the issuance of this letter. Note also that any amendment should respond to all deficiencies listed and that a partial reply will not be

considered for review nor will the review clock be reactivated until all deficiencies have been addressed.

The regulatory responsibility for review and continuing oversight for this product transferred from the Center for Biologics Evaluation and Research to the Center for Drug Evaluation and Research effective June 30, 2003. For further information about the transfer, please see <http://www.fda.gov/cder/biologics/default.htm>. Until further notice, however, all correspondence should continue to be addressed to:

CBER Document Control Center
Attn: Office of Therapeutics Research and Review
Suite 200N (HFM-99)
1401 Rockville Pike
Rockville, Maryland 20852-1448

If you have any questions, please contact the Regulatory Project Manager, James Reese, Ph.D., at (301) 827-4358.

Sincerely,

Marc Walton, M.D., Ph.D.
Director
Division of Therapeutic Biological Internal Medicine Products
Office of Drug Evaluation VI
Office of New Drugs
Center for Drug Evaluation and Research

cc: L. Marzella\HFM-582
E. Barrion\HFD-040
J. Lloyd Johnson\HFD-46
R. LeBlanc\HFM-536
Jianming Li\HFM-599
A. Mucci\HFD-715
E. Dye\HFM-585
M. Walton\HFM-576
J. Famulare\HFM-599
J. Reese\HFM\589
K. Schneider\HFM-589
K Weiss, HFM-500

CDER:DRMP: J. Reese: 5/5/04, 5/6/04:TYPIST INITIALS:DATE
(s:\Reese\BLA\Current BLAs\103000\5050\CR Ltr draft 3)

COMMUNICATION TYPE:

LETTER: Complete Response (CR)
Summary Text: Unsatisfactory Compliance Check Due to Field Inspection

SS & RIS Data Check:

- **Communication**
- **Milestone: Confirm First Action Due Closed Date. Ltr. Date And CR Milestone Date Should Match**
- **Submission Screen: STN Status - Complete Response Ltr.**

Fill-ins:

(1) Submission Tracking Number Assigned.
(2) Name of Authorized Official.
(3) Date of our Information Request Letter.
(4) Date of Manufacturer's amendments.
(5) Date of Form 483 or Warning Letter
(6) Name of Regulatory Coordinator.
(7) Telephone Number

CONCURRENCE PAGE

History: J. Reese: 5/5/04

File Name: (S:\Reese\BLA\Current BLA\103000\5050\CR Ltr draft 3)

Division	Name/Signature	Date
DRMP	J. Reese	5/6/04
OTBTMP		5/6/04
DRMP	Kelly Townsend	5/21/04

Reese, James

From: Reese, James
Sent: Wednesday, April 28, 2004 9:36 AM
To: 'stagg_del@allergan.com'
Subject: Requested document

Hi Del,
Attached is the label. The changes are in red. In some cases, entire paragraphs are red because there were so many changes within.
We intended to submit some post marketing commitments to you with the label, but our proposed wording has not been finalized. They will follow shortly. You may want me to fax them to you instead of email. Please advise.

Jim

Botox_PI_Apr27.doc

63 page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

Sponsor Telecon Summary

Date:	March 17, 2004 **Time:** 5:00 P.M.
FILE:	Supplement to the BLA for BOTOX (STN 103000/5050)
Product:	BOTOX® (Botulinum Toxin Type A) Purified Neurotoxin Complex
Proposed Use:	Treatment of Primary Axillary Hyperhidrosis
Sponsor/Manufacturer:	Allergan, Inc.
Subject:	Request for information regarding additional efficacy analyses regarding Study -016
Allergan Representative:	April Given, Cynthia Letizia, Del Stagg, and Julie Mordaunt
CBER Representative:	Louis Marzella, Elizabeth Sutkowski EMS

****

Summary
CBER called Allergan to request additional information regarding the efficacy analyses already submitted and to request a couple of additional analyses.

TELECON

Please submit the following information regarding Study -016:

1. Regarding the responders based on HDSS (as in Table 14.2-1 (page 1 of 2) in the original sBLA submission), please provide the confidence intervals around the difference between the responders in the two treatment arms and the placebo. Also, regarding the re-calculated responders based on HDSS (re-calculated excluding subjects not reinjected because did not meet gravimetric criteria) as in Table 6b (page 1 of 2) in Am. 5008 to the sBLA dated 2/2/04, please provide the confidence intervals around the difference between the responders in the two treatment arms and the placebo.

2. Regarding the original analysis of the secondary endpoint - 50% reduction in gravimetric measurement (Table 14.2-7). Please clarify whether or not negative values were excluded as there is no footnote indicating it one way or the other in Table 14.2-7. If negative values were excluded, please report the number of such values and perform an analysis including the negative values as failures. Please compare the proportion of responders in each treatment arm and provide 95% confidence intervals for the differences between placebo and each of the treatment arms.

3. Please provide an additional analysis for the duration of the primary response by HDSS in which the interval is defined from injection to last visit at which response was observed, rather than from injection to the first recording of a score of 3 or 4 on the HDSS or discontinuation of a patient from the study prior to a score of 3 or 4.

4. Regarding the immunogenicity data provided for Study -016, please account for the immunogenicity status of all the subjects that were actually injected. Please inform us of the number of subjects that actually had analyzable samples.

The sponsor understood our requests and agreed to provide the requested information as quickly as possible.

Sponsor Telecon Summary

Date:	January 6, 2004 **Time:** 5:00 P.M.
FILE:	Supplement to the BLA for BOTOX (STN 103000/5050)
Product:	BOTOX® (Botulinum Toxin Type A) Purified Neurotoxin Complex
Proposed Use:	Treatment of Primary Axillary Hyperhidrosis
Sponsor/Manufacturer:	Allergan, Inc.
Subject:	Allergan's fax dated 12/18/03, which included their proposed response to CBER's request for additional safety information (discussed in 12/12/03 telecon)
Allergan Representative:	April Given
CBER Representative:	Elizabeth Sutkowski EMS

****

Summary
CBER received Allergan's fax dated 12/18/03, which included their proposed response to CBER's request for additional safety information (discussed in 12/12/03 telecon) and their request for clarification of items discussed in 12/16/03 telecon regarding CBER's request for additional efficacy analyses. Note that CBER already responded on 12/23/03 to their request for clarification of items discussed in 12/16/03 telecon regarding CBER's request for additional efficacy analyses (see follow-up discussion summary at the end of CBER's 12/16/03 telecon summary).

TELECON

Ms. April Given was not in her office; the following message was left on her voice-mail:

In general, the plan for Allergan's response to CBER's safety information request proposed in the fax dated 12/18/03 looks fine with a couple of minor comments or recommendations (if not too late):

- Please include the location of injection site to the Summary of Deaths (for example, under item 2.iv. about product prep. and admin.) and to the Summary of Hypersensitivity (under item 3.iv. about product exposure).
- Also, in item 3.iv under product exposure, rather than limiting to dose distribution, it might be better to include the same items as in 2.iv.1 (i.e., dose, concentration, diluent, and injection site location).
- Allergan should send the information to the hyperhydrosis sBLA.

Ms. Given was informed that she could call Dr. Sutkowski if she had any questions. Ms. Given confirmed that she received the message and understood our additional recommendations.

Sponsor Telecon Summary

Date:	December 23, 2003 **Time:** 3:00 P.M.
FILE:	Supplement to the BLA for BOTOX (STN 103000/5050)
Product:	BOTOX® (Botulinum Toxin Type A) Purified Neurotoxin Complex
Proposed Use:	Treatment of Primary Axillary Hyperhidrosis
Sponsor/Manufacturer:	Allergan, Inc.
Subject:	Request for information and additional efficacy analyses
Allergan Representatives:	Cindy Letizia and April Given
CBER Representative:	Elizabeth Sutkowski EMS

****

Summary

This telecon was a follow-up telecon to the 12/16/03 telecon. On 12/18/03, Allergan faxed to CBER a request for clarification of a couple of items in our 12/16/03 telecon regarding additional efficacy analyses (see attached fax). It is noted that the fax also contained the company's meeting minutes for the 12/12/03 telecon and their proposal for response to our 12/12/03 telecon to request additional safety information, which were discussed with the company at a later date (see 1/6/04 telecon summary).

Questions and responses discussed on 12/23/03:

1. With reference to Study -505 (CBER's draft minutes, Item 2B) regarding sweat production, a figure (with histograms) was requested to depict the loss of response in the two treatment groups, comparing the new baseline to the initial baseline.

Question: Please clarify what timepoint the 'new baseline' should represent. Study -505 is designed with only one treatment session, whereas, study -506 is designed to allow for multiple treatment sessions, but has no placebo group. Is the FDA asking for the baseline comparison analysis within the subgroup of patients with loss of response and subsequent re-treatment in Study -506?

CBER Response: CBER agreed to drop this request for now, but informed the sponsor that it is possible that this type of analysis may be requested for study –016 in the future.

2. With reference to Study -016 (CBER's draft minutes, Item 7), a cross-tabulation was requested for response/lack of response using the HDSS score and gravimetric assessment.

Question: For this analysis, please clarify the dichotomization of the HDSS into response/lack of response. Note, that the protocol definition of a responder based on the

HDSS requires the evaluation over treatment sessions 1 and 2, whereas, the definition of a responder based on the gravimetric is defined within each treatment session.

CBER Response: CBER has requested a cross tabulation based on the protocol definition of response even though the timepoints when response is measured may not be the same. Allergan was informed that CBER was interested in knowing if the company has a suggestion for how else this correlation might be examined, and their suggestion(s) could be included in their proposal for the response to our info request. CBER clarified that the cross-tabulation and per-patient analysis was requested to look at the data they have in different ways in an attempt to tease out whether there is a population that responded in both measures or not. Allergan understood and agreed to address our request in their response.

Sponsor Telecon Summary

Date:	December 16, 2003 **Time:** 3:00 P.M.
FILE:	Supplement to the BLA for BOTOX (STN 103000/5050)
Product:	BOTOX® (Botulinum Toxin Type A) Purified Neurotoxin Complex
Proposed Use:	Treatment of Primary Axillary Hyperhidrosis
Sponsor/Manufacturer:	Allergan, Inc.
Subject:	Request for information and additional efficacy analyses
Allergan Representative:	Cindy Letizia, April Given, Karen Cross, Beta Bowen, Mitchell Brin, Franklin Lum, Simon Daggett, Nina Eadie, Pan-Yu Lai, Julie Mordaunt, Thomas Lin, and Roman Marak
CBER Representative:	Louis Marzella and Elizabeth Sutkowski EMS

****

Summary
CBER requested a telecon with Allergan to request additional analyses of the efficacy data in the sBLA. The following items regarding sBLA STN 103000/5050 (received 7/10/03) were discussed:

Study 505:

Item 1 Regarding Gravimetric Assessment and Responder Rates:
In Section 14.2, please see Table 3.1b (labeled ITT) on p. 132 (see below).

Table 00 Responder Rates: Percentage of Subjects with a 50% Reduction in Axillary Sweating from Baseline (ITT)

		BOTOX (n=242)		Vehicle (n=78)		Treatment effect
Week 1	n	241		77		
	Responders	230	(95.4%)	25	(32.5%)	63% (52, 74)
Week 4	n	233		75		
	Responders	219	(94.0%)	28	(37.3%)	56.7% (45, 68)

CBER Comment: The table is labeled ITT. However, Allergan used a definition of ITT that is not standard/acceptable because at week-4 nine patients in the active group and three patients in the placebo group are excluded from the analysis.

CBER Requests:

1A. CBER requests a conservative analysis that includes all randomized patients and treats patients with missing efficacy data as treatment failures. Please re-analyze with percentages expressed relative to the total N (N=242).

1B. This request relates to all analyses throughout the application (since it seems that the same unacceptable method was utilized in other tables such as the ones above (Table 3.1b and Table 3.3 discussed in Section 14.2 on Duration of Effect.)

Allergan asked for clarification of priority of the analyses requested; CBER clarified that the highest priority analyses would be the primary endpoint (i.e., primary and secondary analyses of the primary endpoint) and the secondary endpoint.

Item 2 Regarding histograms of the percent reduction in sweat production at week 4 for the ITT population (not using the LOCF method) displayed for the BOTOX and vehicle treatment groups (figures A and B) on p.61

CBER Comment: The scales on the ordinate are different in the two figures.

CBER Requests:

2A. Either replace the figure with two figures having the same scale for the ordinate or one figure showing data for both groups (next to one another).

2B. For patients experiencing loss of response, i.e., < 50% reduction from baseline in sweat production, in the two treatment groups, compare the new baseline to the initial baseline and show the distribution.

Item 3 Regarding Duration of Effect:

Table 3.1b in Section 14.2 (below) shows evidence of treatment effect for up to week 16.

Table 00 Responder Rates by Gravimetric Assessment (Intent-to-Treat Analysis)

Week		BOTOX (n=242)		Vehicle (n=78)		Difference (Botox-Vehicle)
Week 1	n	241		77		
	Responders	230	(95.4%)	25	(32.5%)	63.0% (52, 74)
Week 4	n	233		75		
	Responders	219	(94.0%)	28	(37.3%)	56.7% (45, 68)
Week 8	n	232		75		
	Responders	209	(90.1%)	28	(37.3%)	52.8% (41, 64)
Week 12	n	223		72		
	Responders	197	(88.3%)	27	(37.5%)	50.8% (39, 63)
Week 16	n	235		74		
	Responders	192	(81.7%)	16	(21.6%)	60.1% (50, 71)

Also, Table 3.3 shows the number and percentage of patients still responding at week 16 (and that do not have 2 consecutive non-response timepoints).

Gravimetric Assessment
Duration of Effect: Number and Percentage of Patients still Responding at Week 16 (and that do not have 2 Consecutive Non-response Timepoints) (Intent-to-Treat Analysis)

		BOTOX (N=242)	**Vehicle (N=78)**	**Difference (Botox-Vehicle)**
Week 16	N	235	74	
	Still Responders	182 (77.4%)	13 (17.6%)	59.9%

[a] Confidence intervals are based on normal approximation
[b] A Fisher s exact test was performed to evaluate the equality of proportions between groups

CBER Requests:

3A. Do the tables above include week 1? If so, please reanalyze excluding week 1 and begin with week 4.

3B. Please perform an analysis where you compare back to the previous time point and determine what proportion of those are still responders. For example of the subject who were responders at week 4, what proportion of them are still responders at week 8, and of the ones who were responders at week 8 what proportion of them are still responders at week 12 and so on.

3C. For each responder, calculate the duration of response using the following rules:
- onset of response: week 4
- loss of response: sweat production $\leq$50% reduction from baseline or missing data
- onset of loss of response:
  - first visit where loss of response criteria are met,
  - last visit where response documented, and
  - interpolations, e.g., mid-point, between a) and b)

3D. Summarize the duration of response for the active and placebo group.

Item 4 Regarding the SF-12 Health Survey:

Table 11.4.1.7 SF-12 Health Survey – Baseline and Change from Baseline

Visit		BOTOX® N = 242	Vehicle N = 78	P- value[a]
Physical Component Summary Score				
Baseline	N	229	77	
	Mean ± SD	52.2 ± 7.3	52.8 ± 7.2	0.197
	Median	54.8	55.6	
Exit	N	199	69	
	Mean ± SD	0.9 ± 7.6	-1.2 ± 6.7	0.019
	Median	0.6	-0.1	
	p value[b]	0.012	0.221	
Mental Component Summary Score				
Baseline	N	229	77	
	Mean ± SD	49.1 ± 9.5	46.4 ± 10.4	0.023
	Median	52.5	49.3	
Exit	N	199	69	
	Mean ± SD	1.7 ± 9.1	0.5 ± 8.8	0.247
	Median	1.4	0.0	
		0.013	0.890	

[a] Wilcoxon rank-sum test was performed to evaluate the equality of group distributions.
[b] Wilcoxon signed-rank test was performed to evaluate the change from baseline within groups.
Reference: Section 14.6, Tables 7.1 and 7.2; Appendix 16.2.9, Listing A10

CBER Request:
Please explain how you consider this a statistically significant improvement in quality of life when the SD is so high.

Item 5 Regarding Efficacy Results and Responder Rates by Investigator:

CBER Request:
Regarding sub-group analyses, please provide a list of the response rates by investigator with the investigator's name and the study site #. Also, provide the numerator and denominator for each of the 2 arms.

Study –016

Item 6 Regarding the Primary Efficacy Variable(s):

Patients who reported at least a 2-grade improvement 4 weeks following each of the first 2 treatment sessions were considered treatment responders. In addition, the following patients were also considered to be treatment responders:

- Patients with at least a 2-grade improvement in HDSS score at week 4 of treatment session 1 who completed the 52-week study observation period but were precluded from a second injection because of a continuing response to treatment, i.e., patients who met the HDSS score requirements (HDSS score 3 or 4) for reinjection but did not meet the sweat production requirement (gravimetric measurements at least 50 mg)

CBER Requests:

6A. Please tell us how many patients were in this category.

6B. Please re-analyze the treatment response and duration of response excluding patients with HDSS score ≥ 3 but gravimetric measurement ≤ 50 mg.

Item 7 Regarding Agreement Between HDSS and Gravimetric Assessment:

CBER comment:

CBER recommended another way that might also be helpful to look for correlation between HDSS and Gravimetric Assessment, which could help to tease out whether there might be a particular population that has a change in one measure and not in the other.

CBER Request:

7A. Please provide a scatter plot of HDSS versus the gravimetric assessment using actual scores and measurements and changes from baseline.

7B. Please provide a tabular cross-correlation of response/lack of response using HDSS score and gravimetric measurement.

Item 8 Regarding Subject Daily Diary, Questions 4 and 5 (Table 14.2-9.4, p. 194):

CBER comment/request:

In the 75U group, the treatment session 2 mean values at baseline and week 4, 10% and 0.1% respectively, are not consistent. Please confirm.

Conclusion/Agreements:

CBER asked Allergan to submit a proposal in which they describe their plans to address the requested additional analyses along with proposed timelines and Allergan agreed. Also, Allergan asked if CBER could fax or email our draft notes for the telecon to help them prepare the proposal and CBER agreed. CBER emailed the draft telecon notes to A. Given later that day.

Summary of Telecon

Date:	December 4, 2003	**Time:**	4:22 P.M.
FILE:	Supplement to the BLA for BOTOX (STN 103000/5050)		
Product:	BOTOX® (Botulinum Toxin Type A) Purified Neurotoxin Complex		
Proposed Use:	Treatment of Primary Axillary Hyperhidrosis		
Sponsor/Manufacturer:	Allergan, Inc.		
Subject:	Request for information: reconfigured list of concomitant medications for the European Studies –505 and -506		
Allergan Representative:	April Given		
CBER Representative:	Elizabeth Sutkowski EMS		

****

Summary

CBER called Allergan to ask them to provide the following information regarding a portion of the data submitted in the sBLA:

Please compile and submit the following regarding the **European Study -505**:

- A list of the concomitant medications which has been categorized into larger classes of medications (as was recently requested by CBER for the US Study –016) to include the following listings:
  - analgesics
  - anti-inflammatory agents or drugs
  - anti-infectives
  - sedatives/psychotropics/anti-depressants
  - topical agents (to the axillae)

The sponsor was not available; Dr. Sutkowski left the request for information in a voice mail for Ms. Given with a call back number in case of questions.

FOLLOW-UP TELECON

Allergan returned the call and asked if CBER would also like them to submit the reconfigured tabular list of concomitant medications for Study –506, the open label extension to study –505, as well.

Dr. Sutkowski consulted with Dr. Marzella and they agreed that Allergan would need to do the same concomitant medications analysis for the other studies as well. The sponsor was called back on 12/8/03 at 2:43 pm and informed via voice-mail that they should go ahead with the revised analysis for concomitant medications for study –506 as well as –505.

Summary of Telecon

Date:	November 24, 2003	**Time:** 4:45 P.M.	
FILE:	Supplement to the BLA for BOTOX (STN 103000/5050)		
Product:	BOTOX® (Botulinum Toxin Type A) Purified Neurotoxin Complex		
Proposed Use:	Treatment of Primary Axillary Hyperhidrosis		
Sponsor/Manufacturer:	Allergan, Inc.		
Subject:	Request for information		
Allergan Representative:	April Given		
CBER Representative:	Elizabeth Sutkowski E MS		

****

BEGIN TELECON

CBER called Allergan to ask them to provide the following information regarding a portion of the data submitted in the sBLA:

Please compile and submit the following regarding Study -016:

- A list of the concurrent medications (as were listed in Table 14.2-13), which has been categorized into larger classes of medications to include the following listings:
  - analgesics
  - anti-inflammatory agents or drugs
  - anti-infectives
  - sedatives/psychotropics/anti-depressants
  - topical agents (to the axillae)

The sponsor had already left for the day so Dr. Sutkowski left the request for information in a voice mail for Ms. Given with a call back number in case of questions.

END TELECON

Summary of Telecon

Date:	November 13, 2003	**Time:** 2:50 P.M.	
FILE:	Supplement to the BLA for BOTOX (STN 103000/5050)		
Product:	BOTOX® (Botulinum Toxin Type A) Purified Neurotoxin Complex		
Proposed Use:	Treatment of Primary Axillary Hyperhidrosis		
Sponsor/Manufacturer:	Allergan, Inc.		
Subject:	Request for information		
Allergan Representative:	John Spoden		
CBER Representative:	Elizabeth Sutkowski EMS		

****

BEGIN TELECON

CBER called Allergan to ask them to provide the following information regarding a portion of the data submitted in the sBLA:

Please compile and submit the following regarding Study -016:

- A list of the response rates by investigator with the investigator's name and the study site #
- The numerator and denominator for each of the 3 arms
- Also, CBER noted that some investigators are listed in both the List of Investigators Certifying the Absence of Financial Interests and Arrangements (Table 19.1) and the List of Investigators Certifying the Presence of Financial Interests and Arrangements (19.2). Please provide an explanation for this.
- Please submit this information along with a cover letter that references this request for information telecon in an email to Dr. Libero Marzella (and cc Elizabeth Sutkowski and James Reese). In addition, please follow that up with hard copy of the requested information along with a 356H form submitted to the sBLA.

The sponsor understood our request and would check to see if some of the information was provided in the sBLA and if so, point that out to us.

END TELECON

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20852

Our STN: BL 103000/5050

SEP 08 2003

Allergan, Incorporated
Attention: Adelbert Stagg, Ph.D.
Senior Director, Global Regulatory Affairs
2525 Dupont Drive
P.O. Box 19534
Irvine, CA 92623-9534

Dear Dr. Stagg:

This letter is in regard to the supplement to your biologics license application (BLA) submitted under section 351 of the Public Health Service Act.

We have completed an initial review of your supplement dated July 7, 2003 for Botulinum Toxin Type A to determine its acceptability for filing. Under 21 CFR 601.2(a) we have filed your supplement today. The user fee goal date is May 9, 2004. This acknowledgment of filing does not mean that we have issued a license nor does it represent any evaluation of the adequacy of the data submitted.

At this time, we have not identified any potential review issues. Our filing review is only a preliminary review, and deficiencies may be identified during substantive review of your supplement. Following a review of the supplement, we shall advise you in writing of any action we have taken and request additional information if needed.

The regulatory responsibility for review and continuing oversight for this product transferred from the Center for Biologics Evaluation and Research to the Center for Drug Evaluation and Research effective June 30, 2003. For further information about the transfer, please see http://www.fda.gov/cber/transfer/transfer.htm and http://www.fda.gov/OHRMS/DOCKETS/98fr/03-16242.html. Until further notice, however, all correspondence should continue to be addressed to:

CBER Document Control Center
Attn: Office of Therapeutics Research and Review
Suite 200N (HFM-99)
1401 Rockville Pike
Rockville, Maryland 20852-1448

If you have any questions, please contact the Regulatory Project Manager, James H. Reese, Ph.D., at (301) 827-4358.

Sincerely,

Earl Dye

for Glen D. Jones, Ph.D.
Director
Division of Application Review and Policy
Office of Therapeutics Research and Review
Center for Drug Evaluation and Research

CONCURRENCE PAGE

Letter Type: Filing Notification (FL)
No Deficiencies Identified (NDI)

SS Data Check:
- **Communication**
- **Milestone: Confirm Filing Action Entry & Closed Date**
- **If applicable – Confirm Deficiencies Identified Entry & Closed Date**

cc: Division BLA Files
HFM/582 L. Marzella
HFM/602 E. Barrion
HFM-650 J. L. Johnson
HFD-42 M. Kiester
HFM-536 R. LeBlanc
HFD-715 A. Mucci
HFM-589 J. Reese
HFM-481 E Sutkowski

History: J. Reese, 9/04/03: K. Townsend: 9.5.2003: 9.8.2003

File Name: S.: Reese/BLA/Current BLAs/103000/5050/Filing Letter

Division	Name/Signature	Date
DARP	J. Reese	9/8/03
DARP	Schneider	9-8-03
DARP	Dep. for Jones	9-8-03
DARP	Kelly Townsend	9-8-03

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20852

SEP 04 2003

Our STN: BL 103000/5050

Allergan, Incorporated
Attention: Adelbert Stagg, Ph.D.
Senior Director, Global Regulatory Affairs
2525 Dupont Drive
P.O. Box 19534
Irvine, CA 92623-9534

Dear Dr. Stagg:

This letter is in regard to the supplement to your biologics license application for Botulinum Toxin Type A to treat primary axillary hyperhidrosis that interferes with daily activities.

In our letter of July 24, 2003, we indicated that the date this supplement was received was June 30, 2003. This supplement was pre-assigned a Supplement Tracking Number (STN) on June 30, 2003. The actual received date for the supplement was July 10, 2003. All of the pertinent milestones are based on the July 10, 2003, receipt date.

We apologize for this error and hope that it has not caused any undue inconvenience.

If you have any questions, please contact the Regulatory Project Manager, James Reese, Ph.D., at (301) 827-4358.

Sincerely,

for Glen D. Jones, Ph.D.
Director
Division of Application Review and Policy
Office of Therapeutics Research and Review
Center for Drug Evaluation and Research

CONCURRENCE PAGE

History: J. Reese: 8.14.03: K. Townsend: 8.18.2003: 8.29.2003

File Name: (S:\Reese\BLA\Current BLA\103000\Ack Ltr correction 8 14 03 final)

Division	Name/Signature	Date
DARP	J. Reese	8/29/03
DARP	Schneider	9-2-03
DARP	Peg La Fond	9-4-03
DARP	Kelly Townsend	9-4-03

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20852

JUL 24 2003

Allergan, Incorporated
Attention: Adelbert Stagg, Ph.D.
Senior Director, Global Regulatory Affairs
2525 Dupont Drive
P.O. Box 19534
Irvine, CA 92623-9534

Dear Dr. Stagg:

SUBMISSION TRACKING NUMBER (STN) BL 103000/5050 has been assigned to your recent supplement to your biologics license application for Botulinum Toxin Type A received on June 30, 2003, to treat primary axillary hyperhidrosis that interferes with daily activities.

All future correspondence or supportive data relating to this supplemental application should bear the above STN. The regulatory responsibility for review and continuing oversight for this product transferred from the Center for Biologics Evaluation and Research to the Center for Drug Evaluation and Research effective June 30, 2003. For further information about the transfer, please see http://www.fda.gov/cber/transfer/transfer.htm and http://www.fda.gov/OHRMS/DOCKETS/98fr/03-16242.html. Until further notice, however, all correspondence, except as provided elsewhere in this letter, should continue to be addressed to:

CBER Document Control Center
Attn: Office of Therapeutics Research and Review
Suite 200N (HFM-99)
1401 Rockville Pike
Rockville, Maryland 20852-1448

This acknowledgment does not mean that this supplement has been approved nor does it represent any evaluation of the adequacy of the data submitted. Following a review of this submission, we shall advise you in writing as to what action has been taken and request additional information if needed.

If you have any questions, please contact the Regulatory Project Manager, James Reese, Ph.D., at (301) 827-4358.

Sincerely,

Earl Deye

for Glen D. Jones, Ph.D.
Director
Division of Application Review and Policy
Office of Therapeutics Research and Review
Center for Drug Evaluation and Research

CONCURRENCE PAGE

Letter Type: LETTER: Acknowledgment Letter (ACK)
Summary Text: (PAS)

SS & RIS Data Check:
- **If "Unacceptable for Filing" add 2nd LETTER TYPE "UN".**
- **Communication**

RIS Data Check:
- **Submission Screen: In Arrears Box Is Checked**
- **Milestone: Confirm "UN" Entry & User Fees Not Paid -- The Clock Has Stopped. First Action Due Close Date And The New "UN" Entry Date Should Match**
- **No Action Due Date**
- **STN Status – Unacceptable for Filing**

cc: DARP BLA File, HFM-585
Libero Marzella, HFM-582
James Reese, HFM-588

History: K. Townsend: 7.22.2003

File Name: S:\STN 2003\103000.5050.PAS.doc

Division	Name/Signature	Date
DARP	J. Reese	7/22/03
DARP	Schneider	7-23-03
DARP	Dep for Jones	7-24-03
DARP	Kelly Townsend	7-25-03

Regulatory Filing Review Memo for BLAs and Supplements

The filing review should seek to identify all omissions of clearly necessary information such as information required under the statute or regulations or omissions or inadequacies so severe that a meaningful review cannot be accomplished. CBER may refuse to file (RTF) an application or supplement as provided by 21 CFR 601.2, and 21 CFR 314.101, including those reasons consistent with the published RTF policy (http://www.fda.gov/cber/regsopp/8404.htm). An RTF decision may also be appropriate if the agency cannot complete review of the application without significant delay while major repair or augmentation of data is being done. To be a basis for RTF, the omissions or inadequacies should be obvious, at least once identified, and not a matter of interpretation or judgement about the meaning of data submitted. Decisions based on judgments of the scientific or medical merits of the application would not generally serve as bases for RTF unless the underlying deficiencies were identified and clearly communicated to the applicant prior to submitting a license application, e.g., during the review of the IND or during pre-BLA communications. The attached worksheets, which are intended to facilitate the filing review, are largely based upon the published RTF policy and guidance documents on the ICH Common Technical Document (CTD) (see http://www.fda.gov/cber/ich/ichguid.htm).

Where an application contains more than one indication for use, it may be complete and potentially approvable for one indication, but inadequate for one or more additional indications. The agency may accept for filing those parts of the application that are complete for a particular indication, but refuse to file those parts of the application that are obviously incomplete for other indications.

CBER management may, for particularly critical biological products, elect not to use the RTF procedure, even where it can be invoked, if it believes that initiating the full review at the earliest possible time will better advance the public health.

STN: 103000/5050 Product: BOTOX Applicant: Allergan

Final Review Designation (circle one): (Standard) Priority

Submission Format (circle all that apply): Paper Electronic (Combination)

Submission organization (circle one): (Traditional) CTD

Filing Meeting: Date 8·19·03 Committee Recommendation (circle one): File RTF

RPM: J Reese 8/20/03
(signature/date)

Attachments:

- Discipline worksheets (identify the number of lists attached for each part and fill-in the name of the reviewer responsible for each attached list):
  - ✓ Part A – RPM
  - ✓ Part B – Product/CMC/Facility Reviewer(s): LeBlanc _____ _____
  - ____ Part C – Non-Clinical Pharmacology/Toxicology Reviewer(s): _____ _____
  - ✓ Part D – Clinical (including Pharmacology, Efficacy, Safety, and Statistical) Reviewers Marsella _____ _____ _____
- ☐ Memo of Filing Meeting

STN 103000/5050 Product BOTOX

Part A. Regulatory Project Manager (RPM)

CTD Module 1 Contents	Present?	If not, justification, action & status
Cover Letter	(Y) N	
Form 356h completed	(Y) N	
▫ including list of all establishment sites and their registration numbers	(Y) N	
▫ If foreign applicant, US Agent signature.	Y N	N/A
Comprehensive Table of Contents	(Y) N	
Debarment Certification with correct wording (see * below)	Y N	N/A
User Fee Cover Sheet	(Y) N	
User Fee payment received	(Y) N	
Financial certification &/or disclosure information	(Y) N	
Environment assessment or request for categorical exclusion (21 CFR Part 25)	(Y) N	
Pediatric rule: study, waiver, or deferral	(Y) N	
Labeling:	(Y) N	
▫ PI –non-annotated	(Y) N	
▫ PI –annotated	(Y) N	
▫ PI (electronic)	(Y) N	
▫ Medication Guide	Y (N)	
▫ Patient Insert	Y (N)	
▫ package and container	Y (N)	
▫ diluent	Y (N)	
▫ other components	Y (N)	
▫ established name (e.g. USAN)	(Y) N	
▫ proprietary name (for review)	(Y) N	

* The Debarment Certification must have correct wording , e.g. "I, the undersigned, hereby certify that XXX Co. did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food Drug, and Cosmetic Act in connection with the studies listed in Appendix XXX." Applicant may not use wording such as "To the best of my knowledge,.."

Examples of Filing Issues	Yes?	If not, justification, action & status
Content, presentation, and organization of paper and electronic components sufficient to permit substantive review?: Examples include:	(Y) N	
▫ legible	(Y) N	
▫ English (or translated into English)	(Y) N	
▫ compatible file formats	(Y) N	
▫ navigable hyper-links	(Y) N	
▫ interpretable data tabulations (line listings) & graphical displays	(Y) N	
▫ summary reports reference the location of individual data and records	(Y) N	

Examples of Filing Issues	Yes?	If not, justification, action & status
☐ protocols for clinical trials present	(Y) N	
☐ all electronic submission components usable (e.g. conforms to published guidance)	(Y) N	
companion application received if a shared or divided manufacturing arrangement	Y N	N/A
if CMC supplement:		
☐ description and results of studies performed to evaluate the change	Y N	N/A
☐ relevant validation protocols	Y N	
☐ list of relevant SOPs	Y N	
if clinical supplement:		
☐ changes in labeling clearly highlighted	(Y) N	
☐ data to support all label changes	(Y) N	
☐ all required electronic components, including electronic datasets (e.g. SAS)	(Y) N	
if electronic submission:		
☐ required paper documents (e.g. forms and certifications) submitted	(Y) N	

List any issue not addressed above which should be identified as a reason for not filing the BLA/BLS. Also provide additional details if above charts did not provide enough room (or attach separate memo).

Has orphan drug exclusivity been granted to another drug for the same indication?
If yes, review committee informed? NO

Does this submission relate to an outstanding PMC? NO

If an Advisory Committee (AC) discussion may be needed, list applicable AC meetings scheduled to occur during the review period: N/A

- Name:
- Dates:

Recommendation (circle one): (File) RTF

RPM Signature: James Reece Branch Chief concurrence: Schneider

Part D – Clinical (Pharmacology, Efficacy, Safety,and Statistical) Reviewers

CTD Module 2 Contents	Present?		If not, justification, action & status
Overall CTD Table of Contents [2.1]	Y	N	
Introduction to the summary documents (1 page) [2.2]	Y	N	
Clinical overview [2.5]	Y	N	
Clinical summary [2.7] (summary of individual studies; comparison and analyses across studies)	Y	N	
❑ Biopharmaceutics and associated analytical methods	Y	N	– N/A
❑ Clinical pharmacology [includes immunogenicity]	Y	N	– N/A
❑ Clinical Efficacy [for each indication]	Y	N	
❑ Clinical Safety	Y	N	
❑ Synopses of individual studies	Y	N	

CTD Module 5 Contents	Present?		If not, justification, action & status
Module Table of Contents [5.1]	Y	N	
Tabular Listing of all clinical studies [5.2]	Y	N	
Study Reports and related information [5.3]	Y	N	
❑ Biopharmaceutic	Y	N	N/A
❑ Studies pertinent to Pharmacokinetics using Human Biomaterials	Y	N	N/A
❑ Pharmacokinetics (PK)	Y	N	N/A
❑ Pharmacodynamic (PD)	Y	N	
❑ Efficacy and Safety	Y	N	
❑ Postmarketing experience	Y	N	N/A
❑ Case report forms	Y	N	
❑ Individual patient listings (indexed by study)	Y	N	
o electronic datasets (e.g. SAS)	Y	N	
Literature references and copies [5.4]	Y	N	

Examples of Filing Issues	Yes?		If not, action & status
Content, presentation, and organization sufficient to permit substantive review?	Y	N	
❑ legible	Y	N	
❑ English (or certified translation into English)	Y	N	
❑ compatible file formats	Y	N	
❑ navigable hyper-links	Y	N	
❑ interpretable data tabulations (line listings) & graphical displays	Y	N	

Examples of Filing Issues	Yes?	If not, action & status
❑ summary reports reference the location of individual data and records	(Y) N	
❑ protocols for clinical trials present	(Y) N	
❑ all electronic submission components usable	(Y) N	
statement for each clinical investigation: ❑ conducted in compliance with IRB requirements	(Y) N	
❑ conducted in compliance with requirements for informed consent	(Y) N	
adequate and well-controlled clinical study data (e.g. not obviously inappropriate or clinically irrelevant study design or endpoints for efficacy)	(Y) N	
adequate explanation of why results from what appears to be a single controlled trial (or alternate method for demonstrating efficacy) should be accepted as scientifically valid without replication	Y N	N/A
study design not clearly inappropriate (as reflected in regulations, well-established agency interpretation or correspondence) for the particular claim	(Y) N	
study(ies) assess the contribution of each component of a combination product [21 CFR 610.17]	Y N	N/A
total patient exposure (numbers or duration) at relevant doses is not clearly inadequate to evaluate safety (per standards communicated during IND review, or ICH or other guidance documents)	(Y) N	
adequate data to demonstrate safety and/or effectiveness in the population intended for use of the biological product based on age, gender, race, physiologic status, or concomitant therapy	(Y) N	
drug interaction studies communicated as during IND review as necessary are included	Y N	N/A
assessed drug effects whose assessment is required by well established agency interpretation or communicated during IND review	(Y) N	
comprehensive analysis of safety data from all current world-wide knowledge of product	(Y) N	

STN Product Botulinum Toxin Part D Page 3

Examples of Filing Issues	Yes?	If not, action & status
data supporting the proposed dose and dose interval	(Y) N	
appropriate (e.g. protocol-specified) and complete statistical analyses of efficacy data	(Y) N	
adequate characterization of product specificity or mode of action	(Y) N	
data demonstrating comparability of product to be marketed to that used in clinical trials when significant changes in manufacturing processes or facilities have occurred	Y N	N/A
inadequate efficacy and/or safety data on product to be marketed when different from product used in clinical studies which are the basis of safety and efficacy determinations	Y (N)	
all information reasonably known to the applicant and relevant to the safety and efficacy described?	(Y) N	

List of Clinical Studies (protocol number)	Final study report submitted?	Financial disclosure or certification submitted?	SAS & other electonic datasets complete & usable?	BiMo sites identified?
505	(Y) N	(Y) N NR	(Y) N	(Y) N NR
016	(Y) N	(Y) N NR	(Y) N	(Y) N NR
~~015~~ 015	(Y) N	Y N NR	Y (N)	Y N (NR)
	Y N	Y N NR	Y N	Y N NR
	Y N	Y N NR	Y N	Y N NR
	Y N	Y N NR	Y N	Y N NR
	Y N	Y N NR	Y N	Y N NR
	Y N	Y N NR	Y N	Y N NR
	Y N	Y N NR	Y N	Y N NR
	Y N	Y N NR	Y N	Y N NR

Y= yes; N=no; NR=not required

List any issue not addressed above which should be identified as a reason for not filing the BLA/BLS. Also provide additional details if above charts did not provide enough room (or attach separate memo).

None

Is clinical site(s) inspection (BiMo) needed?

Yes

Is an Advisory Committee needed?

NO

Recommendation (circle one): File RTF

Reviewer: BM/CMS 9-3-03 Type (circle one): Clinical Clin/Pharm Statistical
(signature/ date)

Concurrence:

Branch Chief: Jeffrey N. Siegel 9/3/03 Division. Director: [signature] 9/4/03
(signature/ date) (signature/ date)