

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125274Orig1s001

MEDICAL REVIEW(S)



Food and Drug Administration
Center for Drug Evaluation and Research
WO Bldg 51
10903 New Hampshire Avenue
Silver Spring, MD 20993

Date: April 3, 2009
To: Administrative File, STN 125286/0
From: Patricia F. Hughes, Ph.D., CDER/OC/DMPQ/BMT
Through: Kalavati Suvarna, Ph.D., Peer Reviewer, CDER/OC/DMPQ/BMT
Endorsement: Concepcion Cruz, Acting Branch Chief, CDER/OC/DMPQ/MAPCB
Subject: Team Leader Secondary Discipline Review
US License: 1787
Applicant: IPSEN Biopharm Limited
Facility: IPSEN Biopharm Limited, Wrexham, UK (FEI 1000346340)
Product: Reloxin® (*Clostridium botulinum* toxin Type A haemagglutinin complex, CNT-52120)
Dosage: Sterile lyophilized powder for Injection, 300 Units
Indication: Treatment of moderate to severe glabellar lines in adult patients
Due date: April 13, 2009

PR 4/3/09
klw 4/3/09
CR 4/3/09

Recommendation for Approvability:

Both Reloxin® (BLA 125286) and Dysport® (BLA 125274) are manufactured by Ipsen Biopharm Limited. However, Reloxin® is manufactured by Ipsen for Medicis Pharmaceutical Corporation. Medicis is responsible for the interpretation of the non-clinical and clinical contents of the BLA, including labeling. The Agency has communicated to Medicis on March 4, 2008 that only one license could be issued per product. Because two (2) BLAs were submitted to the Agency for the same product (but for different indications), once the first BLA is approved, the second application would be immediately and automatically be converted into a supplement to the licensed *Clostridium botulinum* type A toxin product.

A review of BLA 125274 (the first BLA submitted for the same product) was completed by OC/DMPQ/BMT on December 17, 2008. The CMC portion of BLA 125286 is the same as that described in BLA 125274 for Dysport (*Clostridium botulinum* toxin Type A haemagglutinin complex) from a sterility assurance and product quality microbiology perspective. BLA 125274 for Dysport® by Ipsen Biopharm Limited was reviewed by the Biotech Manufacturing Team reviewers Brenda Uratani, Ph.D. (CMC review dated December 11, 2008), Donald Obenhuber, Ph.D. (review dated December 11, 2008) and Patricia F.

Hughes, Ph.D. (Team Leader review dated December 17, 2008). BLA 125274, as amended, was recommended for approval from a sterility assurance and microbiology product quality perspective.

The manufacturing facilities listed in BLA 125286 are the same as those listed in BLA 125274. A pre-license inspection of the Ipsen Biopharm Ltd. drug substance and drug product manufacturing facility in Wrexham LL13UF, UK was conducted in June 2008 by Michelle Clark-Stuart (OC/DMPQ/BMT) and Enan Guan (OBP/DTP) on June 2-10, 2008. No 483 observations were presented to the firm and the inspection was classified NAI.

Since the Microbiology CMC and manufacturing facilities sections of the BLA are the same for both Reloxin® and Dysport®, reference is made to BLA 125274 for the CMC review of BLA 125286 from a sterility assurance and microbiology product quality perspective for both drug substance and drug product. BLA 125286, as amended, is recommended for approval from a sterility assurance and microbiology product quality perspective.

cGMP Status

The Manufacturing Assessment and Pre-Approval Compliance Branch has completed its review and evaluation of the TB-EER below. Ipsen Biopharm Ltd., Wrexham, UK was last inspected June 2-10, 2008 and classified NAI. The BTP profile was covered and is acceptable. Wickham Laboratories Ltd., Hampshire, UK was last inspected May 16-17, 2005 and classified VAI. The CTL profile was covered and is acceptable. There are no pending or ongoing compliance actions to prevent approval of BLA 125286 at this time.

Conclusion

- I. Cross reference is made to the CMC sections of BLA 125274 and to the CMC microbiology reviews conducted by Brenda Uratani and Donald Obenhuber of December 11, 2008 and Patricia F. Hughes of December 17, 2008 in support of BLA 125286. The drug substance and drug product sections of BLA 125286, including the manufacturing and testing facilities, are the same as those described in BLA 125274. BLA 125286, as amended, is recommended for approval from a sterility assurance and microbiology product quality perspective.
- II. The drug substance and drug product sections not relating to microbiology quality issues should be assessed OBP/DTP reviewers.
- III. A list of CGMP items to be followed up at the next surveillance inspection was included in the drug substance review memo from Brenda Uratani. These items will be communicated to the International Operations Group in Office of Regulatory Affairs by The Division of Manufacturing and Product Quality.

Cc: WO Bldg 51, Uratani
WO Bldg 51, Obenhuber
WO Bldg 51, Hughes
WO Bldg 51, BMT Files (BLA 125286)

Archived File: S:\archive\BLA\125286\125286.0.rev.mem.TL.BLA.04-03-09.doc

Summary Review for Regulatory Action

Date	March 24, 2009
From	Tatiana Oussova, M.D., M.P.H.
Subject	Deputy Director Summary Review
NDA/BLA #	BLA 125286; IND 10,673
Applicant Name	Ipsen Biopharm Ltd.
Date of Submission	March 12, 2008
PDUFA Goal Date	April 13, 2009
Proprietary Name / Established (USAN) Name	TRADENAME (botulinum toxin Type A)
Dosage Forms / Strength	Lyophilized powder/solution
Proposed Indication(s)	Moderate to severe glabellar lines
Action/Recommended Action for NME:	Complete Response

Material Reviewed/Consulted	Names of discipline reviewers
OND Action Package, including:	
Medical Officer Review	Denise Cook, M.D.
Statistical Review	Kathleen Fritsch, Ph.D.
Pharmacology Toxicology Review	Jill Merrill, Ph.D.
CMC Review/OBP Review	Ennan Guan, Ph.D.
Microbiology Review	N/A
Clinical Pharmacology Review	Jang-Ik Lee, Pharm. D., Ph.D.
DDMAC	Andrew Haffer, Pharm.D.
DSI	Roy Blay, Ph.D.
CDTL Review	N/A
OSE/DMEPA	Walter Fava, R.Ph.
OSE/DPV	None
OSE/DRISK	TBD
Other	-

OND=Office of New Drugs
 DDMAC=Division of Drug Marketing, Advertising and Communication
 OSE= Office of Surveillance and Epidemiology
 DMEPA=Division of Medication Error Prevention and Analysis
 DSI=Division of Scientific Investigations
 DPV= Division of Pharmacovigilance
 DRISK=Division of Risk Management
 CDTL=Cross-Discipline Team Leader

Signatory Authority Review Template

1. Introduction

Reloxin is a new molecular entity indicated to achieve and maintain improvement in the appearance of moderate to severe glabellar lines associated with procerus and corrugator muscle activity in adult patients. Reloxin is a purified botulinum type A toxin product. In the current indication, botulinum toxin type A is administered by multiple small injections directly into the affected muscle.

Reloxin, under the name of Dysport, has been marketed in other countries since 1990 and is currently approved in 73 countries for clinical indications including blepharospasm, hemifacial spasm, spasmodic torticollis, equinus foot deformity due to spasticity in pediatric patients with cerebral palsy, hyperhidrosis, and/or spasticity of the arm and leg in patients following a stroke. It is approved for the cosmetic indication (treatment of facial lines) in 23 countries.

The drug product has not been withdrawn from any market for safety reasons. There has been one Direct Healthcare Professional Communication that was distributed in Europe at the request of the EMEA. This was to revise labeling for all therapeutic botulinum toxins to include information on the potential for adverse events due to the spread of the locally injected neurotoxin.

The only product approved for the treatment of glabellar lines in the United States is Botox Cosmetic. The units of Botox Cosmetic are not interchangeable with the Reloxin drug product.

BLA 125274 was submitted on 12/29/07 to the Division of Neurology under the trade name Dysport, for the treatment of cervical dystonia and is under review.

There are a few outstanding issues with this application.

- The major unresolved issue for this application is the postmarketing safety surveillance. The applicant would be required to submit a REMS.
- The applicant proposed tradename Reloxin was found unacceptable by DMEPA. DMEPA recommendation is to use a single name of Dysport for both indications but the final decision is still pending.
- Due to a safety concern (mainly about contamination of unused portion of a 300U vial), the sponsor would be required to develop a 125U single use dosage form. A supplement for approval of this dosage form will be submitted to the Agency.

2. Background

Reloxin blocks neuromuscular transmission by binding to receptor sites on motor 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 sponsor submitted multiple studies in support of efficacy and safety of Reloxin. A phase 2 dose-ranging study 717 was conducted to determine that 50 units of Reloxin is the appropriate dose to treat glabellar lines. Study 096 established a clinical bridge between the CAMR Reloxin and IBL Reloxin. Study 718, one of the pivotal phase 3 studies, used a CAMR Reloxin instead of the to-be-marketed IBL Reloxin, and study 096 data allowed to use study 718 database in the determination of Reloxin efficacy and safety. Studies 718, 719 and 085 databases were used to establish the efficacy and short-term safety of a single dose of Reloxin 50 units for the treatment of moderate to severe glabellar lines. In addition, study 085 database was used to establish the efficacy of repeated doses of Reloxin 50 units. All those studies were found to be sufficient to support the efficacy of Reloxin at a dose of 50 units in subjects ≤ 64 years of age using composite score 2+ as an endpoint. This composite score denotes that both investigator and subject agreed on a 2+ grade improvement.

Additionally, the sponsor conducted a study 2006-01 using higher doses (50 units – 80 units) of Reloxin based on a muscle mass however the data provided were not adequate to establish efficacy and safety of higher doses.

Studies 720 and 732 provided support for the long-term safety of the product. No significant safety issues were raised by a primary reviewer.

However, there are several concerns related to botulinum toxin products that are already on the market. There were post-marketing reports detailing spread of the toxin to both contiguous and distant sites which led to significant morbidity and in some cases has resulted in death. Other potential risk of medication errors related to the lack of interchangeability between different botulinum toxin products by different manufactures. Those concerns prompted multiple reviews of post-marketing data with the resulting boxed warning and request for a REMS for all botulinum toxin products.

3. CMC/Device

The Division of Therapeutic Proteins, Office of Biotechnology Products, OPS, CDER, recommends approval of BLA #125286 for Reloxin manufactured by IPSEN, Biopharm Limited.

The total recommended dose is 50 units in single session. Each vial of Reloxin contains 300 units of lyophilized *C. botulinum* toxin type A complex, 125 ug human albumin and 2.5 mg

lactose, free of preservatives. Reloxin is prepared for intramuscular injection by reconstituting each vial with 1 ml of 0.9% sodium chloride for injection USP.

The data submitted in this application support the conclusion that the manufacture of purified *C. botulinum* neurotoxin type A complex (BoNT/A complex), naturally secreted by *C. botulinum*, is well controlled, and leads to a product that is potent and safe, when used according to the label. The conditions used in manufacturing have been validated, and a consistent product is produced from different production runs.

The CMC reviewer referred to BLA STN 125274 for Post-Marketing Requirement and Commitment.

I concur with the recommendations. Post-marketing commitments and requirement described in the PMCs/PMRs sections below will provide additional information to assure the continued safety and efficacy of the product.

For more details, please see the original review by the Division of Therapeutic Proteins.

4. Nonclinical Pharmacology/Toxicology

The sponsor has submitted studies to satisfy the Division's request for evaluation of both the local and systemic effects of chronic dosing. No systemic toxicity was observed after single (up to 6 U/rat) or repeat (up to 10 U/rat, up to 20 U/rabbit) intramuscular dosing. There were no compound-related lesions of the muscle groups distant to the injection sites or of the peripheral or central nervous systems. Given the structure and mechanism of action of Reloxin, neither genetic toxicology nor carcinogenicity studies were required.

The sponsor has submitted all required reproductive and developmental toxicology studies (fertility in rats, embryotoxicity in rats and rabbits, peri/postnatal in rats). From the Pharmacology/Toxicology standpoint, Botulinum toxin type A hemagglutinin complex has an acceptable safety profile when administered at the appropriate dose by intramuscular injection. However, accidental systemic exposure (inadvertent intravenous injection) could cause systemic toxicity.

At present (11-19-08) the sponsor is seeking a (b) (4) flagellin specification for the drug product. The maximum level of flagellin contamination qualified by the reproductive toxicology studies is (b) (4)%. The maximum level of flagellin qualified by the repeat-dose study to examine the effects at the neuromuscular junction is no more than (b) (4)%. This may be an overestimation of the relative flagellin contamination because flagellin is measured by SDS-PAGE and co-elutes with other small peptides, including nontoxic nonhemagglutinin. Therefore the sponsor will be asked to perform the repeat embryofetal study with drug product containing at least (b) (4)% 'flagellin' contamination. The pharmacology/toxicology recommendation for the final drug product specification should be no higher than the maximum amount qualified nonclinically (i.e., (b) (4)% flagellin), but definitely less than (b) (4)%.

The pharmacology/toxicology review team has determined that Reloxin/Dysport should receive a pregnancy category C designation as does BOTOX® (Botulinum toxin type A, marketed by Allergan). The sponsor will be required as a post-marketing commitment to repeat the pivotal rabbit embryofetal study, which is considered inadequate. It is appropriate to require this as a post-marketing commitment rather than pre-approval because although the data is needed for inclusion in the label, it does not effect how women of child bearing potential would be informed (i.e., Pregnancy Category).

I concur with the conclusion made by pharmacology/toxicology review team. Above mentioned PMC would be issued by the Division of Neurology Product. There will be no separate PMC requirement by DDDP.

5. Clinical Pharmacology/Biopharmaceutics

The sponsor claims that Reloxin is not systemically available when administered using the proposed dose and route since the product would not produce measurable blood concentrations when injected locally in nanogram amounts into the target muscles. Preclinical studies conducted in rats by intramuscular (IM) injection of iodinated toxin complex indicate that toxin was not systemically detectable, whether administered in free or complexed form. After periocular injection into the eyelids of rabbits, both the neurotoxin complex and the free neurotoxin remained localized at the injection site and no labeled toxin spread to the eye. The administration of quantities that would result in systemic measurement would produce serious safety concerns due to the resulting untoward pharmacological activity. Thus, the sponsor decided not to conduct pharmacokinetic studies in humans. No drug interaction studies have been conducted.

From Clinical Pharmacology standpoint, there are no outstanding issues with this application that would preclude its approvability.

I concur with the conclusion of pharmacology/toxicology review team. The issue of potential toxicity associated with higher than labeled doses would be reflected in the label.

6. Clinical Microbiology

No clinical microbiology review was provided.

7. Clinical/Statistical-Efficacy

I concur with the conclusion made by primary clinical reviewer Dr. Denise Cook that the applicant has provided sufficient evidence of efficacy of Reloxin 50 units compared to placebo in achieving and maintaining improvement in the appearance of moderate to severe glabellar lines in adult patients younger than 64 years of age. The subpopulation of patient older than 64 years of age was too small to provide a meaningful conclusion about efficacy and safety of the product in that subpopulation.

The efficacy data were derived from three pivotal phase 3 trials: identical placebo-controlled RCT 718 and 719, and Cycle C of study 085 that provided an adequate database to support the efficacy of a single dose and repeated doses of Reloxin. In study 718, two hundred subjects were treated with CAMR Reloxin 50 units instead of to-be-marketed formulation of IBL Reloxin. CAMR and IBL Reloxin were manufactured at different locations but using the same manufacturing methodology from one of two BAS batches. Study 096 was conducted to establish a clinical bridge between those two formulations. There were 2 co-primary efficacy endpoints used in these phase 3 trials, the investigator's and the patient's assessment of glabellar severity score (GLSS) at maximum frown on day 30 after treatment. The efficacy was observed in 52%-60% of subjects across trials.

8. Safety

The clinical reviewer did not raise any major safety concerns that would preclude the approval of Reloxin 50 units for the treatment of glabellar lines. The safety database consisted of several placebo-controlled trials: 718, 718, 085 and A2006-01, and two long-term safety trials 720 and 732. All trials employed 50 units of Reloxin except for the trial A2006-01 which used various doses of Reloxin between 50 and 80 units. Trials 718, 719 and A2006-01 evaluated a single dose of Reloxin. Trial 085 was a multi-dose open-label trial followed by a placebo-controlled randomized phase. The other trials 720 and 732 were multi-dose trials. Trial 720 was 13 months in duration, and trial 732 was 36 months in duration and is ongoing. Subjects from all the trials were to be rolled-over into trial 732, the 36 month trial and would receive 50 units of Reloxin whenever an additional treatment was necessary.

In addition to 50 unit dose, the sponsor was also seeking variable dosing based on muscle mass however the efficacy and safety database provided with this application were not sufficient to make a definite conclusion about the efficacy or safety of higher doses of Reloxin. The 50 unit dose safety database consisted of 2491 subjects treated with Reloxin and 580 subjects treated with placebo. The long-term trials were designed such that some subjects could receive up to 8 cycles of treatment with Reloxin. An additional 522 subjects received a single dose of 60- 80 units of Reloxin.

Most adverse events in the short-term trials were expected for local injection of botulinum toxin type A products for this indication, e.g., eyelid ptosis, headache, injection site pain, reaction, bruising, and swelling. Most of the cases were mild to moderate and resolved spontaneously. There were no discontinuations because of adverse events in the short-term trials. Long-term data over 21 months with repeated injections demonstrated a slight increase in the percentage of subjects with injection site reactions, 4.0% vs. 3.0%, and subjects who developed contact dermatitis, pharyngolaryngeal pain, and cough (2% each). However, there were no subjects who discontinued the trials secondary to these adverse events. Importantly, there was no increase in the incidence of eyelid ptosis after repeated injections of Reloxin 50 units.

There were no cases of dysphagia or aspiration pneumonia reported in the safety database. These types of adverse events are mostly seen with the use of higher doses of Reloxin for neurologic indications. That population may also be more susceptible to the effects of

botulinum toxin type A. A REMS would be required of all botulinum toxin type A drug product to mitigate this risk.

Since the International Birth Date of Dysport®, 09 December 1990, there have been 1780 adverse events associated with Dysport® use reported, up to and including 30 June 2007, on an estimated (b) (4) patient years of exposure. They are provided by category (glabellar lines, other aesthetic indications, medical indications using doses up to and more than 200 units, unspecified dose, unspecified indications, and literature). The global database includes events reported spontaneously and those drawn from European studies.

There were five patients with ptosis captured in the global database when the drug was being used in the glabellar region, 39 when used for other aesthetic indications.

From July 1, 2007 until December 31, 2007, an update to the post-marketing report revealed 278 AEs. Of these 278 AEs, 26 described eyelid ptosis. The indication for Dysport® use was treatment of glabellar lines in 2 cases. In 8 cases, the product was used for other aesthetic purposes. Of note, 2 of these 8 cases were considered serious (required intervention in 1 case; required hospitalization and intervention in the second case). The remaining 16 AEs were identified in the scientific literature.

There were 2 reports of death secondary to the use of Dysport in the global safety database. Neither of these was secondary to dermatologic indications.

Cross-divisional discussion between DDDP, DNP and OSE of potential safety issues associated with botulinum toxin products resulted in a conclusion that a boxed warning, a REMS consisting of a Medication Guide and a communication plan would be necessary to emphasize the potential risk of local and distant spread of a toxin and the potential adverse events associated with the lack of interchangeability between different botulinum toxin type A products.

I concur with this conclusion and recommend that a REMS is necessary for Reloxin to ensure that the benefits of this drug outweigh its potential risks.

The REMS should contain a Medication Guide, a communication plan, timetable for assessments of the REMS and supporting documents, including Dear Healthcare Provider Letter, Dosing Card, Physician Survey and Patient Survey of understanding of the serious risks of Reloxin.

The Medication Guide should be developed as provided for under 21CFR Part 208. The communication plan must provide for the dissemination of information about the serious product risks including potential systemic spread of botulinum toxin after local injection and lack of interchangeability of Reloxin units with those of other licensed botulinum toxin products.

POSTMARKETING REQUIREMENTS UNDER 505(O)

CMC Post-Marketing Requirement

- To establish tighter potency acceptance criteria for the qualification of new reference standards. The acceptance criteria should ensure consistent potency assessment when different reference standards are used. This is critical as potency is reported relative to the potency of the reference standard. Amended criteria will be submitted to the Agency by [SPONSOR PROPOSE DATE].

Justification for the post-marketing requirement: The potency units for dosing are relative potency units established by normalizing the results of test lots of drug substance or product to the results obtained using the reference standard. This helps ensure consistent dosing from batch to batch. The potency specifications for drug product and drug substance are wide, but are supported by clinical and manufacturing data. Nevertheless, it is unacceptable to allow such wide limits to be applied to the qualification of new reference standards as this could allow the product to drift in potency over time. New reference standards are only infrequently created so this issue can be safely addressed post-approval.

CMC Post-Marketing Commitments

I concur with the recommendations for CMC post marketing commitments including:

1. Regarding specifications
 - a. To establish a drug substance release specification for Clp protease. The proposed specification will be submitted to the Agency by [SPONSOR PROPOSE DATE].
 - b. To establish a drug substance release specification for aggregates using a validated, sensitive method for quantification. The proposed specification will be submitted to the Agency by [SPONSOR PROPOSE DATE].
 - c. To develop and validate a sensitive immunologically based method to replace the FPLC and SDS-PAGE identity tests. The proposed specification will be submitted to the Agency by [SPONSOR PROPOSE DATE].
 - d. To provide information on control of destaining the GelCode Blue gel to prevent over-destaining the minor bands on the gel. The information will be provided to the Agency by [SPONSOR PROPOSE DATE].
2. Regarding stability
 - a. To perform a comprehensive analysis of the degradation products and pathways, including the contribution of the Clp protease system to degradation. A summary report together with any proposed modifications to the process and/or stability protocol that

will improve drug product stability will be submitted to the Agency by [SPONSOR PROPOSE DATE].

3. Regarding additional characterization tests

- a. To develop a Western blot assay for further characterization of the drug substance. Results of this analysis together with the implementation plan for this assay (i.e. specifications or characterization) should be provided to the Agency by [SPONSOR PROPOSE DATE].

4. Regarding potency test

- a. To investigate reducing the observation time period for animal death in the mouse LD50 assay from 96 to 72 hours. A summary report together with any proposed modifications to the method will be submitted to the Agency by [SPONSOR PROPOSE DATE].
- b. To investigate the development and implementation of a non-animal based potency assay(s) for drug substance and drug product release testing. A summary report together with any proposed modifications to the process and/or stability protocol will be submitted to the Agency by [SPONSOR PROPOSE DATE].

5. Regarding drug product identity test

- a. To develop and implement a non-animal based identity test for drug product. The animal based identity test for the first lot of drug product manufactured from every new lot of drug substance should be maintained. A summary report together with any proposed modifications to the process and/or stability protocol will be submitted to the Agency by [SPONSOR PROPOSE DATE].

6. Regarding reference standards:

- a. To develop drug substance and drug product reference standards from material made at the IBL facility. Routine use of new reference standards will be implemented by [SPONSOR PROPOSE DATE].
- b. To provide a protocol that describes extension of the dating period for reference standards. The protocol will be submitted to the Agency by [SPONSOR PROPOSE DATE].

7. Regarding the drug product lot release protocol:

- a. To add SE-HPLC results for bulk drug substance to the lot release protocol upon validation of the SE-HPLC assay(s). A supplement for approval of this drug substance release specification will be submitted to the Agency by [SPONSOR PROPOSE DATE].

To develop a 125U single use dosage form. A supplement for approval of this dosage form will be submitted to the Agency by [SPONSOR PROPOSE DATE].

9. Advisory Committee Meeting

None.

10. Pediatrics

All pediatric age groups are to be waived, as this indication does not occur in the pediatric age group.

11. Other Relevant Regulatory Issues

During the initial steps in the proprietary name review process (Expert Panel Discussion), the DDMAC did not recommend the use of the proposed proprietary name, Reloxin, from a promotional perspective because the name overstates the efficacy of the drug product. Therefore, DMEPA did not proceed with the safety review of the proposed proprietary name, Reloxin, and recommended the sponsor be notified of the decision to object to the name based on promotional concerns and that an alternate proprietary name be submitted for review. In addition, since the product is currently under review with DNP for a different indication by the same manufacturer under the proposed proprietary name Dysport, DMEPA evaluated safety issues which may potentially result from two different proprietary names for this product. In their assessment DMEPA concluded that managing this product under one proprietary name for all indications would be the safest option. DMEPA final review is pending.

12. Labeling

The package insert was reviewed this cycle, however, we will not provide our proposed labeling to the sponsor at this time. We will defer labeling discussion until the next review cycle.

A REMS will be requested that will include a Medication Guide, communication plan and timetable for assessments.

13. Decision/Action/Risk Benefit Assessment

- Recommendation for Regulatory Action: Complete Response
- Risk benefit Assessment will be completed following submission and review of the REMS
- Recommendation for Postmarketing Risk Management Activities: The applicant should provide a REMS consisting of a medication Guide and Communication plan as described above

Deputy Director Summary
BLA 125286

- **Recommendations for other Postmarketing Study Commitments:** These will be conveyed with the approval action



Tatiana Oussova, M.D., M.P.H.
Deputy Division Director for Safety
Division of Dermatology and Dental Products

CLINICAL REVIEW

Application Type BLA
Submission Number 125274
Submission Code 001

Letter Date March 12, 2008
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PDUFA Goal Date April 13, 2009

Reviewer Name Denise Cook, M.D.
Review Completion Date March 4, 2009

Established Name AbobotulinumtoxinA
(Proposed) Trade Name Dysport
Therapeutic Class Toxin
Applicant Ipsen Biopharm Limited

Priority Designation S

Formulation Lyophilized Powder, Solution
Dosing Regimen 50 units; Intramuscular Injection
Indication Moderate to severe glabellar lines
Intended Population Adults, 18 years and older

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

It is recommended that Dysport (abobotulinumtoxinA) receive a complete response for the following reason: the sponsor does not have a REMS for this drug product. It was decided by the Agency, as described in the body of this review, that a REMS will be necessary for all botulinum toxin products because of post-marketing reports detailing spread of the toxin to both contiguous and distant sites, which in some cases has resulted in death. Once an adequate and approved REMS has been received, based on the data provided in the BLA, this drug product will be approved for the treatment of moderate to severe glabellar lines in adults ≤ 64 years of age at a dose of 50 units to be injected intramuscularly into the glabellar region in 5 equal doses. Subsequent treatments should not occur sooner than 90 days after the last treatment.

The sponsor should be advised of the following regarding the REMS for this product:

- You should provide a REMS and supporting documents including a Dear Healthcare Provider Letter (DHCP), [Tradename] Dosing Card, Physician Survey and Patient Survey
- Any statement referring to the treatment of glabellar lines for your botulinum toxin type A product should refer exclusively to the 50 unit dose
- The new established name should be reflected on the label and all documents related to REMS, including the Medication Guide, educational material, and patient and health care provider surveys. You should also prominently include in all documents related to the REMS, including the Medication Guide, educational material, and patient and health care provider surveys, a statement that "[TRADENAME] (established name) is a botulinum toxin product." In the REMS and in the Dear Healthcare Provider Letter, you should state that, "The potency Units of [TRADENAME] are specific to the preparation and assay method utilized. They are not interchangeable with other preparations of botulinum toxin products and, therefore, units of biological activity of [TRADENAME] cannot be compared to or converted into units of any other botulinum toxin products assessed with any other specific assay method."
- In the REMS and in the DHCP, you should provide detailed information about why a REMS is necessary for your product. Since the target audience is the healthcare provider, you should provide the labeling language regarding the Spread of Toxin Effect.
- In the REMS and in the DHCP Letter, state that [TRADENAME] is an "acetylcholine release inhibitor and neuromuscular blocking agent".

1.2 Risk Benefit Assessment

Dysport, at a dose of 50 units, is quite efficacious in the treatment of moderate to severe glabellar lines, in that efficacy was observed in 52% - 60% of subjects for the most stringent efficacy variable, the 2+ composite score. The composite score denotes that both investigator and subject agreed on a 2+ grade improvement. Efficacy was demonstrated in all age groups except in subjects ≥ 65 years of age. There are no safety concerns that preclude the approval of Dysport 50 units for the treatment of moderate to severe glabellar lines. Most adverse events in the short-term use were expected for local injection of botulinum toxin type A products for this indication, e.g., eyelid ptosis, headache, injection site pain, reaction, bruising, and swelling. Most of the cases were mild to moderate and resolved without residua. No subjects discontinued because of adverse events in the short-term trials. Long-term data over 21 months with repeated injections demonstrated a slight increase in the percentage of subjects with injection site reactions, 4.0% vs. 3.0%, and subjects who developed contact dermatitis, pharyngolaryngeal pain, and cough (2% each). However, there were no subjects who discontinued the trials secondary to these adverse events. Importantly, there was not an increase in the incidence of eyelid ptosis after repeated injections of Dysport 50 units.

Although efficacy was observed in subjects treated with 60, 70, or 80 units, the degree of efficacy was not significantly different from those subjects who received 50 units, the parameters used to determine the variable dosing were tenuous at best, and efficacy was not corroborated by a second trial for this cosmetic indication. The safety of using variable dosing of Dysport for this indication is based solely on a single dose trial without any long term safety data. Within this data, it was observed that subjects had an increased incidence of ptosis at the 70 unit dose compared to the 50 unit dose (4% vs. 1%, $p < 0.003$), which raises a safety concern. In each of the variable doses, the number of subjects was less than desirable for evaluating safety; but particularly in those who received the 80 unit dose where the number of subjects was only 33.

The indication will be for the temporary improvement in the appearance of glabellar lines, as this most accurately reflects the physiologic action of botulinum toxin. This is a temporary chemical denervation of the muscles. Whether the patient wants to continue/maintain the paralysis will be an individual decision, as some subjects may revert to baseline status before they can be re-injected at 90 days or may decide against further re-treatments. It will not be recommended for subjects 65 years of age or older because in the few subjects in the placebo-controlled trials at 50 units, none had a success at 30 days.

1.3 Recommendations for Postmarketing Risk Management Activities

All botulinum toxin products, both A and B, will have a REMS because of the lack of interchangeability of the units of the individual products and because of the potential for both contiguous and most particularly, systemic spread of the toxin, which could lead to significant morbidity and in some cases, death.

1.4 Recommendations for other Post Marketing Study Commitments

The sponsor will commit to the development of a single dose unit vial of 125 units. This will replace the current vial of 300 units. Chemistry has concurred that this is the lowest feasible unit dose.

There are no clinical PMR/PMCs that will be asked of the sponsor for the indications that are being recommended for approval under this BLA, either glabellar lines or cervical dystonia. The sponsor will have a PMR to assess distant spread of toxin effects after multiple administrations of Dysport during a minimum period of 12 months, collected in pediatric and adult subjects who are being treated for both lower and upper extremity spasticity. They will also have to assess any effects of Dysport on bone metabolism in pediatric subjects. This PMR is not applicable to the glabellar line indication as there have been no reports of systemic spread of Dysport in the worldwide global database at the 50 unit dose (Dysport has been approved since 1990 worldwide and is approved for the treatment of facial lines in 23 countries); and the treatment of glabellar lines is not a pediatric indication.

2 Introduction and Regulatory Background

2.1 Product Information

Description

DYSPOORT® (Botulinum Type A Toxin–Hemagglutinin Complex) is a sterile, freeze-dried, purified botulinum type A toxin produced by the Hall strain of *Clostridium botulinum* serotype A. It is composed of a 150 kDa polypeptide neurotoxin and accessory proteins.

Each vial of DYSPOORT® contains 300 U of *Clostridium botulinum* type A toxin–hemagglutinin complex, 125 µg of human serum albumin, and 2.5 mg of lactose monohydrate in a sterile, preservative-free, white, freeze-dried pellet for IM injection after reconstitution.

Established Name and Proposed Trade Name

Proposed Established Name: Botulinum Type A Toxin-Hemagglutinin Complex

Proposed Trade Name: Dysport

Reviewer’s Comment: The Agency has decided that Ipsen will not be allowed to add Hemagglutinin Complex to the established name. On the advice of DMEPA, the company also will be advised that the proposed trade name of “Dysport” will not be acceptable, as it tends to overstate the efficacy of the drug product.

Chemical Class

Acetylcholine release inhibitor.

Pharmacologic class

DYSPOORT® blocks neuromuscular transmission by binding to receptor sites on motor 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.

Applicant’s Proposed Indications, dosing regimens and age groups

INDICATIONS AND USAGE

DYSPOORT® is indicated to achieve and maintain improvement in the appearance of moderate to severe glabellar lines associated with procerus and corrugator muscle activity in adult patients.

DOSAGE AND ADMINISTRATION

General Dosing Information

2.2 Tables of Currently Available Treatments for Proposed Indications

The only product approved for the treatment of glabellar lines in the United States is Botox Cosmetic. This is a botulinum Type A drug product that is supplied in 100 unit vials. The dose approved to treat glabellar lines is 20 units. The units of this drug product are not interchangeable with the Dysport drug product.

2.3 Availability of Proposed Active Ingredient in the United States

The product is a new molecular entity that has not been approved in the United States.

2.4 Important Safety Issues With Consideration to Related Drugs

On February 8, 2008, the FDA issued an early communication regarding Botox and Botox Cosmetic (botulinum toxin type A) and Myobloc (botulinum toxin type b). The drugs have been associated with spread of the toxin to areas distant from the site of injections which resulted in cases of systemic botulism. Some of the adverse reactions have been linked to respiratory failure

and death. Many of the deaths were pediatric cases associated with off-label use for limb spasticity in children with cerebral palsy at high doses. Submitted data from the sponsors of these drug products reveal serious adverse events associated with botulinum toxin in both contiguous and non-contiguous areas to the injection site. Further, submitted data from the sponsor and the medical literature reveal that patients with neuromuscular disorders and/or chronic debilitating illnesses seemed to be vulnerable to botulinum toxin's local and systemic adverse events.

The FDA identified 22 cases of diagnosed or suspected iatrogenic botulism associated with cosmetic use. Areas identified as treated included glabellar lines, forehead, "crows feet lines," orbital area, nasolabial folds and neck. The doses ranged from 22 to 500 units of Botox and the time to onset (from last injection until the first presentation of symptoms) ranged from 2 – 21 days (mean - 10 days; median - 14 days).

Of those 22 cases, there were 2 deaths. OSE review on 7/3/08, RCM 200-31, section 5.1 addresses those 2 deaths. The first case was of a patient who had a diagnosis of Guillain-Barre syndrome with CMV infection. The second case was of a patient who had flu-like symptoms that began more than 3 weeks following Botox use, followed by respiratory distress and staphylococcal pneumonia several weeks later. Neither cosmetic case appeared to be clearly due to spread of botulinum toxin.

As a result of these events and after further evaluation by the FDA, it was decided that all botulinum toxin products would have a REMS, which would consist of the following:

- 1) Class labeling for all of the botulinum toxin products
Boxed Warning - regarding distant spread of toxin effect.
Warnings/Precautions - regarding lack of interchangeability between botulinum products, spread of toxin effect, dysphagia and breathing difficulties in treatment of cervical dystonia, and pre-existing neuromuscular disorders. Advice that immediate medical attention for patients may be required for problems with swallowing, speech, or respiratory disorders that can occur within hours to weeks after injection.
- 2) Medication Guide
- 3) Communication Plan
Communication Plan to disseminate information regarding the risks of potential systemic spread of botulinum toxin after local injection and lack of interchangeability of botulinum toxin products. The plan is to be targeted to healthcare providers who are likely to prescribe and/or inject botulinum toxin products. This will include a "Dear Healthcare Professional Letter".
- 4) Additional Trial
Require of all Sponsors a randomized, double-blind, placebo-controlled, multiple fixed doses, parallel group clinical trial of botulinum toxin in botulinum toxin-naïve children with spasticity associated with cerebral palsy. The recommended

duration of the study is 12 weeks. Safety data must be collected in the controlled trial, to include data on the systemic spread of the toxin.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Reviewer's Comment: *A PreIND meeting was held in 1998 but minutes for that meeting are not available.*

PreIND Meeting with CBER - 5/21/2002

The sponsor, Ipsen was advised of the following concerning its drug product, Dysport:

- Success of trials would require the success of both the physician assessment of severity of glabellar lines at maximum frown at Week 4 and the subject assessment of improvement of appearance of glabellar lines

- Follow-up period should be 120 days for all subjects in phase 2 trial
- Changes to phase 3 protocol
 - Enrollment of subjects with moderate to severe glabellar lines
 - Primary efficacy evaluation at day 30 post injection
 - Follow-up period for 150 days.
 - Open-label trial with 1200 subjects to receive 2-4 treatments at 3-6 month intervals "as required".

(b) (4)

- 2:1 randomization acceptable.

EOP2 meeting with CBER – 1/08/2004

FDA agreed to the following for the phase 3 clinical trials:

- Co- primary endpoints would be investigator's and patient's assessment of glabellar lines at maximum frown at day 30 who has a rating of "no" or "mild" lines.
- Blinded assessors as a panel review (Independent Photographic Reviewer) would be an important secondary efficacy variable which should be consistent with the investigator's assessment.
- Dose of 50 units into 5 sites based on the phase 2 trial was deemed appropriate for phase 3.
- Recommended a safety database of at least 1500 subjects with the majority having received multiple courses of therapy
- Integrated safety analysis for all available data from clinical trials and post-marketing reports should be submitted with the filing of the marketing application.

PreBLA Meeting with CDER – 10/16/2007

- The sponsor was advised that the efficacy and safety of the variable dosing would be a review issue. Further, they were advised that study 06-01 may not provide adequate safety (particularly long-term safety) for the higher variable dosing regimen

- The sponsor was asked to provide a composite 2-grade improvement endpoint in the ISE for all trials.
- QTc study appears adequate for BLA submission; however, it was agreed that any additional data needed to address cardiac safety would be a phase 4 commitment.

2.6 Other Relevant Background Information

BLA 125274 was submitted on 12/29/07 to the Division of Neurology under the trade name Dysport, for cervical dystonia in the United States and is under review. Dysport, marketed as Dsyport, has been marketed in other countries since 1990 and is currently approved in 73 countries for clinical indications including blepharospasm, hemifacial spasm, spasmodic torticollis, equinus foot deformity due to spasticity in pediatric patients with cerebral palsy, hyperhidrosis, and/or spasticity of the arm and leg in patients following a stroke. It is approved for treatment of the cosmetic indication of facial lines in 23 countries.

The drug product has not been withdrawn from any market for safety reasons. There has been one Direct Healthcare Professional Communication that was distributed in Europe at the request of the EMEA. This was to revise labeling for all therapeutic botulinum toxins to include information on the potential for adverse events due to the spread of the locally injected neurotoxin. Of the two English-speaking foreign labels submitted, that of the United Kingdom and Australia, Dysport is approved in Australia for the treatment of moderate to severe glabellar lines at a dose of 50 units that may be repeated approximately every 16 weeks but not less than 3 months.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The submission was well organized and in a reviewable format.

3.2 Compliance with Good Clinical Practices

The trials were performed in accordance with the recommendations guiding physicians in biomedical research involving human subjects adopted by the 18th World Medical Assembly, Helsinki, Finland, 1964, and later revisions (insofar as such revisions are consistent with US treaty obligations and in accordance with US law), with the Common Rule (Part 46 of Title 45 of the U.S. Code of Federal Regulations) and with Parts 50 and 56 of Title 21 of the U.S. Code of Federal Regulations.

All trials were conducted under an IRB approval and appropriate reports on the progress and conclusion of the trials by the principle investigator were to be made to the IRB at least annually

in accordance with applicable government regulations. Federal regulations also provide for expedited reporting of certain events to the IRB and the FDA. The Investigator is responsible for such expedited reporting. Additionally, the Investigator is responsible for any additional expedited reporting requirements that may be imposed by his or her IRB.

3.3 Financial Disclosures

The sponsor submitted financial disclosure for the covered clinical trials, as denoted on the following table:

Study Number	Study Description
Y-97-52120-719	Safety and Efficacy
A-2006-01	Safety and Efficacy
Y-97-52120-085	Safety and Efficacy
Y-97-52120-096	Safety and Efficacy
Y-97-52120-718	Safety and Efficacy

The majority of investigators did not have any financial disclosures. Ten investigators did have financial disclosures with reasons that varied from consulting agreements to “significant equity interest, in the form of Medicis stock. There was one investigator from trial 719, three from 06-01, two from 085, 3 from trial 718, and 1 who participated in both 085 and 06-01.

In consultation with Dr. Kathleen Fritsch, biostatistical reviewer, the centers in the trials associated with these investigators did not drive the efficacy results. Further, the trials were double-blind, placebo-controlled and efficacy was determined not only by the investigator’s assessment but also by the subject’s self-assessment.

DSI conducted investigations of 2 study centers, because both of these investigators took part in more than one trial. Frederic Brandt, M.D. participated in trial 719 (site #01) and 06-01 (site #73). Joel Schlessinger, M.D. participated in trial 719 (site #88) and trial 085 (site #6). DSI concluded after its investigations that the centers adequately conducted the trials and that the data generated could be used to support the proposed indication.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The trials that support the use of Dysport in the treatment of glabellar lines are from two different manufacturing sites, the IU facility which manufactured CAMR Dysport and the IBL facility that manufactured IBL Dysport. According to the chemistry reviewer, “Manufacturing

process did not have significant changes from IU facility to IBL facility. Modifications are considered as manufacturing improvement since new equipments and higher grade raw materials were used in the IBL facility.” The reviewer goes on to state, “Drug substances produced in IU facility and IBL facility are similar in terms of biochemistry of key components, biological activity (potency) and pre-clinical animal study.”

The trials used 3 lots of drug product. One of the lots was out of spec and lost 20% of its potency. This lot was used in the long-term safety trial, 732, which was a roll-over trial of 36 months duration. The suspect lot was used over a six month period from July 24, 2007 – January 2008. It appears from the listing that each affected subject received 1 to 2 cycles from it with cycles 4, 5, and 6 being affected the most.

Reviewer’s Comment: *This small loss of potency that was used in some subjects for at most 2 out of 8 cycles in one long term trial comprises a small percentage of subjects in the entire safety database (approximately 460/2491, 18%). Study 720- which is a long term safety trial comprising 1200 subjects over 5 cycles of treatment is more than adequate to assess the safety of long term use of Dysport. Also, the number of cycles is small in which this lot was used and there are 6 other cycles in which to assess safety. In summary, this should have little effect on the overall safety assessment of Dysport in the treatment of glabellar lines. The chemistry reviewer, Ennan Guan, states in her review that the manufacturing process is well-controlled and consistently delivers a quality product suitable for its intended use. Chemistry, however, has determined that the sponsor, as a post-marketing commitment, has to perform a comprehensive analysis of the degradation products and pathways along with any proposed modifications to the process and /or stability protocol that will improve drug product stability. They must also establish tighter potency acceptance criteria for the qualification of new reference standards. Chemistry has further stated that since new reference standards are only infrequently created, this issue can be safety addressed post-approval.*

Flagellin

The following is excerpted from the chemistry review:

“Flagellin is present in the Dysport with relative quantity ranging from undetectable to (b) (4). Flagellin is a proinflammatory protein that binds to the Toll-like receptor 5 (TLR5). The Toll like receptor family, which is critically involved in innate immunity, consists of 13 mammalian members. TLRs are preferentially expressed in professional antigen-presenting cells such as dendritic cells (DCs) and macrophages. They recognize specific conserved patterns of proteins or carbohydrates associated with microorganisms. Each TLR activates specific signaling pathways that elicit biological responses to microorganisms including DC maturation and cytokine production that shape adaptive immune responses. When stimulated by the TLR5-ligand flagellin, TLR5 lamina propria dendritic cells induced the differentiation of naïve B cells into immunoglobulin A-producing plasma cells and promote the differentiation of antigen-specific interleukin 17-producing T helper cells (S. Uematsu, et al., Volume 9 Number 7 July 2008, Nature Immunology). Blohmke reports that the inhibition of TLR5 abolished the damaging inflammatory response generated by Cystic fibrosis airway cells following exposure to P.

aeruginosa (J. immunology, 2008, 180: 7764-7773). However, studies of TLR5 distribution have not reported expression in muscle cells and neuronal cells. Since Dysport is administered intramuscularly and acts on neuromuscular junction site, the risk for activating the TLR5 signaling pathway is minimal.

Concern is further minimized by the fact that humans are colonized by multiple flagellin expressing organisms (e.g. E. coli) and most people have anti-flagellin antibodies. Therefore the main risk is increased injection site reactions and increased anti-BNT/A immune responses.”

Chemistry will be asking for the following post-marketing commitment regarding flagellin:

Validate the toll like receptor binding assay for detection of flagellin in drug substance and drug product.

***Reviewer’s Comment:** Dr. Guan is probably correct that the risk for activating the TLR5 signaling pathway from an intramuscular injection in human subjects is minimized by the presence of anti-flagellin antibodies. However, it is important to note the role of this protein in inducing inflammation through dendritic cells. Langerhans cells are dendritic cells that are present in the epidermis and also can be found in the dermis of human skin. Injection site reactions occurred in the clinical trials in 3% of the subjects in the short-term and in 4% of subjects in the long-term safety data. Given that this occurs with IM injection where little of the drug should be exposed to the skin, Dysport should not be used off-label in diseases such as hyperhidrosis where the drug product is injected intradermally. This is an approved indication for Botox, another botulinum toxin type A. It will be important to note this for labeling that the drug products are not interchangeable and using Dysport intradermally could illicit an adverse immune reaction.*

4.2 Clinical Microbiology

There is no clinical microbiology.

4.3 Preclinical Pharmacology/Toxicology

It was determined for this drug product, a preclinical study was necessary in rats to evaluate the effects of chronic dosing at nerve terminals. Dr. Jill Merrill states the following in her review concerning this study:

“This study consisted of three monthly intramuscular injections at two dose levels (0.1 and 2 U/injection) followed by a 13-week or 26-week recovery period. This treatment regimen induced a reduction of the fiber size in the gastrocnemius muscle and was observed clinically as an apparent shrinkage of the injected muscle and reduced locomotory activity. Most of the fibers had returned to their normal size after a 13-week recovery period. Recovery of the muscle fiber was essentially complete after 26 weeks, with full recovery of locomotory activity at 17 weeks post treatment.”

Reviewer’s Comment: *This data is supportive to suggest that complete muscle recovery probably occurs in human subjects as well. One cannot rule out, however, that muscle activity in humans may not exactly mimic that of animals.*

In conjunction with the pharmacology toxicology reviewer in DNP, Dr. Merrill has determined that Dysport should receive a pregnancy category C designation.

4.4 Clinical Pharmacology

The following was excerpted from the biopharmacology review of Dysport from Dr. Veneeta Tandom of the Neurology division:

“This BLA has no clinical pharmacology/pharmacokinetics study because valid direct techniques are not yet available for measuring botulinum toxin type A (BTX-A) in blood samples. The administration of quantities that would result in peripheral measurement would be unethical due to the resulting untoward pharmacological activity. The IM injection of BTX-A toxin complex remains at the injection site, with very little distributed beyond the muscle injected. Therefore, DYSPORE is not likely to have any measurable systemic exposure at the doses administered. Pharmacokinetic section of Botox (botulinum toxin type A) label also states that botulinum toxin type A is not expected to be present in peripheral blood at measurable levels following intramuscular or intradermal injection at recommended doses.”

Specifically for the Dysport BLA and according to the review by Dr. Tapash Ghosh, immunogenic potential of Dysport was investigated through a radioimmunoprecipitation assay (RIPA-C) and through a mouse preprotection assay (MPA). Of the subjects tested, 5/1554, 0.32% were seropositive on anti-product antibodies by RIPA-C but not by MPA. These subjects had no evidence of reduced efficacy or of an altered safety profile.

5 Sources of Clinical Data

5.1 Tables of Clinical Studies

Study ID	Study start Enrollment status, date	Design Control Type	Study & Ctrl Drugs Dose, Route & Regimen	#Subjects by arm entered/completed	Duration	Gender M/F Median Age (Range)	Diagnosis Inclusion Criteria	Primary Endpoints
Number of Study Centers Locations	Total enrollment/ Enrollment goal							

Placebo-Controlled Studies

Y-97-52120-717 (717) 5 sites United States - 4 Canada - 1	7/28/2004 Completed 12/12/2002 373/360	Multi-center, randomized, parallel-group, placebo-controlled, double-blind, dose-finding	Single dose reconstituted solution; Dysport (CAMR) 20, 50 or 75 units IM into 5 locations along glabellar muscles	Dysport (CAMR) 20 u – 90/87 50 u – 95/91 75 u – 94/93 Placebo – 94/93	4 months Single dose	13%/87% 23%/78% 18%/82% 11%/89% 42 years (20 – 76 years)	Moderate to severe glabellar lines	Investigator's assessment of glabellar (g) lines at maximum frown at day 30; patient global assessment of change of g lines at day 30
Y-97-52120-718 (718) 5 sites in the United States	4/26/2004 Completed 12/20/2004 300/300	Multicenter, randomized, double-blind, placebo controlled, 2:1	Single dose reconstituted solution; Dysport (CAMR) 50 units IM injection	Dysport (CAMR) 50 units – 200/190 Placebo – 100/92	5 months Single dose	14%/86% 12%/88% 44.5 years (21 – 71 years)	Moderate to severe glabellar lines	Investigator's assessment of glabellar (g) lines at maximum frown at day 30; patient global assessment of change of g lines at day 30
52120-719 (719) 3 sites in the United States	11/18/2005 Completed 7/28/2006 158 subjects enrolled	Multicenter, randomized, double-blind, placebo-controlled 2:1	Single dose reconstituted solution of Dysport Single dose of placebo IM injection	Dysport (IBL) 50 u – 105/97 Placebo – 53/46	6 months Single dose	14%/86% 15%/85% 44 years (19-75 years)	Moderate to severe glabellar lines	Investigator's assessment of glabellar (g) lines at maximum frown at day 30; patient global assessment of change of g lines at day 30; Composite 2-grade improvement at day 30
Y-97-52120-085 (085) 6 sites in the United States	6/20/05 Completed 4/11/2007 466/466	Multicenter, randomized double-blind placebo-controlled 1:1 after 2 open label treatments	Multiple-dose reconstituted solution of Dysport Placebo – single dose; IM injection	Dysport (IBL) 50 u – 311 Placebo – 155	17 months Multiple dose	14%/86% 10%/90% 46 years (21-74 years)	Moderate to severe glabellar lines	Investigator's assessment of glabellar (g) lines at maximum frown at day 30; patient global assessment of change of g lines at day 30; Composite 2-grade improvement

A-2006-01 (06-01)	12/7/06	Multicenter, randomized, double-blind placebo-controlled 1:1	Reconstituted solution; 50, 60, 70, 80 units; single dose; IM injection	Dysport 50 u – 22/22	5 months	0%/100%	Moderate to severe glabellar lines	at day 30	
27 U.S. sites	Completed 7/17/07			Placebo - 11/11	Single dose	0%/100%			
	816			Dysport 60 u - 282/281		2%/98%			
	12/7/06	Substudy to detect any treatment related QT interval changes		Placebo – 144/142		2%/98%			
5 U.S. sites	Completed 2/12/07			Dysport 70 u – 206/204		12%/88%			
				Placebo – 90/88		4%/96%			
				Dysport 80 u – 33/31		100%/0%			
				Placebo – 27/26		100%/0%			
Long-term Safety Studies									
Y-97-52120-720 (720)	10/7/04	Multicenter Open-label	Multiple dose Dysport 50 units IM injection	940 subjects	13 months	10%/90%	Moderate to severe glabellar lines	Assess the safety of Dysport	
2 U.S. sites	Completed 3/1/06			5 cycles	48 years (21,80)				
Y-97-52120-732 (732)	11/14/05	Multicenter Open-label	Multiple dose Dysport 50 units IM Injection	1349 subjects	24 months	8%/92%	Moderate to severe glabellar lines	Assess the safety of Dysport	
24 U. S. sites	Ongoing; 95% complete			8 cycles	49 years (23, 81) (for 768 of subjects)				
Other Studies									
Y-07-52120-096 (096)	2/24/2005	One center, randomized double-blind controlled comparability 1:1	Single dose IM injection of Dysport 50 units (CAMR or IBL product)	Dysport CAMR 50 u – 50/48	1 month	4%/96%	Moderate to severe glabellar lines	Assess the relative clinical safety and efficacy of two batches of Dysport of similar potency	
1 site United States	Completed 4/4/2005			IBL 50 u – 50/46	Single dose	6%/88%			
	94/100					48 years (25 – 71)			
A-2006-01 (06-01)	12/7/06	Sub-study to detect any treatment related QT interval changes	EKG evaluation	Total 89/79	14 days		Moderate to severe glabellar lines; Naïve to Dysport or Botox exposure within 12 months of study; baseline nl EKG	The mean time-averaged change from Baseline in QTcB interval as between treated and placebo groups.	
5 centers United States	Completed 2/12/07			Baseline;		Dysport group =50			2%/98%
	89/75		30 minutes post treatment;	Placebo group = 29		48 years (29- 67 years)			
			14 day post-treatment			7%/93%			
						49 years (34 – 68 years)			

Source: BLA 125256, ISE, table 1, pages page 23, table 2, page 26, ISS table 1, page 17 and individual study reports
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5.2 Review Strategy

There are several components to the review strategy to determine the efficacy and safety of Dysport in the treatment of moderate to severe glabellar lines. First, trial 717, a phase 2 dose-ranging trial, is reviewed to demonstrate how the sponsor determined that 50 units of Dysport is the appropriate dose to treat glabellar lines. Second, trial 096 is reviewed to establish a clinical bridge of equivalent efficacy and safety between the CAMR Dysport and IBL Dysport. This is important, as it allows trial 718, a CAMR Dysport phase 3 trial, to be used as a pivotal trial to establish the efficacy of the IBL Dysport product, the to-be-marketed Dysport. Third, trials 718, 719, and 085 are the primary sources of data to establish the efficacy and short-term safety of Dysport 50 units for the treatment of moderate to severe glabellar lines and in the case of trial 085, the establishment of efficacy after repeated doses of Dysport 50 units. Fourth, trials 720 and 732 are reviewed to establish long-term safety. Finally, trial 06-01 is reviewed as the sponsor attempts with this one trial, with only one treatment cycle, to make a case for using higher doses (50 units – 80 units) to treat moderate to severe glabellar lines based on muscle mass.

5.3 Discussion of Individual Studies

5.3.1 Trial Y-97-52120-717

Title: “A phase 2, Randomized, Double-Blind Placebo-Controlled, Dose-Finding Study to Determine the Optimal Dose of 52120 (Dysport) in the Treatment of Glabellar Lines”

This is a dose-ranging trial that evaluated 3 doses of Dysport against placebo in the treatment of glabellar lines, 20 units, 50 units, and 75 units. The main inclusion criteria were subjects at least 18 years of age and glabellar lines of at least moderate severity. The disposition of subjects is illustrated in table 1.

Table 1
Disposition of Subjects – ITT Population

	Placebo (N=94)	52120 Dose			Total (N=373)
		20 Units (N=91)	50 Units (N=93)	75 Units (N=95)	
Patient completed study					
Yes	93 (98.9%)	87 (95.6%)	91 (97.8%)	94 (98.9%)	365 (97.9%)
No	1 (1.1%)	4 (4.4%)	2 (2.2%)	1 (1.1%)	8 (2.1%)
Primary reason for discontinuation					
Patient decision	0	0	2 (2.2%)	0	2 (0.5%)
Patient non-compliance	1 (1.1%)	2 (2.2%)	0	1 (1.1%)	4 (1.1%)
Lost to follow-up	0	2 (2.2%)	0	0	2 (0.5%)

BLA 125256 study report 717, table 3, page 41

The mean age of subjects in the trial was 42 years old and the majority of subjects were female, 83.9%. Table 2 describes the demographics of the ITT population.

Table 2
Demographics – ITT Population

	Placebo (N=94)	52120			Total (N=373)
		20 units (N=91)	50 units (N=93)	75 units (N=95)	
Age (years)					
n	94	91	93	95	373
mean	42.5	41.5	41.9	42.1	42.0
SD	9.9	9.7	10.1	10.3	10.0
median	43.0	42.0	42.0	42.0	42.0
range	20 – 63	20 – 64	23 – 67	20 – 76	20 – 76
Sex					
male	10 (10.6%)	12 (13.2%)	21 (22.6%)	17 (17.9%)	60 (16.1%)
female	84 (89.4%)	79 (86.8%)	72 (77.4%)	78 (82.1%)	313 (83.9%)
Race/ethnicity					
Caucasian	70 (74.5%)	70 (76.9%)	64 (68.8%)	74 (77.9%)	278 (74.5%)
Native American	0	0	1 (1.1%)	0	1 (0.3%)
Hispanic	22 (23.4%)	16 (17.6%)	25 (26.9%)	18 (18.9%)	81 (21.7%)
African-American	0	2 (2.2%)	1 (1.1%)	1 (1.1%)	4 (1.1%)
Asian	0	0	2 (2.2%)	1 (1.1%)	3 (0.8%)
Other	2 (2.1%)	3 (3.3%)	0	1 (1.1%)	6 (1.6%)
Total non-Caucasian	24 (25.5%)	21 (23.1%)	29 (31.2%)	21 (22.1%)	95 (25.5%)

Source: BLA 125286, Study report 717, table 7, page 44

The assessment of severity of glabellar lines was according to the following scale:

Grade	Severity of Glabellar Lines
0	None
1	Mild
2	Moderate
3	Severe

Source: BLA 125286, Study report 717, table 2, page 34

A responder was defined as a subject who had a score of 0 or 1 on day 30.

The patient’s assessment was based on the following question, “How would you rate the change in the appearance of your glabellar lines compared with immediately before the injection?” A responder was defined as having a grade of at least +2 at day 30 based on the following scale:

- +4 (complete improvement, about 100%)
- +3 (marked improvement, about 75%)
- +2 (moderate improvement, about 50%)

- +1 (minimal improvement, about 25%)
- 0 same
- 1 (slight worsening, about 25%)
- 2 (moderate worsening, about 50%)
- 3 (marked worsening, about 75%)
- 4 (very marked worsening, about 100%)

Efficacy Results

There was no statistical difference between treatment arms at baseline according to the investigator assessment with respect to severity of glabellar lines: at maximum frown, $p=0.334$ or at rest, $p=0.982$. Results are shown in table 3.

Table 3
Investigator’s Assessment of Glabellar Lines at Baseline
ITT Population

	Placebo (N=94)	52120		
		20 units (N=91)	50 units (N=93)	75 units (N=95)
Glabellar lines at maximum frown				
2	42 (44.7%)	43 (47.3%)	35 (37.6%)	48 (50.5%)
3	52 (55.3%)	48 (52.7%)	58 (62.4%)	47 (49.5%)
Glabellar lines at rest				
0	3 (3.2%)	5 (5.5%)	4 (4.3%)	5 (5.3%)
1	42 (44.7%)	35 (38.5%)	42 (45.2%)	40 (42.1%)
2	44 (46.8%)	47 (51.6%)	41 (44.1%)	46 (48.4%)
3	5 (5.3%)	4 (4.4%)	6 (6.5%)	4 (4.2%)

Source: BLA 125286, Study Report 717, table 8, page 45

Efficacy was observed at maximum frown at day 30 for all three arms as compared to placebo, with statistical significance established at $p<0.001$. The proportion of subjects who were responders, increased across doses. The difference between the higher two doses, however, is very small (see table 4).

Table 4
Proportion of Responders at Day 30
Investigator’s Assessment – ITT Population

	Placebo (N=94)	52120		
		20 units (N=91)	50 units (N=93)	75 units (N=95)
With missing values imputed				
n	6	59	72	81
proportion	0.064	0.648	0.774	0.853
95% CI	(0.015, 0.113)	(0.550, 0.746)	(0.689, 0.859)	(0.782, 0.924)
p-value	--	<0.001	<0.001	<0.001
With missing values treated as non-responders				
n	6	59	72	81
proportion	0.064	0.648	0.774	0.853
95% CI	(0.015, 0.113)	(0.550, 0.746)	(0.689, 0.859)	(0.782, 0.924)
p-value	--	<0.001	<0.001	<0.001
Source: BLA125826, adapted from table 9, page 47, study report 717				

The results of the patient’s assessment were similar as described in table 5.

Table 5
Proportion of Responders at Day 30
Patient’s Assessment – ITT Population

	Placebo (N=94)	52120		
		20 units (N=91)	50 units (N=93)	75 units (N=95)
With missing values imputed				
n	10	65	79	80
proportion	0.106	0.714	0.849	0.842
95% CI	(0.044, 0.168)	(0.621, 0.807)	(0.776, 0.922)	(0.769, 0.915)
p-value	--	<0.001	<0.001	<0.001
With missing values treated as non-responders				
n	10	65	79	79
proportion	0.106	0.714	0.849	0.832
95% CI	(0.044, 0.168)	(0.621, 0.807)	(0.776, 0.922)	(0.757, 0.907)
p-value	--	<0.001	<0.001	<0.001
Source: BLA 125286, adapted from table 10, study report 717, page 48				

There was also a statistically significantly larger proportion of responders using the investigator assessment for all other post-baseline visits ($p \leq 0.004$) except the 20-unit group at day 120 ($p=0.071$).

Safety

In this dose-ranging trial, there were no events of eyelid ptosis at the 20 unit dose, 1 event at the 50 unit dose and 3 events at the 75 unit dose, comprising 0%, 1.1%, and 2.1%, respectively of subjects. The events were mild to moderate in severity.

Reviewer's Comment: *It is important to note that there is not much difference between the 50 unit dose and the 75 unit dose in terms of efficacy. Indeed, the sponsor states, "The 50-unit dose was as effective as the 75-unit dose, and the duration of action was similar between the 50-unit and 75-unit groups." In terms of safety, the dose-ranging trial suggests an increase in eye disorders (ptosis) with increasing dose. Thus, the choice of 50 units appears to have the best risk/benefit analysis.*

5.3.2 Trial Y-97-52120-096

Title: "A Phase 2, Randomized, Double-blind, Controlled Study to Assess the Safety of One Treatment Cycle of Dysport (50 units) Formulated from Bulk Active Substances (BAS) Manufactured at Different Locations (Ipsen Biopharm Limited [IBL], UK and Center for Applied Microbiology and Research [CAMR], UK) for the Treatment of Glabellar Lines"

The primary objective of this trial was to assess the relative clinical safety of two batches of Dysport of similar potency (50 units) when used in a single administration for the treatment of glabellar lines. Secondary objectives evaluated efficacy of the drug products via assessment of the proportion of responders at maximum frown on day 30 based on the investigator's live assessment and the patient's self-assessment.

One hundred subjects were randomized in a 1:1 ratio to either receive 50 units of Dysport (CAMR) or Dysport (IBL). These subjects had to be botulinum naïve and could not have received any other toxin treatment to any areas of the body at any time. Subject demographics are represented in table 6.

Table 6
Subject Demographics
Study 096 – ITT Population

	Dysport® 50 units IBL BAS N = 50	Dysport® 50 units CAMR 96-02 BAS N = 50	Total N = 100
Age (years)			
Mean ± SD	47.2 ± 9.21	47.2 ± 10.69	47.2 ± 9.93
Median	48.0	47.0	48.0
Minimum, maximum	25, 69	25, 71	25, 71
Sex n (%)			
Male	6 (12%)	2 (4%)	8 (8%)
Female	44 (88%)	48 (96%)	92 (92%)
Race n (%)			
Caucasian	49 (98%)	46 (92%)	95 (95%)
African-American	1 (2%)	3 (6%)	4 (4%)
Hispanic	0	1 (2%)	1 (1%)
Source: BLA 125286, study report 096, table 3, page 44			

Table 7 shows that the majority of subjects at baseline had an evaluation of severe glabellar lines.

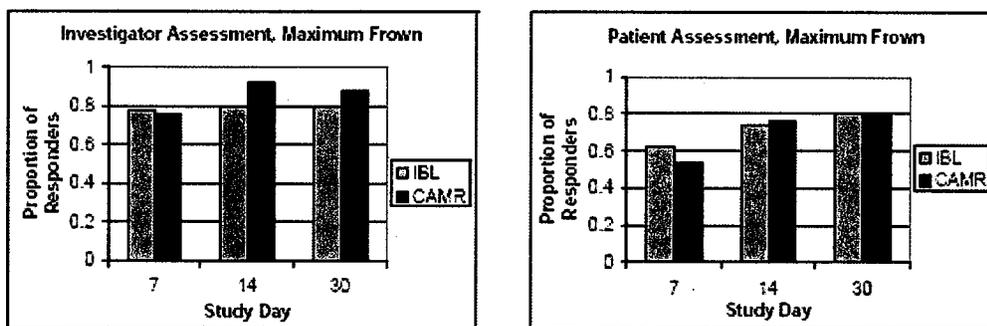
Table 7
Investigator and Patient Assessments
Of Glabellar lines at Baseline – ITT Population

Baseline Assessment	Dysport® 50 units IBL BAS N = 50	Dysport® 50 units CAMR 96-02 BAS N = 50	Total N = 100
Patient Assessment			
At Maximum Frown, n (%)			
Moderate	23 (46)	26 (52)	49 (49)
Severe	27 (54)	24 (48)	51 (51)
Investigator Assessment			
At Maximum Frown, n (%)			
Moderate	15 (30)	14 (28)	29 (29)
Severe	35 (70)	36 (72)	71 (71)
Investigator Assessment			
At Rest, n (%)			
None	1 (2)	0	1 (1)
Mild	14 (28)	12 (24)	26 (26)
Moderate	24 (48)	29 (58)	53 (53)
Severe	11 (22)	9 (18)	20 (20)
Source: BLA 125286, study report 096, table 4, page 46			

Efficacy

The proportion of responders by both Investigator and patient assessments, were very similar for both products (see Figure 1). The proportion of responders for Dysport IBL and Dysport CAMR were clinical indistinguishable, 0.800 and 0.880, respectively for the Investigator assessment, and 0.800 for both based on the patient assessment.

Figure 1
Proportion of Responders
ITT Population



Source: BLA 125286, study report 096, figure 3, page 47.

Safety

Twelve patients (12%) experienced a total of 16 TEAEs: seven patients (14%) receiving 50 units IBL Dysport® had 7 TEAEs and five patients (10%) receiving 50 units CAMR Dysport® had 9 TEAEs. All the TEAEs were mild, except for one event of moderate headache, experienced by one patient in the IBL Dysport® group and considered unrelated to study treatment.

Three patients in the IBL Dysport® treatment group experienced eye disorders. One female patient experienced asthenopia (“tired eyes”) and two female patients experienced unilateral ptosis: these TEAEs were all considered probably related to study drug by the Investigator. Two patients in the CAMR Dysport® treatment group experienced eye disorder TEAEs: one female patient experienced eyelid edema and one female patient experienced glaucoma. These TEAEs were considered unrelated to study drug by the Investigator. The two subjects who experienced ptosis had resolution 46 days later. Table 8 gives a summary of the adverse events in the trial.

Table 8
Summary of Treatment-Emergent AEs
ITT Population – Trial 096

Dysport® IBL-BAS, 50 units, N=50				
Patient	Adverse Event Preferred Term	Relationship to Study Medication	Severity	Duration (Days)
0027	Upper Respiratory Tract Infection	Not related	Mild	8
0036	Asthenopia	Probably related	Mild	7
0038	Seasonal Allergy	Not related	Mild	Cont
0052	Eyelid Ptosis	Probably related	Mild	Cont 1
0067	Eyelid Ptosis	Probably related	Mild	Cont 2
0083	Headache	Not related	Moderate	Cont
0088	Injection Site Pain	Probably related	Mild	7
Dysport® CAMR 96-02, 50 units, N=50				
Patient	Adverse Event Preferred Term	Relationship to Study Medication	Severity	Duration (Days)
0006	Eyelid Edema Injection Site Hemorrhage Injection Site Pain	Not related Not related Not related	Mild Mild Mild	2 2 2
0013	Injection Site Hemorrhage Injection Site Pain Injection Site Swelling	Not related Not related Not related	Mild Mild Mild	4 4 4
0029	Glaucoma	Not related	Mild	Cont
0063	Injection Site Reaction	Probably Related	Mild	2
0075	Sinusitis	Not Related	Mild	18
<small>1Patient reported resolution of ptosis on 4/25/05 – 46 days duration 2Patient reported resolution of ptosis on 4/30/05 – 46 days duration Source: BLA 125286, study report 096, table 10, page 57</small>				

As far as laboratory evaluation of hematology and chemistry parameters, the two are were very similar and there were not any clinically significant abnormal lab values. The two treatment groups were very similar in terms of mean values and lack of change from baseline to day 30 for all the measured clinical chemistry parameters. No subjects in either arm met the definition of seroconversion as it relates to the development of antibodies to botulinum toxin.

Reviewer's Comment: *The sponsor was asked to demonstrate through a clinical trial the comparability of the CAMR manufactured Dysport and the IBL manufactured Dysport. The trial did demonstrate that efficacy and safety of the two products are similar and thus an adequate clinical bridge has been established. Therefore, the phase 3 trial, 718, conducted with the CAMR product, will be used to support efficacy of the 50 unit dose of Dysport IBL, the to-be-marketed drug product.*

5.3.3 Trial A-2006-01

Title: “A Phase 3, Randomized, Placebo-Controlled, Multi-Center, Double-Blind Study of the Safety and Duration of Efficacy of Dysport® (Botulinum Type A Toxin) in Correction of Moderate to Severe Glabellar Lines (and Including a Sub-Study to Detect Any Treatment-Related QT Interval Changes)”

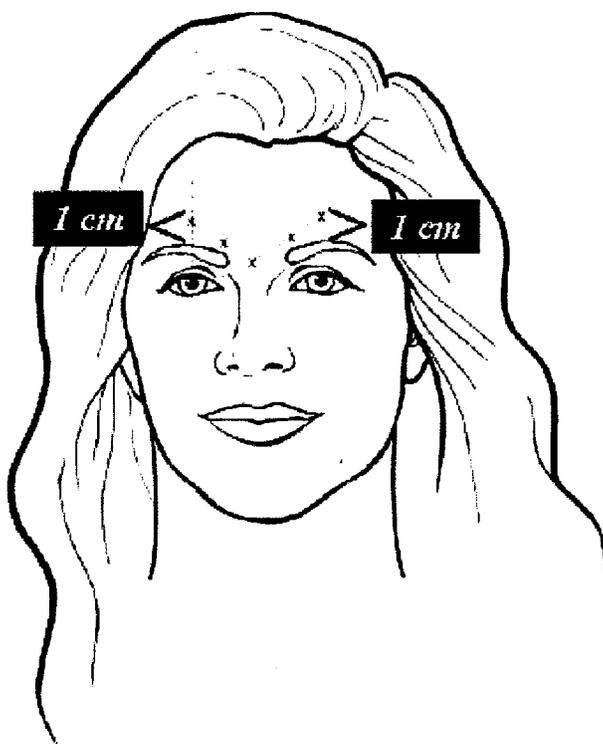
Reviewer’s Comment: *This is a phase 3 efficacy and safety trial that the sponsor submitted in an attempt to obtain varying dosage for the treatment of moderate to severe glabellar lines. It also was undertaken to look at an under-represented ethnic group in the other efficacy trials, African Americans. It will be reviewed separately from section 6, as a fixed dose of 50 units will be recommended for approval. The efficacy summary under section 6, will detail reasons why the variable dosing schedule will not be recommended for approval. Safety will be integrated into section 7. The sub-study to detect any QT interval abnormalities will be discussed under section 7.*

Overall Design

This was a multi-center, Phase 3, randomized, placebo-controlled, double-blind study conducted in the United States to evaluate the efficacy of variable dosing of Dysport® (50, 60, or 70 units in females and 60, 70, or 80 units in males) in the treatment of glabellar lines with a Baseline severity score of 2 or 3. The Baseline severity was assessed separately and independently by a Blinded Evaluator, the patient, and the Investigator. Approximately 750 patients who met predefined entry criteria were selected at 27 US investigative sites. A subset of these patients (N = 75) was enrolled in an EKG sub study, and received a 12-lead EKG with a 10-second rhythm strip at Screening, Day 0 (30 minutes post-injection) and Day 14. Enrollment was targeted to include at least 150 patients of African-American ethnicity and Fitzpatrick Skin Types IV, V, or VI.

All enrolled patients were randomized (separately for African-American patients with Fitzpatrick Skin Types IV, V, or VI and all other patients) in a 2:1 ratio to either Dysport® or placebo, respectively; to be administered at 5 injection sites in the glabellar region according to the figure 2 below. Dysport® was provided in a 300 U vial and reconstituted to 2.5 mL with saline.

Figure 2
Injection Sites for Dysport



Procerus and corrugator muscle mass will be subjectively graded by visual appearance separately for males and females as +, ++, +++.¹ Grading was recorded in the CRF. Males received a total volume of 0.5 mL to 0.7 mL (60, 70, or 80 units) in five equally divided doses. Females received 0.4 mL to 0.6 mL (50, 60, or 70 units) in five equally divided doses and actual delivered volume was recorded. Each active dose had a matched placebo for volume of injection so that the blind was maintained.

Reviewer's Comment: *The doses that are given above are not accurate because reconstitution of a 300 unit vial with 2.5 mL of saline yields 12 units/0.1 ml. Thus only the 60 unit dose is accurate with the lowest dose being 48 units and the highest dose 84 units according to the following table:*

¹ BLA 125286, Study Report, 06-01, Appendix 16.1.1, Protocol and Protocol Amendments, page 21.

**Dosing schedule for Variable Dose Trial (12 U/ 0.1 mL)
Trial 06-01**

Gender	Muscle mass	Total Dose (U)	Injection Volume (mL)
Female	Small	48	0.4
	Medium	60	0.5
	Large	72	0.6
Male	Small	60	0.5
	Medium	72	0.6
	Large	84	0.7

Patients remained under observation at the study site for 30 minutes post-injection and were contacted by telephone 7 days post-injection (Day 7) to check for potential adverse events and concomitant medications. Follow-up clinic visits occurred on Days 14, 30, 60, 90, 120, and 150. A diary was used from Day 1 to Day 14 to record the onset of efficacy effect. Blinded evaluation of glabellar line severity score (GLSS) was performed at Days 14, 30, 60, 90, 120, and 150. The Blinded Evaluator was limited to GLSS scoring alone. To preclude unblinding, the Blinded Evaluator was not aware of the dose group to which the patient was assigned or involved with safety evaluations. Patient participation was generally limited to 150 days from treatment.

Inclusion Criteria

Male or female patients who met all of the following criteria were eligible:

- Eighteen years of age or older.
- Moderate to severe vertical glabellar lines at maximum frown (score of 2 or 3 by the patient's assessment using a static 4-point categorical scale (no wrinkles [0], mild wrinkles [1], moderate wrinkles [2], or severe wrinkles [3])). The patient's static assessment was performed prior to, and independent of, the Investigator's and Blinded Evaluator's live assessment at maximum frown.
- Moderate to severe vertical glabellar lines (score of 2 or 3) by the Investigator's assessment using a validated 4-point Photo Scale of none [0], mild [1], moderate [2], or severe [3]) at maximum frown.
- Moderate to severe vertical glabellar lines (score of 2 or 3) by the Blinded Evaluator's assessment using a validated 4-point Photo Scale of none [0], mild [1], moderate [2], or severe [3]) at maximum frown.
- Nonpregnant females as assessed by negative urine pregnancy test result for females of childbearing potential or as assessed by menopausal status and use of birth control.
- Time and ability to complete the study and comply with instructions.
- Understanding of the study and the contents of the informed consent and agreement indicated by signature thereto.

Exclusion Criteria

Patients who met any of the following criteria were not eligible for this study:

- Inability to substantially lessen glabellar lines by physically spreading them apart.

- Concurrent therapy that, in the Investigator’s opinion, would have interfered with the evaluation of the safety or efficacy of the study medication including but not limited to:
 - Soft tissue augmentation of the glabella (e.g., hyaluronic acid or collagen-type implants) within the previous 6 months or use of any unapproved or semipermanent dermal fillers in the glabellar area.
 - Ablative skin resurfacing on the glabellar area within the previous 3 months.
 - Non-ablative dermal treatment of the glabellar area (e.g., light-emitting diodes, intermittent pulse light, laser, and radio-frequency treatments) within the previous 3 months.
 - Upper eyelid blepharoplasty or brow lift within 6 months of the study.
 - Retinoid, microdermabrasion, or glycolic acid treatments to the glabellar area within two weeks of study participation.
 - Active infection in the glabellar area (e.g., acute acne lesions or ulcers).
- Women who were planning pregnancy during the study.
- Current history of chronic drug or alcohol abuse.
- Enrollment in any study involving the use of investigational devices or drugs in the preceding 30 days.
- History of facial palsy.
- Marked facial asymmetry, ptosis, excessive dermatochalasis, deep dermal scarring, or thick sebaceous skin.
- Neuromuscular junctional disorders (e.g., myasthenia gravis).
- Known allergy or hypersensitivity to any botulinum toxin.
- Clinically diagnosed anxiety disorder, or any other significant psychiatric disorder (e.g., depression) that, in the opinion of the Investigator, might have interfered with the patient’s participation in the study or affect patient’s ability to objectively assess improvements in wrinkle severity.
- Concurrent use of medications that affect neuromuscular transmission, such as curare-like depolarizing agents, lincosamides, polymyxins, anticholinesterases, and aminoglycoside antibiotics.
- Treatment with Botox® within 150 days of participation.

For the EKG subset:

- Family history of prolonged QT-interval syndrome or abnormal Baseline EKG (an abnormal EKG is defined as a heart rate >90; PR >240 msec; QRS complex >110 msec; an abnormal corrected QT interval such as QTcB >470 msec in females or a QTcB >450 msec in males; or any significant morphological changes other than nonspecific T-wave changes).
- Prior exposure to Botox®, Dysport® or other botulinum toxin within the prior 12 months (defined as “botulinum toxin naïve”).
- Concurrent use of any prescription medication other than estrogens or progestones.

Tables 9, 9a-9c describes the two co-primary efficacy variables, the Investigator assessment and patient assessment of glabellar lines severity.

Table 9
Primary Efficacy Variables – Trial 2006-01

Blinded Evaluator’s/Investigator’s Assessment (Primary Efficacy Endpoint)	Patient’s Assessment (Primary Efficacy Endpoint)
<p>Blinded Evaluator’s live assessment using the Photographic Scale (text Table 9a) to evaluate duration of treatment response.</p> <p>Duration of treatment response was defined as the span of time (in days) between onset of response and loss of response (GLSS greater than [1] as per Blinded Evaluator’s live assessment)</p> <p>A Composite 2+ Grade Improvement was also measured to determine the proportion of Responders (see table 9c).</p>	<p>Patient’s self-assessment using the Patient’s Static 4-point Categorical Scale (text Table 9b) to evaluate duration of treatment response.</p> <p>Duration of treatment response was defined as the span of time (in days) between onset of response and loss of response (GLSS greater than [1] as per patient’s assessment).</p> <p>A Composite 2+ Grade Improvement was also measured to determine the proportion of Responders (see table 9c).</p>
<p>Source: BLA 125286, ISE, adapted from table 12, page 41.</p>	

Table 9a
Blinded Investigator’s/Blinded Evaluator’s Photographic Scale to Assess the Severity of Glabellar Lines at Maximum Frown¹

Grade	Severity of Glabellar Lines	Description
0	None	Relaxed skin tension line – no wrinkle.
1	Mild	Glabellar depression(s) – a mild depression(s) in the glabellar area (inter-brow space) surrounded by bulging of the glabellar muscles.
2	Moderate	Glabellar groove – moderate depression(s) of the inter-brow space surrounded by moderate to significant muscle contraction and bulging.
3	Severe	Glabellar furrow – deep grooves(s) in the glabellar are (inter-brow space) surrounded by profound muscle contraction and bulging.

¹this scale was used in all adequate and well-controlled phase 3 trials.
Source: BLA 125286, ISE, table 4, page 29

Table 9b
Patient’s Static 4-Point Categorical Scale to Assess the Severity of Glabellar Lines at Maximum Frown¹

Grade	Severity of Glabellar Lines	Description
0	No Wrinkles	Smooth skin
1	Mild Wrinkles	Fairly smooth skin
2	Moderate Wrinkles	Glabellar lines
3	Severe Wrinkles	Deep glabellar lines

¹This scale was used in all adequate and well controlled trials.
 Source: BLA 125286, ISE, table 6, page 30.

Table 9c gives a summary of the 2+ and 1+ criteria for improvement at Day 30 of maximum frown where in order to be a responder. The Agency asked for a 2+ composite score where a person who entered the trial with moderate severity of glabellar lines would have to have a score of 0 or “none” on the severity scale to be considered a responder and both the investigator and the patient would have to score the response the same.

Table 9c
Efficacy Endpoint Outcome Summary for 2+ and 1+ Grade Improvement

Assessment	Baseline Evaluation	Post-Baseline Visit Possible Outcome
2+ Grade Improvement		
<ul style="list-style-type: none"> • Composite Response • Blinded Evaluator’s/ Investigator’s response (as per text Table 9a) • Patient response (as per text Table 9b) 	‘Moderate’ [2]	‘None’ [0]
	‘Severe’ [3]	‘None’ [0] or ‘Mild’ [1]
1+ Grade Improvement		
<ul style="list-style-type: none"> • Composite Response • Blinded Evaluator’s/ Investigator’s response (as per text Table 9a) • Patient response (as per text Table 9b) 	‘Moderate’ [2]	‘None’ [0] or ‘Mild’ [1]
	‘Severe’ [3]	‘None’ [0] or ‘Mild’ [1]

Source: BLA 125286, ISE, adapted from table 7, page 31.

Efficacy Results

Exactly 816 patients were treated and analyzed: 54 placebo-treated and 106 Dysport®-treated patients were of African-American ethnicity. A total of 79 eligible patients were enrolled in the EKG subset. A total of 799/816 patients completed the study: 534/544 (98%) in the active group and 265/272 (97%) in the placebo group. Overall, the mean age was 49 years with a majority of female (88%) and White (placebo: 70%; Dysport®: 67%) patients.

A total of seven placebo-treated patients and ten Dysport®-treated patients discontinued the study. Most non-completing patients discontinued due to patient decision (6/7 placebo-treated patients and 2/10 Dysport®-treated patients) or because they were lost to follow-up (1/7 placebo-treated patients and 7/10 Dysport®-treated patients). One patient in the Dysport® group was discontinued because of non-compliance with study requirements. No patient discontinued due to adverse event or lack of product efficacy.

Baseline assessment was very similar between placebo and Dysport treated subjects as described in table 10.

Table 10
Blinded Evaluator’s Live Assessment, Investigator’s Live Assessment, and Patient’s Self-Assessment of Glabellar Lines by Treatment Group at Baseline: ITT Population

Baseline Assessment	Placebo (N=272)	Dysport (N=544*)
Blinded Evaluator’s Assessment at Maximum Frown		
Moderate [2]	81 (30%)	193 (35%)
Severe [3]	191 (70%)	350 (64%)
Patient’s Assessment at Maximum Frown		
Moderate [2]	113 (42%)	249 (46%)
Severe [3]	159 (58%)	295 (54%)
Blinded Evaluator’s Assessment at Rest		
None [0]	31 (11%)	70 (13%)
Mild [1]	120 (44%)	250 (46%)
Moderate [2]	112 (41%)	209 (38%)
Severe [3]	9 (3%)	15 (3%)

Source: BLA 125286, Study Report A-2006-01, table 6, page 87

Although the above assessment was collected at baseline, the sponsor used another variable to assess the dose of drug that the subject would receive: muscle mass of the procerus and corrugator muscles. This was done by visual inspection and assigned a grade of +, ++, +++. Table 11 shows the muscle mass and compares it to baseline glabellar line severity.

Table 11
Muscle Mass by Baseline Glabellar Line Severity Using the Investigator’s Live Assessment at Maximum Frown and Gender – Variable Dose ITT Population

OVERALL (N=816)			
Muscle Mass	Moderate, n (%)	Severe, n (%)	Total, n (%)
Light/Small (+)	25 (66)	13 (34)	38 (5)
Moderate/Medium (++)	206 (46)	244 (54)	450 (55)
Heavy/Large (+++)	23 (7)	305 (93)	328 (40)
Total	254 (31)	562 (69)	
MALE (N=97)			
	Moderate, n (%)	Severe, n (%)	Total, n (%)
Light/Small (+)	1 (20)	4 (80)b	5 (5)a
Moderate/Medium (++)	17 (59)	12 (41)b	29 (30)a
Heavy/Large (+++)	6 (10)	57 (90)b	63 (65)a
Total	24 (25)	73 (75)a	
FEMALE (N=719)			
	Moderate, n (%)	Severe, n (%)	Total, n (%)
Light/Small (+)	24 (73)b	9 (27)b	33 (5)a
Moderate/Medium (++)	189 (45)b	232 (55)b	421 (59)a
Heavy/Large (+++)	17 (6)b	248 (94)b	265 (37)a
Total	230 (32)a	489 (68)a	

Reviewer’s Comment: *The above variable, muscle mass size by visual inspection, is not a validated variable and does not seem to correlate well with the severity of glabellar line severity. For example, 27% of women were deemed to have a light/small muscle mass, but actually had severe glabellar lines. Those women would only get the lowest dose of drug. Conversely, those women deemed to have heavy/large muscle mass, but only had moderate severity of glabellar lines, may have gotten too much drug product (getting the highest dose).*

Table 12 shows the efficacy results in the overall trial. Efficacy was statistically significant for all efficacy variables, with $p < 0.001$ when comparing the Dysport arm versus the placebo arm.

Table 12
Success at Maximum Frown
ITT Population – Study 2006-01

	Dysport N = 544	Placebo N = 272
Blinded Evaluator Assessment		
Responders at any time (None/Mild)	511 (93.9%)	31 (11.4%)
Median duration of response to treatment (days) ¹	109	0
Day 30 Responders (None/Mild) ²	453 (83.3%)	9 (3.3%)
Day 30 Responders (None/Mild with 2 grades reduction)	393 (72.2%)	2 (<1%)
Subject Assessment		
Responders at any time (None/Mild)	511 (93.94%)	31 (11.4%)
Median duration of response to treatment (days) ¹	107	0
Day 30 Responders (None/Mild) ²	465 (85.5%)	12 (4.4%)
Day 30 Responders (None/Mild with 2 grades reduction)	375 (68.9%)	5 (1.8%)

¹ Blinded evaluator and subject assessments of duration of response were co-primary endpoints.

² 1+ grade improvement

Source: BLA 125286, study report 06-01, tables 7&8, pages 88, 90.

Table 13 denotes the responders with a composite 2+ improvement. Note that the proportion of responders is lower (59%) than the response of the individual 2+ improvement (72% & 69%), but is still statistically significant, p<0.001.

Table 13
Proportion of Composite Responders 2+ Grade Improvement at Maximum Frown
At Day 30 in Study 06-01 by Treatment
Group – ITT Population

	Placebo (N = 272)	Dysport® (N = 544)
Composite Responders 2+ Grade Improvement		
n	267	538
Responders, n	1	319
Proportion	0.004	0.593
95% CI	(0.000, 0.021)	(0.550, 0.635)
p-value ¹		<0.001
¹ Comparison between treatment groups performed using the Mantel-Haenszel chi-square test stratified by race (Caucasian, African-American, and any other race) and center. Source: BLA 125286, adapted from table 9, study report 06-01, page 93.		

The statistical analysis by FDA biostatistician, Dr. Kathleen Fritsch, is very similar to the sponsor’s analysis, except that missing values were treated as non-responders (see table 13a).

Table 13a
Biostatistical Analysis
Success at Maximum Frown on Day 30
Study 06-01

	Investigator (BE) Assessment		Subject Assessment		Composite	
	Dysport	Placebo	Dysport	Placebo	Dysport	Placebo
	N=544	N=272	N=544	N=272	N=544	N=272
1+	455 (84%)	9 (3%)	469 (86%)	12 (4%)	428 (79%)	6 (2%)
2+	398 (73%)	2 (<1%)	379 (70%)	5 (2%)	319 (59%)	1 (<1%)

Table 14 describes the proportion of responders with a composite 2+ improvement at day 30 at maximum frown by gender and dose. It should be noted that the number of men in each treatment group is small and therefore, to make efficacy conclusions from this data is not reliable.

Table 14
Proportion of Composite Responders 2+ Grade Improvement at Day 30 Using the Blinded Evaluator’s/Blinded Investigator’s and Patient’s Assessments of Glabellar Lines at Maximum Frown by Gender and Treatment Group – Variable Dose ITT Population

	60 Unit Dose		70 Unit Dose		80 Unit Dose	
	Placebo (N=3)	Reloxin® (N=5)	Placebo (N=4)	Reloxin® (N=25)	Placebo (N=27)	Reloxin® (N=33)
MALE						
n	3	5	4	25	26	31
Responders, n	0	3	0	11	0	14
Proportion	0.000	0.600	0.000	0.440	0.000	0.452
95% CI	(0.000, 0.709)	(0.147, 0.947)	(0.000, 0.802)	(0.244, 0.651)	(0.000, 0.132)	(0.273, 0.640)
p-value ¹		0.090		0.113		<0.001
FEMALE						
	50 Unit Dose		60 Unit Dose		70 Unit Dose	
	Placebo (N=11)	Reloxin® (N=22)	Placebo (N=141)	Reloxin® (N=277)	Placebo (N=86)	Reloxin® (N=181)
n	11	22	139	278	84	179
Responders, n	0	16	1	158	0	118
Proportion	0.000	0.727	0.007	0.572	0.000	0.648
95% CI	(0.000, 0.285)	(0.498, 0.993)	(0.000, 0.039)	(0.512, 0.632)	(0.000, 0.043)	(0.573, 0.718)
p-value ¹		<0.001		<0.001		<0.001

Source: BLA 125286, ISE, table 54, page 120.

The sponsor proposes that from this data, men need to have a higher dose, namely 84 units, in order to have a response when as will be shown in the 50 unit dose efficacy trials, men do

respond, albeit in a lower proportion than women. Women do respond across the board, but the proportion of responders does not significantly vary between doses, and does not increase from lowest to highest dose. This trial does not support variable dosing based on muscle mass size. Further, for a cosmetic indication, the sponsor should have more than one trial to demonstrate efficacy with validated assessments, and because of the increased incidence of ptosis seen in women on the 70 unit dose after one treatment, as compared to the 50 and 60 unit doses, safety of these higher doses has not been adequately established (see section 7).

6 Review of Efficacy

Efficacy Summary

Several trials make up the basis for efficacy in phase 3 of Dysport: trial 719, Cycle C of trial 085, trial 718 and trial 096. Together these trials comprised an evaluation of 700 subjects, 476 subjects on Dysport and 224 on placebo. Of these subjects, 600 took part in the short term placebo controlled trials with Dysport 50 units, 376 treated with Dysport and 224 treated with placebo.

Two hundred subjects treated with Dysport 50 units were treated with CAMR instead of the to-be-marketed IBL Dysport (trial 718). Thus before trial 718 could be used to support efficacy of Dysport, the sponsor was asked to perform a clinical bridging study to establish equivalence of clinical efficacy and safety between the two manufacturing sites. Trial 096 is that trial. CAMR and IBL Dysport were manufactured at different locations but using the same manufacturing methodology from one of two BAS batches. In trial 096, there were 2 active arms, CAMR and IBL, each subject receiving one 50 unit dose to treat moderate to severe glabellar lines. The co-primary efficacy endpoints of the trial were an Investigator's live assessment and a patient self-assessment of 1+ grade improvement of glabellar lines at maximum frown on Day 30. There were 50 botulinum naïve subjects in each arm. The results of the trial demonstrated that IBL BAS and CAMR BAS were not clinically different as assessed by Investigator and patient assessments, adverse events, clinical laboratory tests, and vital signs (see section 5.3.2, for more details).

Trials 718 and 719 were similar trials. They were designed as double-blind placebo controlled, randomized trials to assess the effectiveness of 50 units of Dysport versus placebo in the treatment of moderate to severe glabellar lines based on the results of the phase 2 dose ranging trial, trial 717 (see section 5.3.1 for details of that trial). Subjects in these trials were botulinum toxin naïve subjects. They were randomized 2:1, Dysport: placebo, with the following inclusion/exclusion criteria:

Inclusion Criteria

Male and female patients who met all of the following criteria were eligible:

- Eighteen years of age or older.
- Moderate to severe vertical glabellar lines (score of [2] or [3]) at maximum frown by the patient's assessment, using a static 4-point categorical scale (see Section 5.3.3). The patient's static assessment must have been performed prior to, and independent of, the Investigator's live assessment at maximum frown.

- Moderate to severe vertical glabellar lines (score of [2] or [3]) at maximum frown by the Investigator's assessment, using a Study Photographic Scale (see Section 5.3.3).
- Negative pregnancy test result for women of childbearing potential.
- Time and ability to complete the study and comply with instructions.
- Understanding of the study and the contents of the informed consent.

Exclusion Criteria

Patients who met any of the following criteria were not eligible:

- Previous treatment with Dysport® or other botulinum toxin or toxin treatment (other than study treatment) to any areas of the body at any time (prior to or during the study) (*i.e.*, patients were naïve to therapeutic botulinum toxin complex).
- Inability to substantially lessen glabellar lines by physically spreading them apart.
- Soft tissue augmentation of the glabella (e.g., collagen-type implants, such as Zyderm® or Zyplast®) within the previous 12 months or during the study.
- Permanent or semi-permanent dermal fillers in the glabellar area at any time.
- Ablative skin resurfacing on the glabellar area within 12 months or during the study.
- Upper eyelid blepharoplasty or brow lift within 12 months of the study or during the study.
- Non-ablative treatments in the glabellar area for skin dyschromias (e.g., Intense Pulsed Light, light-emitting diodes) within the previous 12 months or during the study.
- Non-ablative dermal treatment in the glabellar area for skin tightening (e.g., radio-frequency treatments) within the previous 12 months or during the study.
- Retinoid, microdermabrasion, or prescription level glycolic acid treatments to the glabellar area within two weeks prior to study participation or during the study.
- Concurrent therapy that, in the Investigator's opinion, would interfere with the evaluation of the safety or efficacy of the study medication.
- Active infection in the glabellar area (e.g., acute acne lesions or ulcers).
- Pregnant women, nursing mothers, or women who are planning pregnancy during the study, or think they may be pregnant at the start of the study. Throughout the course of the study, women of childbearing potential must use reliable forms of contraception (e.g., abstinence, oral contraceptives for more than 12 consecutive weeks prior to enrollment, or spermicide and condoms).
- Current history of chronic drug or alcohol abuse.
- Enrollment in any active study involving the use of investigational devices or drugs.
- Current facial palsy.
- Marked facial asymmetry, ptosis, excessive dermatochalasis, deep dermal scarring, or thick sebaceous skin.
- Neuromuscular junctional disorders (e.g., myasthenia gravis).
- Known allergy or hypersensitivity to any botulinum toxin or any component of Dysport®.
- Clinically diagnosed anxiety disorder, or any other significant psychiatric disorder (e.g., depression) that, in the opinion of the Investigator, might interfere with the patient's participation in the study.
- Concurrent use of medications with Dysport® treatment that affect neuromuscular transmission, such as curare-like depolarizing agents, lincosamides, polymyxins, anticholinesterases affecting the striated muscle, and aminoglycoside antibiotics.

- Presence of any other condition (e.g., neuromuscular disorder or other disorder that could interfere with neuromuscular function) or circumstance that, in the judgment of the Investigator, might increase the risk to the patient or decrease the chance of obtaining satisfactory data to achieve the objectives of the study.

Trial 085 was different from trials 718 and 719 in that the primary objective was to demonstrate the efficacy of Dysport (50 units) after repeat administrations in the treatment of glabellar lines. This objective was examined in part C of the trial (see Figure 3, section 6.1.8). Therefore, there were additional inclusion criteria for trial 085 for re-randomization as follows:

- Patients who achieve a glabellar severity score of moderate [2] or severe [3] at maximum frown on both the Investigators live assessment using a validated Photographic Scale, and the patient’s static self-assessment, using a 4 point categorical scale. Patients who do not achieve a glabellar severity score of moderate [2] or severe [3] at maximum frown on both scales at the end of the first randomization phase may enroll in the re-randomization phase at a later time point.
- Prior participation in all phases of the 085 study.
- Willing to sign a new ICF for the re-randomization phase.
- Patients treated with active Dysport® in the earlier randomization phase of the 085 Amendment 2 protocol.

Table 15 denotes the differences in the 3 trials as far as randomization, numbers of subjects, and duration. Otherwise, the design of the trials and endpoints were the same. See Figure 1 for administration of the drug product or placebo in section 5.3.3.

Table 15
Differences in Placebo-Controlled
Efficacy Trials

Study Identifier	Objectives	Study Design and Type of Control	Test product; dosage regimen;	Number of Subjects	Duration of Study
718	Efficacy of Dysport	Randomized, double-blind, placebo controlled, 2:1	Dysport 50 units (CAMR BAS)	300	5 months Single dose
719	Efficacy of Dysport	Randomized, double-blind, placebo controlled, 2:1	Dysport 50 units (IBL BAS)	158	6 months Single dose
085	Efficacy of Dysport in the retreatment of glabellar lines following open-label treatment	Randomized, double-blind, placebo-controlled, 1:1	Dysport 50 units (IBL BAS)	Total –311 Part C – 142	23 months Multiple dose

There were 2 co-primary efficacy endpoints for these phase 3 trials, the investigator’s and the patient’s assessment of glabellar severity score (GLSS) at maximum frown on day 30 after treatment, according to tables 9-9c found in section 5.3.3.

Efficacy Results

Table 16 demonstrates the efficacy results for the placebo controlled trials of Dysport 50 units versus placebo. Dysport was statistically significantly better than placebo ($p < 0.001$) for all efficacy endpoints. The median time to onset of effect was 3 days and median duration of response was 88 days.

Table 16
Efficacy Results – Proportion of Responders
On Day 30 at Maximum Frown
ITT Population (Trials 718, 719, and 085 Part C)

	2+ Grade Improvement			1+ Grade Improvement		
	Composite Responders	Patient's Assessment	Blinded Evaluator's/ Investigator's Live Assessment	Composite ¹ Responders	Patient's Assessment	Blinded Evaluator's/ Investigator's Live Assessment
Study 718						
Placebo						
n	100	93	93	100	100	100
Responders, n	0	0	0	0	2	0
Proportion	0	0	0	0	0.020	0
95% CI	(0.000, 0.036)	(0.000, 0.039)	(0.000, 0.039)		(-0.01, 0.05)	NA
Dysport						
n	200	192	192	200	200	200
Responders, n	120	136	157	152	163	171
Proportion	0.600	0.708	0.818	0.76	0.815	0.855
95% CI	(0.529, 0.668)	(0.639, 0.772)	(0.756, 0.870)		(0.76, 0.87)	(0.81, 0.90)
p-value	<0.001	<0.001	<0.001		<0.001	<0.001
Study 719						
Placebo						
n	51	51	51	53	53	53
Responders, n	0	0	0	3	5	2
Proportion	0.000	0.000	0.000	0.019	0.094	0.038
95% CI	(0.000, 0.070)	(0.000, 0.070)	(0.000, 0.070)	(0.00, 0.101)	(0.031, 0.207)	(0.005, 0.130)
Dysport						
n	103	103	103	105	105	105
Responders, n	58	65	79	76	78	92
Proportion	0.563	0.631	0.767	0.724	0.743	0.876
95% CI	(0.462, 0.661)	(0.530, 0.724)	(0.673, 0.845)	(0.628, 0.807)	(0.648, 0.823)	(0.798, 0.932)
p-value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Study 085, Cycle C						
Placebo						
n	71	71	71	71	71	71
Responders, n	0	1	0	0	1	3
Proportion	0.000	0.014	0.000	0.000	0.014	0.042
95% CI	(0.000, 0.051)	(0.000, 0.076)	(0.000, 0.051)	(0.000, 0.051)	(0.000, 0.076)	(0.009, 0.119)
Dysport						
n	71	71	71	71	71	71
Responders, n	37	43	47	54	56	60
Proportion	0.521	0.606	0.662	0.761	0.789	0.845
95% CI	(0.399, 0.641)	(0.483, 0.720)	(0.540, 0.770)	(0.645, 0.854)	(0.676, 0.877)	(0.740, 0.920)
p-value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

¹Biostatistical Review, for the 1+ composite analysis trial 718, table 27, page 36
Source: BLA 125286, adapted from study report 718, table 10, page 62, ISE table 25, pages 74
BLA 125286, amendment dated 10/10/08, tables 1, 2, and 3 pages 4-6

Biostatistical analysis by FDA biostatistician, Dr. Kathleen Fritsch, was very similar to the sponsor’s for trials 718 and 719 except for minor differences accounted for any missing data (see tables 16a and 16b). The analysis was the same for trial 085, part C.

Table 16a
Biostatistical Analysis
Success at Maximum Frown on Day 30
Study 718

	Investigator Assessment		Subject Assessment		Composite	
	Dysport N=200	Placebo N=100	Dysport N=200	Placebo N=100	Dysport N=200	Placebo N=100
1+	171 (86%)	0 (0%)	163 (82%)	2 (2%)	152 (76%)	0 (0%)
2+	157 (79%)	0 (0%)	136 (68%)	0 (0%)	120 (60%)	0 (0%)

Table 16b
Biostatistical Analysis
Success at Maximum Frown on Day 30
Trial 719

	Investigator Assessment		Subject Assessment		Composite	
	Dysport N=105	Placebo N=53	Dysport N=105	Placebo N=53	Dysport N=105	Placebo N=53
1+	92 (88%)	2 (4%)	78 (74%)	5 (9%)	76 (72%)	1 (2%)
2+	79 (75%)	0 (0%)	65 (62%)	0 (0%)	58 (55%)	0 (0%)

In trial 085, subjects had received up to 3 treatments of Dysport 50 units to the glabellar area in the open-label portion of the trial before being re-randomized to Dysport vs. placebo after day 360 of the trial. Thus, the subjects in trial 085, cycle C were not botulinum toxin naïve and the results demonstrated that even after multiple treatments, a statistical significance was observed of responders in the Dysport arm vs. the placebo arm ($p < 0.001$). This suggests that subjects do not develop a tolerance to repeated injections of botulinum toxin. This supports the pharmacologic viewpoint that botulinum toxin type A is not expected to be present in the peripheral blood at this recommended dose.

In summary, the data demonstrates that Dysport, botulinum toxin type A, is efficacious in the treatment of moderate to severe glabellar lines at a dose of 50 units. This efficacy is supported by multiple trials, and by repeated cycles of the drug at a dose of 50 units.

6.1 Indication

The sponsor’s proposed indication is as follows:

Dysport is indicated to achieve and maintain improvement in the appearance of moderate to severe glabellar lines associated with procerus and corrugator muscle activity in adult patients.

6.1.1 Methods

Several trials make up the basis for efficacy in phase 3 of Dysport: trial 718, trial 719, and part C of trial 085. Trial 096, a clinical bridging trial, is important because it allowed us to use trial 718 as an equal partner in the support of Dysport in a dose of 50 units for the treatment of moderate to severe glabellar lines (see efficacy summary). These trials used a 500 unit vial of Dysport which when reconstituted with 2.5 mL of normal saline yielding 200 units of Dysport per mL.

Trial 06-01 is a variable dose trial that the sponsor submitted in support for a dose between 48 units and 84 units (the actual dose after a 300 unit vial is reconstituted with 2.5 mL of normal saline). This trial was not considered pivotal and is reviewed under section 5.3

6.1.2 Demographics

Demographics – ITT Population Placebo Controlled Trials

	Placebo (N=235) ¹	Dysport (N=398) ²
Age (Years)		
Mean	43.9	44.6
Standard Deviation	10.29	10.5
Median	44.3	45
Min, Max	24, 72	19, 75
Age Category, n (%)		
≤ 50 years	179 (76%)	300 (75%)
>50, <65 years	47 (20%)	84 (21%)
≥ 65 years	9 (4%)	14 (4%)
Gender		
Male	29 (12%)	54 (14%)
Female	206 (88%)	344 (86%)
Race/Ethnicity, n (%)		
White	167 (71%)	274 (69%)
Non-White	68 (29%)	124 (31%)
Black or African-American	8 (3%)	13 (3%)
Hispanic or Latino	50 (15%)	94 (24%)
Asian	5 (2%)	8 (2%)
American Indian or Alaska Native	0	5 (1%)
Other ³	5 (2%)	4 (1%)
Botulinum Toxin Naïveté		
Naïve	230 (98%) ⁴	391 (98%) ⁵
Non-Naïve	5 (2%)	7 (2%)

Clinical Review
Denise Cook, M.D.
125274/1
Dysport – abobotulinumtoxinA

Baseline Glabellar Line Severity ⁶	91 (39%) 144 (61%)	157 (39%) 241 (61%)
¹ Includes 11 subjects from trial 06-01 ² Includes 22 subjects from trial 06-01 ³ Includes subjects indicating 'Other' as their race/ethnicity ⁴ 100 subjects based on exclusion criteria of study 718 ⁵ 200 subjects based on exclusion criteria of study 718 ⁶ Investigator's live assessment of glabellar severity at maximum frown Source: BLA 125286, ISE, table 20, page 66, study report 718, table 6, page 56, and study report 718, appendix 16.2.4, listing 61.2.4.1, study report 718, table 14.1.4.3, page 117.		

6.1.3 Patient Disposition

	Treatment Group		Total (N=633)
	Placebo (N=235)	Dysport 50 units (N=398)	
Treatment Group in adequate and well-controlled IBL Studies			
Y-97-52120-719 [719], n (%) ¹	53 (23)	105 (26)	158 (25)
Y97-52120-085 [085 Cycle C], n (%) ¹	71 (30)	71 (18)	142 (22)
A-2006-01 [06-01], n (%) ¹	11 (5)	22 (6)	33 (5)
Treatment Group in adequate and well-controlled CAMR Study			
Y-97-52120-718 [718], n (%) ¹	100 (43)	200 (50)	300 (47)
Patient Completed in adequate and well-controlled IBL & CAMR Studies			
Y-97-52120-718 [718], n (%)	100	200	300
Yes, n (%) ²	92 (92)	190 (95)	282 (94)
No, n (%) ²	8 (8)	5 (5)	18 (6)
Y-97-52120-719 [719], n	53	105	158
Yes, n (%) ²	46 (87)	97 (92)	143 (91)
No, n (%) ²	7 (13)	8 (8)	15 (9)
Y-97-52120-085 [085 Cycle C], n	71	71	142
Yes, n (%) ²	68 (96)	70 (99)	138 (97)
No, n (%) ²	3 (4)	1 (1)	4 (3)
A-2006-01 [06-01], n	11	22	33
Yes, n (%) ²	11 (100)	22 (100)	33 (100)
No, n (%) ²	0	0	0
Primary Reason for Discontinuation in adequate and well-controlled IBL Studies			
Failed to Meet Entry Criteria, n (%) ¹	0	0	0
Lack of Efficacy, n (%) ¹	0	1 (< 1)	1 (< 1)
Adverse Event, n (%) ¹	0	0	0
Investigator Decision, n (%) ¹	0	0	0
Patient Decision, n (%) ¹	6 (3)	8 (2)	14 (2)
Patient not Compliant with Study Requirements, n (%) ¹	2 (< 1)	1 (< 1)	3 (< 1)
Lost to Follow-up, n (%) ¹	10 (4)	9 (2)	19 (3)
¹ Percentages are based on the total number of patients in each treatment group. ² Percentages are based on the total number of patients in each treatment group in the Study. Source: BLA 125286, study report 718, table 5, page 54; ISE table 23, page 70			

6.1.4 Analysis of Primary Endpoint(s)

As stated in section 6, the efficacy summary, there were 2 co-primary efficacy endpoints for the phase 3 trials, the investigator's and the patient's assessment of glabellar severity score (GLSS) at maximum frown on day 30 after treatment. The original protocols used a 1+ grade improvement as the measurement of success. However, the Agency also requested that the sponsor provide analysis for a 2+ grade improvement and a composite score for the 2+ grade improvement, according to tables 9-9c in section 5.3.3 of this review. The composite score for the 2+ grade improvement denotes success as that of a 2+ grade improvement for the same patient by both the investigator's and patient's assessment of glabellar severity score at maximum frown on day 30 after treatment. These efficacy endpoints have been used in trials for another drug product to assess glabellar line severity.

In trial 718, for the Investigator 1+ assessment, the proportion of responders was statistically greater in the Dysport® treated group, 171/200 (86%) compared to placebo, 0/100, (0%) based on the Investigator assessment at maximum frown ($p < 0.001$). The same can be said for the patient's self-assessment for the Dysport treated group, 163/100 (82%) vs. the placebo group, 2/100 (2%), $p < 0.001$. For the Investigator 2+ assessment, the proportion of responders was statistically greater in the Dysport treated group, 157/192 (82%) compared to the placebo, 0/93 (0%) based on the Investigator assessment at maximum frown at day 30 ($p < 0.001$). The patient self assessment at 2+ grade improvement was similar with 136/197 (71%) compared to placebo, 0/93 (0%) at maximum frown on day 30 ($p < 0.001$). The Dysport group maintained a statistically superior response at maximum frown at day 30 for the composite 2+ response, albeit lower than the individual assessments. Using missing data imputed as a non-response, 120/200 (60%) in the Dysport group vs. 0/100 (0%) in the placebo group had a response ($p < 0.001$).

In trial 719, for the Investigator 1+ assessment, 92/105 (88%) subjects were responders in the Dysport arm vs. 2/53 (4%) subjects in the placebo arm ($p < 0.001$). Patient self assessment at 1+ was also statistically significant ($p < 0.001$), although lower with 78/105 (74%) subjects being classified as responders in the Dysport arm vs. 5/53 (9%) responders in the placebo arm. For the 2+ grade improvement in glabellar lines, the results were lower but continued to be statistically significant ($p < 0.001$) for all categories: investigator assessment (79/103 – 77% on Dysport vs. 0% on placebo), patient assessment (65/103 – 63% on Dysport vs. 0% on placebo). For the composite responders, the proportion was lower than for the 1+ or 2+ grade improvement but still statistically significant for Dysport vs. placebo [58/103 (56%) vs. 0%, $p < 0.001$].

In trial 085, part C, a significantly higher proportion of Responders was observed with a 1+ grade improvement for Dysport-treated patients than for placebo-treated patients, as determined by the Investigator's live assessment (85% versus 4%, $p < 0.001$), patient's self assessment (79% versus 1%, $p < 0.001$). The 2+ grade improvement analysis also demonstrated that the Investigator's live assessment and patient's self-assessment of glabellar lines at maximum frown on Day 30 each demonstrated a significantly higher proportion of responders compared to

placebo (66% vs. 0%, $p < 0.001$ for the Investigator's assessment, and 61% vs. 1%, $p < 0.001$ for the patient's assessment, respectively). The composite responders for the 2+ grade improvement was also statistically significant, $p < 0.001$ for the Dysport arm (37/71, 52%) vs. the placebo arm (0%).

6.1.5 Analysis of Secondary Endpoints(s)

An important secondary efficacy endpoint is the Independent Photographic Reviewer's Assessment (IPR). The purpose of this endpoint was to be supportive of the primary endpoints and to determine efficacy with respect to an independent reviewer's assessment of photographs of the patient's glabellar lines at maximum frown at day 30.

For the IPR assessment, a responder was defined as a patient who had a rating of none [0] or mild [1] in glabellar lines at maximum frown at Day 30 and a rating of moderate [2] or severe [3] at maximum frown at Baseline (Day 0). The proportions of responders were summarized at Day 30. Patients with a Baseline score of none [0] or mild [1] according to the IPR assessment were not included in this analysis. Agreement between the IPR scores (the median of three independent reviewers' scores) and the Investigators' scores at Day 0 (Baseline) and Day 30 was investigated using kappa statistics and associated 95% CIs.² Table 17 demonstrates the efficacy for the IPR Assessment for a 1+ grade improvement.

² BLA 125286, study report 718, page 47.

Table 17
IPR Assessment at Maximum Frown Day 30
Efficacy Trials at Fixed Dose of Dysport 50 units

	IPR's Assessment
Study 718	
Placebo	
n	100
Responders, n/N*	2/77
Proportion	0.026
95% CI	(-0.01, 0.06)
Dysport	
n	200
Responders, n/N*	162/169
Proportion	0.959
95% CI	(0.93, 0.99)
p-value	<0.001
Study 719	
Placebo	
n	53
Responders, n/N*	2/44
Proportion	0.045
95% CI	(0.006, 0.155)
Dysport	
n	105
Responders, n/N*	81/91
Proportion	0.890
95% CI	(0.807, 0.946)
p-value	< 0.001
Study 085, Part C	
Placebo	
n	71
Responders, n/N*	2/570.036
Proportion	(0.004, 0.121)
95% CI	
Dysport	
n	71
Responders, n/N*	54/60
Proportion	0.900
95% CI	(0.795, 0.962)
p-value	< 0.001
*The denominator for proportions is the number of patients with non-missing data at the visit in each treatment group.	
Source: BLA 125286, study report 718, table 11, page 63 and ISE table 25, page 74	

In trials 718, 719, and 085 part C, the IPR Assessment confirmed the efficacy of Dysport 50 units over placebo in the treatment of moderate to severe glabellar lines. The correlation between the two endpoints, IPR assessment and Investigator's live assessment was moderate to good. In trial 718, agreement between the IPR assessment and Investigator's live assessment occurred 56.1% of the time at baseline and 65.8% of the time at day 30. In trial 719, agreement between the IPR assessment and Investigator's live assessment occurred 60% of the time at

baseline and 70% of the time at day 30. A shortcoming of the photographic assessment was revealed in that the degree of severity was graded one grade less at baseline many times as compared to the live assessment. This revealed a difference in a three-dimensional analysis of live muscle activity vs a static two-dimensional evaluation (photographs). However, as a supportive tool, it supports the primary efficacy endpoints for Dysport efficacy.

Duration of response was another important secondary efficacy endpoint. Duration of response was defined as the time (number of days) from onset of response as recorded on the patient’s diary card or by Investigator’s assessment at maximum frown on Day 14 or patient’s self-assessment at maximum frown on Day 14, to reappearance of a severity grade of [2] or [3], based on the Investigator’s live assessment at maximum frown. Patients who do not respond by Day 14, are included in the analysis with a zero duration. Patients who did not return to a score of [2] or [3] following onset of response were censored at the time of study completion/withdrawal.

The duration of response was consistent across all three efficacy trials for the 50 unit dose of Dysport (see table 18). Median duration of response was 0 days for the placebo arms in the trials and no response in the placebo arms lasted beyond 33 days.

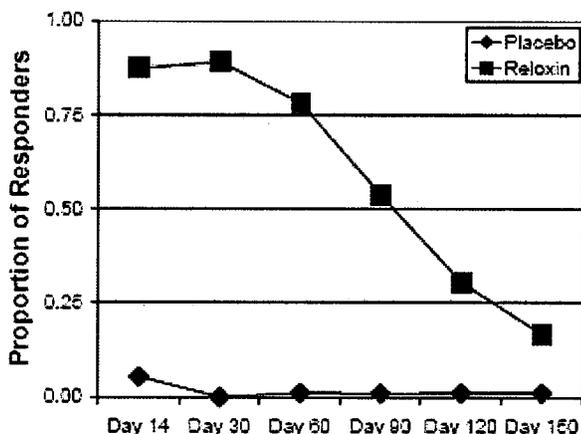
Table 18
Duration of response
ITT Population – Efficacy Trials

	Median Duration of Response (days)	
	Investigator’s Assessment	Patient Assessment
Trial 718	117	117
Trial 719	85	85
Trial 085, Cycle C	89	87
BLA 125286, study report 085, page 116, ISE. Page 158, and study report 718, page 75		

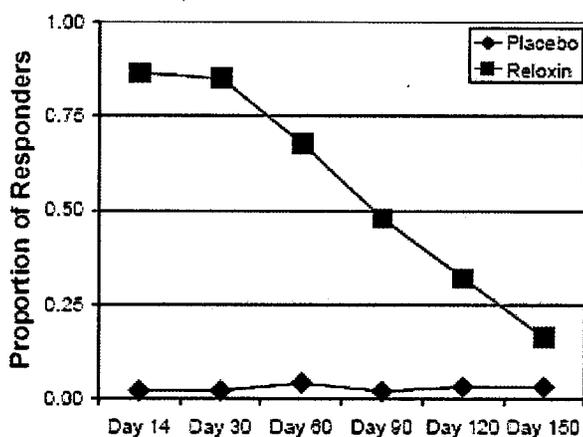
Figure 3, from trial 718, illustrates the proportion of responders over time. This response, as stated above is consistent across all single-dose trials of 50 units of Dysport.

Figure 3
Proportions of Responders over Time
ITT Population – Trial 718

A: Proportion of Responders by Visit, Investigator Assessment at Maximum Frown



B: Proportion of Responders by Visit, Patient Self-Assessment at Maximum Frown



Source: BLA 125286, study report 718, figure 4, page 65

Based on this duration of response, it will be advised in labeling that patients not receive additional treatments less than 90 days apart. Indeed, this was the interval for the long term trials of repeated 50 unit doses of Dysport.

6.1.6 Subpopulations

In the placebo controlled trials, 718, 719, and 085 cycle C, the response rate of Dysport 50 units for the Composite 2+ Grade Improvement was higher for younger patients (≤ 50 years, 63% [177/283]) than for older patients ($>50, <65$ years, 44%, [38/87]) and was higher for female (40% [129/320]) than for male patients (37% [20/54]).

The number of subjects in the efficacy trials for the 50 unit dose that were ≥ 65 years of age was only 8, 3 on Dysport and 1 on placebo in trial 719, and 1 on Dysport and 3 on placebo in trial 085 part C. In these trials, 0/4 of the subjects treated with Dysport 50 units had a response. As such, Dysport cannot be recommended for approval for geriatric subjects ≥ 65 years of age.

Trial 06-01, the variable dose trial, had the largest population of non-Caucasians being treated with Dysport. In table 19, non-Caucasians had a slightly better response at day 30 than did Caucasians, thus corroborating the response that was found in the 50 unit fixed dose trials. This is mentioned because this trial had more non-Caucasian subjects than the other trials combined.

Table 19
Proportion of Responders at Day 30
Sub-group Analysis – Race/Ethnicity* Trial 06-01

Race/Ethnicity	Treatment Group	N	Responders	Proportion	95% Confidence Interval	P - value
Caucasian	Placebo (N=191)	186	7	0.038	(0.015, 0.076)	<0.001
	Dysport (N=364)	358	299	0.835	(0.793, 0.872)	
	Difference			-0.798	(-0.839, -0.743)	
African American	Placebo (N=54)	54	2	0.037	(0.005, 0.127)	<0.001
	Dysport (N=106)	105	93	0.886	(0.809, 0.940)	
	Difference			-0.849	(-0.910, -0.739)	
Any Other Race	Placebo (N=27)	27	0	0.000	(0.000, 0.128)	<0.001
	Dysport (N=74)	74	63	0.851	(0.750, 0.923)	
	Difference			-0.851	(-0.913, -0.702)	

* See appendix 9.4 for ethnic efficacy breakdown; Source: BLA 125286, adapted from study report 06-01, table 14.2.7.1, page 530

6.1.7 Analysis of Clinical Information Relevant to Dosing Recommendations

The sponsor has two trials that look at variable dosing, a phase 2 dose ranging trial, trial 717 and a phase 3 variable dose trial, 06-01. Trial 717 looked at a 20 unit dose, a 50 unit dose, and a 75 unit dose. Trial 06-01, according to the sponsor, looked at a 50 unit dose, a 60 unit dose, a 70 unit dose, and an 80 unit dose. However, given the dilution of their new unit vial of 300 units, for this trial only, diluted with 2.5 mL of saline giving 12 units/0.1mL, subjects actually received 48 units, 60 units, 72 units, and 84 units. There were 3 efficacy trials, 718, 719, and 085, which looked at a fixed dose of 50 units of Dysport. The sponsor claims primarily that men need a higher dose and some women based on muscle mass need a higher dose and in practice, subjects get variable dosing with Botox Cosmetic, off label. (see section 5.3.3). It should be noted that the percentage of men participating in the trials of this BLA was small, approximately 12%.

Efficacy results of the phase 2 dose ranging trial revealed that efficacy was comparable between the 50 unit dose and the 75 unit dose for the investigator’s assessment, 77% vs. 85% respectively, and the patient’s assessment, 85% and 84%, respectively. For this reason, the sponsor had chosen 50 units as the dose to be studied in phase 3 (see tables 4 and 5, section

5.3.1). In this review, the data from variable dose and the fixed dose trials, support the initial findings of the phase 2 dose ranging trial. Table 20 shows the percentage of responders from the Investigator’s Live Assessment for the fixed dose (50 units) and the variable dose (50-80 units). Note in the table the composite responders, which are those subjects who scored the same from both the investigator and the patient. It is the most stringent endpoint, and somewhat lower than the individual assessments.

Table 20
Responders (%) Investigator’s Live Assessment

Dose	1+ grade improvement	1+ composite ¹	2+ grade improvement	2+ composite ¹
Fixed 50 unit dose	87	76	72	57
Variable dose ²	89	80	80	59

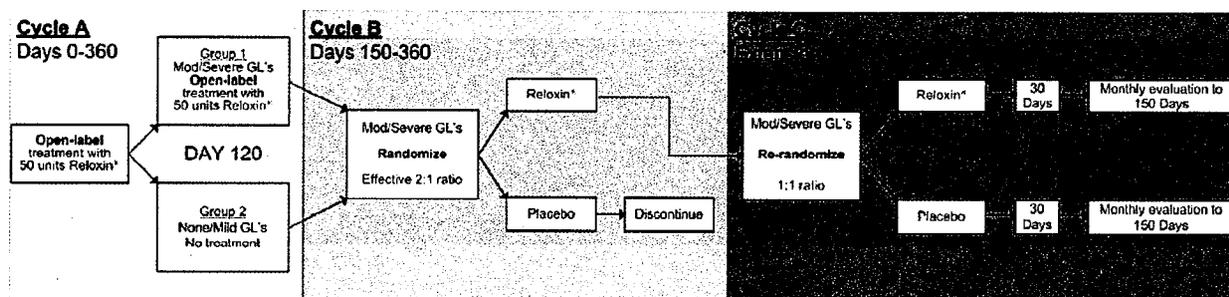
¹Subjects who had the same score from both the investigator’s live assessment and the patient’s assessment
²Given the sponsor’s dilution and unit vial, the doses instead of 50 – 80 units, they are actually 48 – 84 units
Source: BLA 125286, ISE, pages 76-81

There is not justification for approving an increased dose for many of the parameters that the sponsor claims: efficacy, onset of response, and men vs. women. When one compares the fixed dose regimen of 50 units with the variable dose regimen from 50 units to 80 units, the overall difference in efficacy is marginal. The proportion of 1+ grade responders with the Investigator’s live assessment fixed vs. variable was 87% vs. 89%, and for the composite it was 76% vs. 80%, respectively. For the 2+ grade responders with the Investigator’s live assessment, fixed vs. variable was 72% vs. 80%, respectively, and for the composite it was 57% vs. 59%, respectively. The time to onset was 3 days for the fixed dose, and 4 days for the variable dose, not a major difference. Male response was somewhat better; however the number of males in the trials was very small. The response of male subjects at day 30 for the 2+ composite grade improvement in the variable dose was 46% (28/61) vs. 37% (20/54) in the fixed (50u) dose. Female subjects remained virtually the same, 61% (291/478) for the variable dose vs. 62% (211/342) for the fixed dose. At day 90, 25% of composite responders at 2+ grade improvement continued to have a statistically significant response with the variable dose, compared to 9% with the fixed 50 unit dose. Although 16% of subjects maintained a longer duration of response with the variable dose vs. the fixed dose, the data suggests it comes with an additional risk of ptosis.

6.1.8 Discussion of Persistence of Efficacy and/or Tolerance Effects

Trial 085 was designed to evaluate if tolerance would develop after repeated injections of Dysport 50 units for the treatment of moderate to severe glabellar lines. Another point to be made about trial 085, even though there was a randomization problem for part B of the trial, its ultimate goal was to demonstrate that efficacy could be maintained after subjects had received multiple treatments with Dysport. Figure 4 illustrates the design of trial 085.

Figure 4
Schematic Design of Trial 085



The results of this trial are found in table 16 and discussed in section 6 under “Efficacy Summary.” In that table, for cycle C of the trial, efficacy was demonstrated across all three variables, 1+ improvement, 2+ improvement, and 2+ composite responders, for the investigator’s and patient’s assessments for Dysport vs. placebo ($p < 0.001$ for all categories). For example, under the 2+ grade improvement, for the Investigator’s Live Assessment, 47/71 (66%) in the Dysport arm were responders vs. 0% in the placebo arm and for the patient’s assessment, 43/71 (61%) were responders vs. 1/71 (0.05%) in the placebo arm. When one examines the 2+ composite response in this trial where subjects were not botulinum toxin naïve to those in trial 719, for example, who were botulinum toxin naïve, the results are comparable. For the 2+ composite responders, there were no responders in the placebo arm of either trial, and 52% were responders in trial 085 cycle C, compared to 56% responders in trial 719 (see table 16). This suggests that tolerance to Dysport does not develop after multiple treatments.

7 Review of Safety

Safety Summary

The safety database consists of the placebo-controlled trials, 718, 719, 085, and A2006-01, and two long term safety trials, 720 and 732. All of the trials involved a 50 unit dose of treatment except for the placebo-controlled trial A2006-01 which varied the dose between 50 and 80 units. Trials 718, 719, and A2006-01 evaluated a single dose of Dysport. Trial 085 was a multi-dose open-label trial followed by a placebo-controlled randomized phase. The other trials 720 and 732 were multi-dose trials. Trial 720 was 13 months in duration, and trial 732 was 36 months in duration and is ongoing. Subjects from all the trials were to be rolled-over into trial 732, the 36 month trial and would receive 50 units of Dysport whenever an additional treatment was necessary. An important omission in this BLA where the sponsor is seeking variable dosing is that there is no long term safety data on the variable dosing, 60 units – 80 units of Dysport.

The number of subjects in the safety data base of the 50 unit dose comprised 2491 subjects treated with Dysport and 580 subjects treated with placebo. The long-term trials were designed such that some subjects could receive up to 8 cycles of treatment with Dysport. An additional 522 subjects had a one-time treatment between 60 – 80 units of Dysport.

At the time of submission, which included safety data from the short-time trials, the 13 month long term safety trial, and 768 subjects from the 36 month safety trial, 382 subjects had received up to 5 cycles, with less receiving more cycles, and none receiving 8 cycles. Two cycles of Dysport had been administered to 987 subjects and 4 cycles had been administered to 555 subjects. In total, there were 480 administrations of placebo to 480 subjects and 4880 administrations of Dysport to 2041 subjects. The median number of months to receive four treatments of Dysport was approximately 12 months for patients without a middle placebo cycle.

The 120-day safety update provided for additional exposure and safety data for exposure of Dysport administered over approximately 21 months from trial 732. In this update, 1349 patients were treated in Cycle 1, 768 in Cycle 2, 636 in Cycle 3, 477 in Cycle 4, 313 in Cycle 5, 186 in Cycle 6, 81 in Cycle 7 and four patients were treated in Cycle 8. Therefore, as of September 30, 2007, 581 patients had received a total of one treatment, 132 patients had received a total of two treatments, 159 patients had received a total of three treatments, 164 patients had received a total of four treatments, 127 patients had received a total of five treatments, 105 patients had received a total of six treatments, 77 patients had received a total of seven treatments, and four patients had received a total of eight treatments (50 units of Dysport® per treatment) for the 120 Day safety analysis period. A total of 3814 treatments of 50 units of Dysport® were administered during the study up to the 120 Day safety cut-off.

In the placebo-controlled trials using a 50 unit dose of Dysport, of the 398 subjects, 191 (48%) experienced 398 Treatment Emergent Adverse Events (TEAEs). Of the 496 subjects treated with placebo, 164 (33%) experienced 300 TEAEs. Most adverse events were mild or moderate in both the Dysport and placebo treatment groups. Most adverse events were not related or unlikely related to treatment in both the Dysport and placebo treatment groups. Two percent of the Dysport and placebo treatment groups experienced TEAEs judged to be severe. TEAEs judged to be possibly or probably related to study treatment occurred in 16% and 9% of subjects in the Dysport and placebo treatment groups, respectively.

The most common adverse events in the placebo-controlled, single dose trials that occurred in at least 1% of subjects in the Dysport group vs. the placebo group, respectively were nasopharyngitis (10% vs. 4%), headache (9% vs. 5%), upper respiratory tract infection (3% vs. 2%), injection site reaction (3% vs. 0.4%), injection site pain (3% vs. 2%), sinusitis (2% vs. 1%), eyelid ptosis (2% vs. 0.2%), eyelid edema (2% vs. 0%), and nausea (2% vs. 1%).

Across all studies for the 50 unit dose of Dysport, of the 2491 subjects treated, 1425 (57%) experienced 5176 Treatment Emergent Adverse Events (TEAEs). Of the 580 subjects treated with placebo, 186 (32%) experienced 331 TEAEs. Most adverse events were mild or moderate in both the Dysport and placebo treatment groups, with 2% of patients in both groups experiencing TEAEs judged to be severe. Additionally, most adverse events were not related or

unlikely related to treatment in both the Dysport and placebo treatment groups. TEAEs judged as possibly or probably related to study treatment occurred in 19% and 8% of patients in the Dysport and placebo treatment groups, respectively.

The most common adverse events across all studies at the 50 unit dose that occurred in at least 1% of subjects in the Dysport group vs. the placebo group respectively were headache (12%, 4%), nasopharyngitis (11%, 4%), upper respiratory tract infections (5%, 2.0%), sinusitis (6%, 1%), injection site pain (6%, 1%), injection site bruising (4%, 1%), injection site reaction (4% vs. 0.3%), bronchitis (3% vs. 0.7%), influenza (3%, 0.5%), injection site swelling (2% vs. 0.5%), injection site discomfort (2% vs. 0.2%), eyelid ptosis (2%, 0.2%), pharyngolaryngeal pain (2% vs. 0.3%), and cough (2% vs. 0.7%).

The most frequently reported adverse events in the Dysport and placebo treatment groups respectively, compared to the number of treatments across cycles, were nasopharyngitis (2.7%, 4.0%), headache (2.5%, 3.3%), injection site pain (1.5%, 1.5%), upper respiratory tract infection (1.3%, 0.8%), sinusitis (1.2%, 0.8%), eyelid ptosis (0.7%, 0.2%), injection site bruising (0.7%, 1.5%), influenza (0.7%, 0.6%) and bronchitis (0.6%, 0.6%). Again, the majority of AEs were mild to moderate in severity with only 2% rated as severe for both Dysport and placebo. The incidence of AEs also decreased with subsequent cycles.

There were only 10 (<1%) discontinuations in the Dysport group due to SAEs and 9 of these were not considered treatment related. The AE that was possibly related was a subject with keratitis where the symptoms of eyelid edema, pruritus, and infection were thought to be possibly related to treatment.

One area of special interest, given the proximity of injections to the orbit, is ocular effects. In the Dysport treatment group 356 (99%) of 361 ocular AEs were mild (84%) or moderate (14%) in severity. All of the 15 ocular AEs in the placebo treatment group were mild in severity. The incidence of ocular AEs was greatest in cycle 1 in the Dysport group at 3% compared to placebo at 1%. This decreased to 2% in cycle 2 and 3 and 1% in cycles 4 and 5 for the Dysport group. The ocular AEs in the placebo group fell to <1% for those remaining cycles. Sixty-one (98%) of the 62 eyelid ptosis AEs in the Dysport treatment group were mild (84%) or moderate (15%) in severity. The only eyelid ptosis AE occurring in the placebo group was mild in severity. The three severe ocular AEs occurring in the Dysport treatment group were one instance each of ptosis, ocular hyperemia, and keratitis.

The only ocular event that occurred at $\geq 1\%$ was eyelid ptosis. As stated above, eyelid ptosis across all studies occurred in 2% of subjects on Dysport and 0.2% on placebo. Across all treatment cycles, the incidence of eyelid ptosis was 0.7% of subjects on Dysport and 0.2% of subjects on placebo. In a subgroup analysis of gender and dose, the incidence of ptosis for men receiving 50 units (n=161) was the same as for women receiving between 50 (n=1358) and 60 (n=277) units; that is 1%. Men did not experience any eyelid ptosis in the 60, 70, or 80 unit arms but the numbers were too small, namely 5, 25, and 33, respectively, to make any meaningful conclusion regarding the safety of the higher doses. Women did experience more eyelid ptosis at the 70 unit dose, 4% (8/181) of subjects. The difference in eyelid ptosis between doses for

women was statistically significant with a $p=0.003$. Most events of ptosis resolved within 2 weeks, although the longest duration, albeit rare, took 4 weeks to resolve.

A small placebo-controlled QTc study in subjects treated with 50 – 80 units of Dysport did not reveal any subject who had a QT interval >500 ms from baseline to 30 minutes and 14 days post injection and the mean increase in QT interval between Dysport and placebo groups from baseline to 30 minutes and at 14 days after injection was less than 10 milliseconds.

There were no cases of dysphagia or aspiration pneumonia reported in the safety database. This is important to note, as a REMS will be a part of any botulinum toxin type A drug product because of the risk of both local and systemic spread of the toxin which could result in fatalities. This has been observed primarily with the higher doses for neurologic indications. This population may also be more susceptible to the effects of botulinum toxin type A.

There was a 2% incidence each of pharyngolaryngeal pain and cough in the long-term safety trials that was not reported in the short-term single dose trials at 50 units. It is not clear that this might be due to spread of the toxin. If it is, the subjects may not have been as sensitive because of no underlying neurologic disorder and also because the total dose was small. No subject discontinued because of this adverse event.

Dysport does have the presence of a contaminant, flagellin, which is a proinflammatory protein that binds TLR5 receptors. This does not present a problem for the current indication, as TLR5 receptors are not found in muscle or neuronal cells. However, it should be noted in labeling that Dysport should not be used off-label for the treatment of hyperhidrosis, as TLR5 receptors are found in macrophages and dendritic cells (see section 4.1).

When comparing the adverse events in the short term trials versus the adverse events across all studies at the 50 unit dose, which include the long-term trials, the most common adverse events are primarily the same, namely, headache (9% vs. 12%), nasopharyngitis (10% vs. 11%), sinusitis (2% vs. 6%), URI (3% vs. 5%), and injection site pain (3% vs. 6%), and injection site reaction (3% vs. 4%), respectively.

The safety data for the 50 unit dose of Dysport to be administered in 5 equal injections is robust and overall the expected adverse events are tolerable and reversible. There is a paucity of safety data for the higher doses, 60 – 80 units. The increased incidence of ptosis after only one injection, coupled with lack of long-term safety precludes consideration of approval of these doses for the treatment of moderate to severe glabellar lines.

7.1 Methods

7.1.1 Clinical Studies Used to Evaluate Safety

All of the trials that are listed in the table of clinical studies under section 5.1 except trial 717, the dose ranging trial, were included in the safety evaluation of Dysport. The study design,

dosing schedule, study location, treatment groups and doses, N's, and patient population can be found in that table. It should be noted that trial 06-01 contained a sub-study to look at QT/QTc changes.

7.1.2 Adequacy of Data

The coding for safety appeared to be appropriate as far as could be evaluated. The sponsor used the MedDRA dictionary of preferred terms for coding safety adverse events. Most adverse events were straightforward without much room for misinterpretation, ie. injection site bruising or swelling, eyelid drooping/ptosis. One exception was of a subject in trial 085 with bipolar disorder, who was hospitalized for what the patient described as “overexertion” and it was coded as “fatigue”. This is a reasonable assessment of that symptom reported. The subject spent 7 days in the hospital, recovered fully, and completed the trial.

7.1.3 Pooling Data Across Studies to Estimate and Compare Incidence

The placebo controlled trials that included subjects who received one 50 unit dose of Dysport were pooled. This included trials 718, 719, 085 part C, and 06-01. The overall long-term safety analysis pooled all trials where subjects received a 50 unit dose of Dysport. Finally, safety was assessed looking at those subjects who received a fixed dose (50 units) in the placebo controlled trials compared to those subjects who received a variable dose (60 – 80 units) in trial 06-01.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The following table demonstrates the demographics of the IBL-initiated trials for the safety population. This does not include the CAMR trial 718, but the demographics for that trial were similar and were incorporated into the placebo-controlled trials table found in section 6.1.2 of this review. There were no age limits to the trial, however, the majority of subjects were 50 years of age or younger. The majority of subjects in the trials was female and classified as white, although approximately 18% of the population on Dysport were classified as non-white. Males on Dysport accounted for only approximately 11% of the population.

**Demographics by Initial Treatment Group
In IBL-Initiated Studies – Safety Population**

	Placebo (N=325)	Dysport® (N=2016)
Age (Years)		
Mean	48.1	48.0
SD	10.39	9.78
Median	49.0	48.0
Min, Max	23, 80	19, 80
Age Category, n (%)		
≤ 50 years	192 (59)	1238 (61)
> 50,	113 (35)	684 (34)
< 65 years ≥ 65 years	20 (6)	94 (5) *
Gender, n (%)		
Male	42 (13)	221 (11)
Female	283 (87)	1795 (89)
Race/Ethnicity, n (%)		
White	216 (66)	1653 (82)
Non-White	109 (34)	363 (18)
Black or African-American	54 (17)	122 (6)
Hispanic or Latino	44 (14)	178 (9)
Asian	5 (2)	31 (2)
American Indian or Alaska Native	2 (<1)	7 (<1)
Other ¹	4 (1)	25 (1)
Botulinum Toxin Naivete, n (%)		
Naïve	273 (84)	1505 (75)
Non-Naïve	52 (16)	511 (25)
Baseline Glabellar Line Severity², n (%)		
Moderate	96 (30)	757 (38)
Severe	229 (70)	1259 (62)

*This includes subjects from trial 06-01 and long term safety trials, 720 and 732.
Source: BLA 125286, ISS, table 11, page 60

Exposure

Table 21 denotes the exposure of the population to multiple treatments (cycles) with Dysport 50 units. With the 120 day safety update, which describes more treatment cycles of the ongoing trial 732, there is enough safety data to evaluate Dysport up to 6 cycles of treatments, which would cover 15 – 18 months of safety data, given that subjects could not be retreated sooner than 90 days after the previous treatment (see section 7.7). The median number of months to receive 4 treatments of Dysport was 12 months without a middle placebo cycle and 20 months for those subjects with a middle placebo cycle. The data base is still too small to make valid safety assessments for the small number of subjects who received 7 or 8 treatments (133 subjects or 4 subjects, respectively).

Table 21
Exposure by Treatment Group
Safety Population

	Placebo (N=480)	Dysport® (N=2041)
Cycle 1	325	2016
Cycle 2	13	987
Cycle 3	99	705
Cycle 4	43	555
Cycle 5	0	382
Cycle 6	0	179
Cycle 7	0	56
Cycle 8	0	0

Source: BLA 125286, ISS, table 5, page 46

7.2.2 Explorations for Dose Response

The placebo controlled trials demonstrated a median time to onset of response of 3 days in the IBL treated Dysport subjects who had 50 units of Dysport to treat moderate to severe glabellar lines. The median duration of treatment response based on Investigator's live assessment at maximum frown was 85 days in the Dysport arm when compared to placebo, where duration was 0 days. Some subjects did have response durations of 5-6 months.

7.2.3 Special Animal and/or In Vitro Testing

A preclinical study was performed to assess the ability of complete muscle recovery after intramuscular injection of Dysport.

7.2.4 Routine Clinical Testing

Laboratory data, serum chemistry and hematology, were collected in Studies 085, 096 and 719, which is a subset of the Safety Population. This subset is composed of all patients who received either placebo (N=208) or Dysport® (N=491) in those studies. In all three studies data were collected at Day 0, and on Day 30 in Studies 719 and Study 096, as well as at the end of Study 719 and on Day 360 of the first cycle of Study 085. This was more than adequate for a drug that performs its action locally into the muscle injection and is not expected to have systemic absorption or spread of effect at this dose.

7.2.5 Metabolic, Clearance, and Interaction Workup

This section is not applicable to botulinum toxin type A products, of which Dysport is one. The drug is a neurotoxin and therefore trials were not performed to look at pk/pd parameters.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Botulinum toxin type A is a neurotoxin that in high enough doses can cause death. There have been post-marketing reports of systemic spread of the toxin with the higher doses used for other indications such as the treatment of cervical dystonia and limb spasticity. There have been 22 cases of systemic spread reported in the cosmetic indication where botulinum toxin type A is used in much lower doses (see section 2.4). Review of the BLA did not reveal any evidence of local spread of the toxin resulting in an adverse event other than those expected: eyelid ptosis, injection site swelling and injection site bruising. Evaluation for QT prolongation did not demonstrate any potential for arrhythmias of Dysport at a dose of 50 units (see section 7.4.5).

7.3 Major Safety Results

7.3.1 Deaths

There were 2 deaths in the 120 day safety update data base, from long-term trial 732. One was a 59 year old Caucasian female, patient 01.056, who received two treatments of Dysport 50 units, one on 3/24/06 and 8/22/06. The subject was reported to have died on (b) (6) (during cycle 2) related to complications from chronic alcoholism. The second death was a 63 year old Caucasian female, patient 09.026, who received two treatments of Dysport on 2/10/06 and 8/28/06. The subject reported metastatic rectal cancer on 10/31/06 and study drug was discontinued. Her last visit was on 2/22/07 and she succumbed to the cancer on (b) (6). There was also one death due to a gunshot wound in a subject 15 days after receiving Dysport.

Reviewer's Comment: *There is no evidence that these deaths were related to Dysport injection in the glabellar area of the face.*

7.3.2 Nonfatal Serious Adverse Events

Subject 720.12.00009 discontinued from the trial because of keratitis that was determined to be severe (see table below for discontinuations). She was a 55 year-old Caucasian female who received a single treatment of Dysport on 11/22/05. On 2/3/06, cycle 1, day 73, the patient experienced keratitis that resolved 11 days later after treatment with Acular and Vigamox eye drops. The subject discontinued 3/27/06. The subject's past medical history which may have been relevant to the event included trigeminal neuralgia in 1985 which was treated with a glycerin injection in the infraorbital area of her right eye. Since that time the subject has not been able to produce tears and has had to use eye drops every hour. Other serious adverse events are listed in table 22. None of these serious adverse events in either the placebo or

Dysport group even approached affecting 1% of the population, the highest being 0.03% for general disorders and administration site conditions.

Table 22
Summary of Treatment Emergent Serious Adverse Events by System Organ Class, Preferred Term, and Treatment Group – Safety Population

System Organ Class Preferred Term	Placebo (N=480)		Dysport® (N=2041)	
	Patients: n (%)	Events ³	Patients: n (%)	Events ³
Any Treatment Emergent Adverse Event	6 (1)	7	36 (2)	60
Cardiac Disorders	0	0	4 (<1)	5
Angina Pectoris	0	0	2 (<1)	2
Arrhythmia	0	0	1 (<1)	1
Atrial Fibrillation	0	0	1 (<1)	1
Cardiomyopathy	0	0	1 (<1)	1
Eye Disorders	0	0	1 (<1)	1
Keratitis	0	0	1 (<1)	1
Gastrointestinal Disorders	0	0	2 (<1)	2
Small Intestine Obstruction	0	0	1 (<1)	1
Vomiting	0	0	1 (<1)	1
General Disorders and Administration Site Conditions	0	0	7 (<1)	8
Condition Aggravated	0	0	3 (<1)	3
Chest Pain	0	0	2 (<1)	2
Asthenia	0	0	1 (<1)	1
Fatigue	0	0	1 (<1)	1
Non-Cardiac Chest Pain	0	0	1 (<1)	1
Hepatobiliary Disorders	0	0	3 (<1)	3
Cholelithiasis	0	0	2 (<1)	2
Biliary Colic	0	0	1 (<1)	1
Infections and Infestations	1 (<1)	1	3 (<1)	3
Appendicitis	0	0	1 (<1)	1
Postoperative Wound Infection	0	0	1 (<1)	1
Urinary Tract Infection	0	0	1 (<1)	1
Diverticulitis	1 (<1)	1	0	0
Injury, Poisoning and Procedural Complications	0	0	2 (<1)	3
Brain Contusion	0	0	1 (<1)	1
Patella Fracture	0	0	1 (<1)	1
Traumatic Intracranial Haemorrhage	0	0	1 (<1)	1
Investigations	0	0	1 (<1)	1
Heart Rate Irregular	0	0	1 (<1)	1
Metabolism and Nutrition Disorders	1 (<1)	1	0	0
Dehydration	1 (<1)	1	0	0
Musculoskeletal and Connective Tissue Disorders	0	0	3 (<1)	3
Intervertebral Disc Protrusion	0	0	1 (<1)	1
Spinal Osteoarthritis	0	0	1 (<1)	1
Synovial Cyst	0	0	1 (<1)	1

Neoplasms Benign, Malignant and Unspecified (Incl. Cysts and Polyps)	1 (<1)	1	7 (<1)	9
Malignant Melanoma	0	0	2 (<1)	3
Lung Carcinoma Cell Type Unspecified Stage 1	0	0	1 (<1)	1
Ovarian Cancer	0	0	1 (<1)	1
Metastatic Rectal Cancer	0	0	1 (<1)	1
Squamous Cell Carcinoma of Skin	0	0	1 (<1)	1
Uterine Leiomyoma	0	0	1 (<1)	1
Uterine Neoplasm	0	0	1 (<1)	1
Oesophageal Adenocarcinoma	1 (<1)	1	0	0
Nervous System Disorders	0	0	2 (<1)	2
Cerebrovascular Accident	0	0	1 (<1)	1
Dizziness	0	0	1 (<1)	1
Pregnancy, Puerperium and Perinatal Conditions	3 (<1)	3	3 (<1)	4
Pregnancy	2 (<1)	2	3 (<1)	3
Abortion Spontaneous	0	0	1 (<1)	1
Unintended Pregnancy	1 (<1)	1	0	0
Psychiatric Disorders	0	0	2 (<1)	5
Suicidal Ideation	0	0	2 (<1)	2
Bipolar I Disorder	0	0	1 (<1)	1
Depression	0	0	1 (<1)	1
Paranoia	0	0	1 (<1)	1
Reproductive System and Breast Disorders	1 (<1)	1	1 (<1)	1
Hypertrophy Breast	0	0	1 (<1)	1
Menorrhagia	1 (<1)	1	0	0
Respiratory, Thoracic and Mediastinal Disorders	0	0	3 (<1)	5
Chronic Obstructive Pulmonary Disease	0	0	1 (<1)	1
Dysnoea	0	0	1 (<1)	1
Emphysema	0	0	1 (<1)	1
Pulmonary Embolism	0	0	1 (<1)	1
Pulmonary Infarction	0	0	1 (<1)	1
Vascular Disorders	0	0	4 (<1)	5
Deep Vein Thrombosis	0	0	2 (<1)	2
Atherosclerosis	0	0	1 (<1)	1
Hypotension	0	0	1 (<1)	1
Vascular Calcification	0	0	1 (<1)	1

Source: BLA 125286, ISS, table 23, page 92

7.3.3 Dropouts and/or Discontinuations

Overall Discontinuations

In the adequate and well-controlled placebo trials of the 50 unit dose, very few subjects discontinued. None discontinued because of an adverse event. Six and 4 subjects in the Dysport group and placebo group, respectively discontinued because of patient decision. Three and 6 subjects in the Dysport group and placebo group, respectively were lost to follow-up.

Discontinuations Due to An Adverse Event

There were no subjects in the placebo-controlled 50 unit, single-dose trials that dropped out due to an adverse event. In the long-term safety trials, the drop-outs for adverse events represented a small fraction of the total number of subjects in the trials (10/2491 = 0.4%). Eye disorders

accounted for the reason that 2 subjects dropped out and were the only events probably related to Dysport injection (see table 23).

Table 23
Discontinuations Due to An Adverse Event
Overall Safety Population

Pt. No.	System Organ Class Preferred Term	Relationship	Severity	Outcome	Cycle / Study Day	Duration (Days)
Discontinuations due to Adverse Events reported in the Interim Clinical Study Report						
732.01.056	Injury, Poisoning and Procedural Complications Alcohol Poisoning	Not Related	Severe	Death	2 / 111	N/A
720.04.002a	Pregnancy, Puerperium and Perinatal Conditions Pregnancy	Not Related	Severe	R-S*	1 / 139	262
720.12.00009	Eye Disorders					
	Dry Eye	Unlikely	Moderate	R-S	1 / 73	11
	Keratitis	Not Related	Severe	R-S	1 / 73	11
	Erythema of Eyelid	Unlikely	Moderate	R-S	1 / 73	11
	Eyelid Oedema	Possibly	Moderate	R-S	1 / 73	11
	Eye Pruritus Infections and Infestations	Possibly	Moderate	R-S	1 / 73	11
	Eye Infection	Possibly	Moderate	R-S	1 / 73	11
085.01.00127	Abdominal Pain from recurrent metastatic ovarian cancer ¹	Not related	Severe	NR*	1/167	N/A
01.152	CVA ²	Not related	Severe	Improving	2/10	Lost to f/u
New Discontinuations due to Adverse Events reported since the Interim Clinical Study Report						
732.09.026	Neoplasms Benign, Malignant and Unspecified (including cysts and polyps)					
	Rectal Cancer Metastatic	Not Related	Severe	Death	2 / 272	N/A
732.41.102	Ptosis ³	Probably	Moderate	R-S	4/7	120
Source: BLA 125286, 120-day safety update, table 15, page 82. *R-S: Resolved without sequelae NR: Not reported 1 Source: BLA 125286, ISS , page 92 and study report 085, page 171 2 Source: BLA 125286, study report 085, page 172 3Sponsor reports “patient decision” as reason for discontinuation. However, subject discontinued 28 days after prolonged ptosis resolved.						

In addition, one patient discontinued secondary to breast cancer and 2 others related to pregnancy.

7.3.4 Significant Adverse Events

In trial 720, a long term safety trial, subject 04.034, a 37- year-old Caucasian female, developed pneumonia. The subject has multiple medical illnesses including chronic sinusitis, hypertension, GE reflux disease, anemia, hypothyroidism, migraine, and depression. She was on multiple medications including prednisone. The subject received 3 cycles of Dysport on 12/20/04, 5/23/05, and 11/21/05. The event of pneumonia occurred during cycle 2, day 175 on 11/14/05. The subject was hospitalized and the event resolved on 12/7/05. The subject completed the study on 12/21/05.

***Reviewer's Comment:** Given the dates of the subject's 2nd injection, 5/23/05 and the fact that the pneumonia occurred 6 months later and before her 3rd injection, it is unlikely to be related to Dysport injections. Furthermore, there is no mention that this was a case of aspiration pneumonia which has been the type of pneumonia associated with toxicity due to botulinum toxin. It should be noted, that these cases have been associated with higher doses for other indications and were cases of aspiration pneumonia.*

7.3.5 Submission Specific Primary Safety Concerns

Eyelid ptosis is a primary safety concern with the use of botulinum toxin type A for the treatment of moderate to severe glabellar lines. The incidence of ptosis in the short-term trials using 50 units of Dysport, and across all trials using that dose, the incidence of ptosis remained constant at 2% of subjects. When one looks across cycles in the long term studies, the incidence of ptosis does not increase. Most events of ptosis resolved within 2 weeks. However, there were a couple of subjects who had ptosis lasting several months. These 2 subjects are described below>

Subject 41.102, a 54 year-old Caucasian female, received four treatments with 50 units of Dysport[®] at the five designated injection sites in the glabellar region according to the study Y-97-52150-732 protocol on December 6, 2006; March 1, 2007; March 6, 2007; and August 29, 2007.

At Baseline, the Investigator reported the patient's medical history included fibromyalgia, gingivitis, and seasonal allergies.

On September 5, 2007 (Cycle 4, Day 7), the patient experienced right eyelid ptosis, which was treated with corticosteroid eye drops combined with antibiotics from 9/5/07 to 9/12/07 and with apraclonidine hydrochloride from September 12, 2007 through November 10, 2007. The event resolved without sequelae on January 2, 2008 after 120 days duration. The Investigator assessed the event as moderate in severity and probably related to the study treatment. The patient withdrew from the study on January 30, 2008 due to patient decision.³

Subject 74.007, a 46 year-old African-American female, received a single treatment with 50 units of Dysport[®] at the five designated injection sites in the glabellar region according to study Y-97-52150-732 protocol on August 21, 2007.

At Baseline, the Investigator reported the patient's medical history included seasonal allergies and tubal ligation.

On September 1, 2007 (Cycle 1, Day 11), the patient experienced bilateral eyelid ptosis. No treatment was administered. The event resolved without sequelae on December 17, 2007 after 108 days of duration. The Investigator assessed the event as mild in severity and possibly related to the study treatment. The patient is still actively participating in the study. The patient received two subsequent treatments on April 18, 2008 and August 21, 2008 without ptosis reoccurring.⁴

These 2 cases do illustrate outliers in the duration of ptosis that may occur. Significantly, it should be noted that the prolonged duration of ptosis cannot be ascribed to the number of treatments, as subject 74.007 had only 1 treatment at the time of her ptosis and the duration of the ptosis was only 18 days less than subject 41.102, who had had 4 treatment cycles. Importantly, both had resolution. Thus, this would not preclude approving the drug product for the 50 unit dose.

However, in the variable dose trial, where subjects were injected with variable dosing because of a “perceived” increase in muscle mass, there was a statistically significant difference in the percentage of subjects who experienced ptosis. This was found in female subjects, who make up the majority (~88%) of the trial. While the incidence in female subjects of eyelid ptosis was 1% in those receiving 50 units or 60 units, it rose to 4% in those receiving 70 units ($p = 0.003$). Male subjects experienced ptosis in 1% of subjects who received 50 units (in all other trials). The fact that ptosis is absent in male subjects in the variable dose trial is irrelevant, as the numbers are too small to draw any conclusions. Table 24 shows the results. Eyelid ptosis has been singled out for clarity. The remainder of the table is included for completeness of all ocular adverse events in trial 06-01.

Table 24
Summary of Ocular Treatment Emergent Adverse Events by Preferred Term, Gender, and Units of Dysport Received – Safety Population

MALE						
Preferred Term, n (%)	Placebo (N=57)	50 Units (N=161)	60 Units (N=5)	70 Units (N=25)	80 Units (N=33)	p-value
Any Ocular TEAE	1 (2)	6 (4)	0	0	0	0.791
Eyelid Ptosis	0	2 (1)	0	0	0	0.792
Blepharospasm	1 (2)	0	0	0	0	0.070
Dry Eye	0	2 (1)	0	0	0	0.792
Ocular Hyperaemia	0	1 (<1)	0	0	0	0.852
Eye Pain	0	1 (<1)	0	0	0	0.852
Conjunctivitis	0	1 (<1)	0	0	0	0.852
Eye Irritation	0	1 (<1)	0	0	0	0.852
FEMALE						
Preferred Term, n (%)	Placebo (N=423)	50 Units (N=1358)	60 Units (N=277)	70 Units (N=181)	80 Units (N=1)	p-value
Any Ocular TEAE	11 (3)	80 (6)	10 (4)	11 (6)	0	0.024
Eyelid Ptosis	1 (<1)	19 (1)	4 (1)	8 (4)	0	0.003
Blepharospasm	3 (<1)	11 (<1)	1 (<1)	0	0	0.623
Dry Eye	1 (<1)	11 (<1)	0	1 (<1)	0	0.478
Asthenopia	0	11 (<1)	1 (<1)	2 (1)	0	0.080
Vision Blurred	1 (<1)	4 (<1)	1 (<1)	4 (2)	0	0.124
Eyelid Oedema	0	7 (<1)	0	2 (1)	0	0.128
Ocular Hyperaemia	1 (<1)	6 (<1)	0	0	0	0.945
Eye Swelling	1 (<1)	5 (<1)	1 (<1)	0	0	0.916
Lacrimation Increased	0	6 (<1)	0	1 (<1)	0	0.251
Blepharitis	0	4 (<1)	1 (<1)	0	0	0.378
Eye Pruritus	0	5 (<1)	0	0	0	0.499
Eye Pain	1 (<1)	2 (<1)	0	0	0	0.422
Conjunctivitis	0	1 (<1)	1 (<1)	0	0	0.452
Eye Irritation	1 (<1)	1 (<1)	0	0	0	0.231
Cataract	0	2 (<1)	0	0	0	0.669
Diplopia	1 (<1)	1 (<1)	0	0	0	0.231
Erythema of Eyelid	0	2 (<1)	0	0	0	0.669
Eyelid Irritation	0	2 (<1)	0	0	0	0.669
Madarosis	0	2 (<1)	0	0	0	0.669
Chalazion	0	1 (<1)	0	0	0	0.763
Conjunctival						
Haemorrhage	0	1 (<1)	0	0	0	0.763
Eye Allergy	0	1 (<1)	0	0	0	0.763
Eye Discharge	0	0	0	1 (<1)	0	0.222
Eyelid Disorder	0	1 (<1)	0	0	0	0.763
Eyelid Function Disorder	0	1 (<1)	0	0	0	0.763
Eyelid Pain	1 (<1)	0	0	0	0	0.046
Glaucoma	0	1 (<1)	0	0	0	0.763

Source: BLA 125286, ISS, table 27, page 98

Of the 8 subjects that experienced eyelid ptosis, two subjects experienced bilateral ptosis and one of the events of eyelid ptosis was severe. Given this result, based on just one treatment, coupled with the results of the phase 2 dose-ranging trial (see section 5.3), and the fact that there are no long term trials further examining the safety of these higher doses, these doses will not be recommended for approval.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Table 25 describes the common adverse events that occurred in the short term trials (after 1 treatment with Dysport 50 units to the glabellar region).

Table 25
Summary of Treatment Emergent Adverse Events with Incidence of Greater than 1%
Safety Population (Trials 718,719, 085 Part C, and A-2006-01)

System Organ Class Preferred Term	Placebo (N=496)		Dysport® 50 Units (N=398)	
	Patients n, %	Events	Patients n, %	Events
Any Treatment Emergent Adverse Event	163 (33)	300	191 (48)	393
Eye Disorders	10 (2)	12	27 (7)	38
Eyelid Oedema	0	0	8 (2)	9
Eyelid Ptosis	1 (<1)	1	6 (2)	6
Gastrointestinal Disorders	18 (4)	23	17 (4)	23
Nausea	5 (1)	5	6 (2)	6
General Disorders and Administration Site Conditions	35 (7)	43	47 (12)	58
Injection Site Reaction	2 (<1)	2	12 (3)	12
Injection Site Pain	8 (2)	8	11 (3)	12
Infections and Infestations	69 (14)	86	82 (21)	110
Nasopharyngitis	21 (4)	21	38 (10)	45
Upper Respiratory Tract Infection	9 (2)	10	12 (3)	13
Sinusitis	6 (1)	6	8 (2)	8
Investigations	5 (1)	5	10 (3)	10
Blood Urine Present	1 (<1)	1	6 (2)	6
Nervous System Disorders	27 (5)	29	50 (13)	60
Headache	23 (5)	25	37 (9)	45

Source: BLA 125286, amendment dated 9/23/08, table 8, page 44.

Table 26 describes the common adverse events across all studies, including the long-term trials for subjects treated with Dysport 50 units.

Table 26
Summary of Treatment Emergent Adverse Events with Incidence Greater than 1% Safety Population (Trials 718, 719, 096, 085, A-2006-01, 720 and 732)

System Organ Class Preferred Term	Placebo (N=580)		Dysport® 50 Units (N=2491)	
	Patients n, %	Events	Patients n, %	Events
Any Treatment Emergent Adverse Event	186 (32)	331	1425 (57)	5176
Eye Disorders	12 (2)	15	241 (10)	361
Eyelid Ptosis	1 (<1)	1	54 (2)	62
General Disorders and administration Site Conditions	41 (7)	47	471 (19)	800
Injection Site Pain	8 (1)	8	145 (6)	187
Injection Site Bruising	7 (1)	7	102 (4)	118
Injection Site Reaction	2 (<1)	2	102 (4)	120
Injection Site Swelling	3 (<1)	3	59 (2)	
Injection Site Discomfort	1 (<1)	1	42 (2)	
Immune System Disorders	6 (1)	6	66 (3)	90
Seasonal Allergy	5 (<1)	5	38 (2)	47
Infections and Infestations	73 (13)	91	753 (30)	1350
Nasopharyngitis	23 (4)	23	280 (11)	367
Sinusitis	6 (1)	6	155 (6)	185
Upper Respiratory Tract Infection	9 (2)	10	128 (5)	163
Bronchitis	4 (<1)	4	77 (3)	86
Influenza	3 (<1)	3	73 (3)	80
Urinary Tract Infection	1 (<1)	2	38 (2)	44
Musculoskeletal and Connective Tissue Disorders	11 (2)	12	223 (9)	333
Back Pain	3 (<1)	3	59 (2)	74
Nervous System Disorders	30 (5)	32	400 (16)	551
Headache	25 (4)	27	299 (12)	380
Respiratory, Thoracic and Mediastinal Disorders	8 (1)	11	137 (5)	173
Pharyngolaryngeal Pain	2 (<1)	2	44 (2)	47
Cough	1 (<1)	1	39 (2)	40
Skin and Subcutaneous Tissue Disorders	14 (2)	14	254 (10)	380
Acne	2 (<1)	2	40 (2)	48
Dermatitis Contact	4 (<1)	4	39 (2)	42
Vascular Disorders	6 (1)	6	75 (3)	89
Hypertension	5 (<1)	5	58 (2)	65

Source: BLA 125286, amendment dated 9/23/08, table 1, page 4

Patients in the Dysport group may have received up to 12 treatments over 36 months, but patients in the placebo treatment group received only a single treatment and were followed for 3 months. Thus, the total observation time for the Dysport group was much longer than that of the placebo group. This may have contributed to the observed higher number of related events (from receiving multiple treatments), as well as non-treatment related AEs (due to longer observational period) in the Dysport group. When the total number of AEs (5176 events and 331 events for Dysport and placebo, respectively) is compared to the total number of treatments (9198 treatments and 580 treatments for Dysport and placebo, respectively) the number of events per treatment is very similar between the Dysport and placebo groups (0.56 for the Dysport treated group versus 0.57 for placebo).

When comparing the adverse events in the short term trials versus the adverse events across all studies, which include the long-term trials, the most common adverse events are primarily the same, namely, headache (9% vs. 12%), nasopharyngitis (10% vs. 11%), sinusitis (2% vs. 6%), URI (3% vs. 5%), and injection site pain (3% vs. 6%), and injection site reaction (3% vs. 4%), respectively.

New adverse events that may be related to repeated injections that were revealed across all studies to occur at greater than 1% in the safety population were injection site bruising (4%), injection site swelling and discomfort, and contact dermatitis (each at 2%). These reactions did not lead to patient discontinuation.

Two other adverse events that deserve mention here that occurred across all studies at greater than 1% which was not evident after only 1 treatment of Dysport (short-term studies) was a 2% (44 and 39/2491 subjects, respectively) incidence each of pharyngolaryngeal pain and cough. This type of adverse event occurred in less than 1% in the placebo group. No subject discontinued from the trials because of this adverse event. There have been some post-marketing reports of botulinum toxin type A (Botox) having systemic spread from local injection with some life-threatening results, even death. This has been with higher dose than the dose that will be recommended with Dysport. However, it may be plausible that for some subjects, total recovery of the muscle has not occurred and repeated injections may cause a cumulative dose and allow systemic spread of the toxin. It will be important that subjects are not treated sooner than 90 days after their last injection, if indeed, this is due to spread of the toxin.

7.4.2 Laboratory Findings

Laboratory data, serum chemistry and hematology, were collected in Studies 085, 096 and 719, which is a subset of the Safety Population. This subset is composed of all patients who received either placebo (N=208) or Dysport® (N=491) in those studies. In all three studies data were collected at Day 0, and on Day 30 in Studies 719 and Study 096, as well as at the end of Study 719 and on Day 360 of the first cycle of Study 085. Laboratory values were considered abnormal if there was at least a 10% change from baseline, either high or low. Table 27 shows the incidence of abnormal lab values in any cycle by treatment group.

Table 27
Incidence of Abnormal Laboratory Values in Any Cycle by Treatment Group – Safety Population

	Placebo (N=208)\	Dysport® (N=491)\
Hemoglobin		
Any Post-Baseline Assessment, n	184	423
Low and 10% Decrease from Baseline, n (%)	1 (<1)	11 (2)
High and 10% Increase from Baseline, n (%)	0	0
White Cell Count		
Any Post-Baseline Assessment, n	184	423
Low and 10% Decrease from Baseline, n (%)	2 (<1)	19 (4)
High and 10% Increase from Baseline, n (%)	3 (1)	10 (2)
Urea Nitrogen		
Any Post-Baseline Assessment, n	186	424
Low and 10% Decrease from Baseline, n (%)	0	4 (<1)
High and 10% Increase from Baseline, n (%)	2 (<1)	9 (2)
Creatinine		
Any Post-Baseline Assessment, n	186	424
Low and 10% Decrease from Baseline, n (%)	0	0
High and 10% Increase from Baseline, n (%)	2 (<1)	3 (<1)
Glucose		
Any Post-Baseline Assessment, n	186	424
Low and 10% Decrease from Baseline, n (%)	9 (4)	41 (8)
High and 10% Increase from Baseline, n (%)	14 (7)	52 (11)
Potassium		
Any Post-Baseline Assessment, n	186	424
Low and 10% Decrease from Baseline, n (%)	1 (<1)	1 (<1)
High and 10% Increase from Baseline, n (%)	4 (2)	8 (2)
Sodium		
Any Post-Baseline Assessment, n	186	424
Low and 10% Decrease from Baseline, n (%)	0	0
High and 10% Increase from Baseline, n (%)	0	0
Cholesterol, Total		
Any Post-Baseline Assessment, n	186	424
Low and 10% Decrease from Baseline, n (%)	0	0
High and 10% Increase from Baseline, n (%)	19 (9)	66 (13)

Overall, the incidence of abnormal laboratory values was low. Although, they were somewhat higher in the Dysport group, the changes were not considered to be clinically significant and no subject discontinued from the trials because of a laboratory event.

7.4.3 Vital Signs

Vital signs measured in the trials were blood pressure, heart rate and respiration rate. Vital signs were measured at 30 minutes after treatment, on day 7, 14, and 30 and at 30 day intervals up to day 360 in all trials except 06-01 where vital signs were not collected. Table 28 describes what was considered abnormal. An abnormal had to meet this minimum criterion and also have a 10% change from baseline.

**Table 28
Abnormal Vital Sign Values**

Vital Sign Parameter	Abnormal Low	Abnormal High
Systolic Blood Pressure	Not Applicable	>140 mmHg
Diastolic Blood Pressure	Not Applicable	>90 mmHg
Heart Rate	<50 Beats per Minute	>120 Beats per Minute
Respiration Rate	<10 Breaths per Minute	>30 Breaths per Minute

Source: BLA 125286, ISS, table 42, page 123.

Table 29 describes the abnormal vital signs that occurred in any cycle.

**Table 29
Incidence of Abnormal Vital Signs in Any Cycle
by Treatment Group – Safety Population**

	Placebo (N=208) ¹	Reloxin® (N=1497) ¹
Systolic Blood Pressure Any Post-Baseline Assessment, n >140 mmHg and 10% Increase from Baseline, n (%)	208 22 (11)	1497 290 (19)
Diastolic Blood Pressure Any Post-Baseline Assessment, n >90 mmHg and 10% Increase from Baseline, n (%)	208 26 (13)	1497 289 (19)
Pulse Rate Any Post-Baseline Assessment, n <50 Beats per minute and 10% Decrease from Baseline, n (%) >120 Beats per minute and 10% Increase from Baseline, n (%)	208 4 (2) 0	1497 51 (3) 3 (<1)
Respiration Rate Any Post-Baseline Assessment, n <10 Breaths per minute and 10% Decrease from Baseline, n (%) >30 Breaths per minute and 10% Increase from Baseline, n (%)	208 0 0	1497 2 (<1) 0

Source: BLA 125286, table 43, page 124

The incidence of abnormal pulse rate and respiration rate was low and similar for both placebo and study drug. Although there were more abnormalities in the Dysport group for blood pressure, there was no apparent relationship of abnormal values to time after treatment or to

treatment cycle. Indeed, in the short term trial, 718, there were no meaningful differences in blood pressure between the placebo arm and the Dysport arm through day 150.⁵

7.4.4 Electrocardiograms (ECGs)

See section 7.4.5.

7.4.5 Special Safety Studies

A sub-study was undertaken to detect any treatment-related QT interval changes in subjects exposed to Dysport in trial 06-01. The study took place at 5 of the 27 study sites. Subjects were stratified to ensure that at least 75 subjects were enrolled in the EKG study subset, independent of demographic/ethnic factors. The randomization held such that 50 subjects were received Dysport and 29 subjects received placebo. As this was the variable dose trial, female subjects received between 50 and 70 units of Dysport and males received between 60 and 80 units of Dysport (see table 30).

Table 30
Dose Distribution for QTc Study

Summary Table for the EKG sub study				
Reloxin Group Distribution				Placebo
80 units	70 units	60 units	50 units	0 units
N = 0	N = 18	N = 31	N = 1	N = 29

Source: BLA 125286, amendment dated 11/6/08, page 1.

Cardiovascular safety was assessed by the effect of Dysport® on the QT interval by examining the mean change from time-matched Baseline in QT/QTc interval by QTcB and QTcF to two post-treatment time points for both Dysport® and placebo.

Evaluations were for QT/QTc prolongation using a 12-lead EKG with 10-second rhythm tracings at three protocol-specified time points: 1) any time between signing informed consent and receiving treatment on Study Visit Day 0; 2) after 30 minutes following study treatment administration on Study Visit Day 0; and 3) post-treatment on Study Day 14

EKGs were repeated until a good quality final tracing was obtained with adequate readability for evaluation of QT/QTc prolongation. Screening EKGs determined patient eligibility by ensuring that values were sufficiently within normal limits to permit assessment of QTc interval changes.

There is no consensus concerning the choice of upper limit values for absolute QT/QTc interval and changes from Baseline. While lower limits increase the false-positive rate, higher limits

⁵ <\\cbsap58\M\eCTD Submissions\STN125286\125286.enx>; section 5, clinical study reports, trial 718, pages 512-524

increase the risk of failing to detect a signal of concern. In clinical trials, a prolongation of QTc > 500 msec during therapy has been a threshold of particular concern. FDA Guidance (ICH Guidance E14) indicates a drug is not considered to have a negative effect on QT if the largest time-matched mean difference between the drug and placebo for the QT interval is ≤ 10 msec or less. Accepted ranges used for this study were set as shown in table 31.

Table 31
Accepted Ranges for QT Intervals in Study A-2006-01

Parameter	Accepted Range	Definition
PR	50 – 350 msec	Time interval between initiation of P wave and the beginning of the QRS complex
RR	500 – 1500 msec	Heart rate multiplied by minute/second and measured by the interval between upward components of the QRS complex
HR	30 – 120 bpm	Heart rate in beats per minute
QRS	40 – 200 msec	EKG complex corresponding to activation of ventricular contraction
QT	250 – 600 msec	Time interval between initiation of QRS complex and T wave on the EKG
QTcB	250 – 600 msec	Time interval between initiation of QRS complex and T wave on the EKG corrected for heart rate using Bazett's formula
QTcF	250 – 600 msec	Time interval between initiation of QRS complex and T wave on the EKG corrected for heart rate using Friderica's formula

Source: BLA 125286, ISS table 44, page 126

Measurements used in this clinical study were based on FDA recommendations (ICH Guidance E14) concerning the design, conduct, analysis, and interpretation of assessments that evaluate the potential of a drug to delay cardiac repolarization. These assessments included testing the effects of a new drug for QT/QTc interval prolongation, as well as reporting/collection of cardiovascular and any other adverse events.

Results

Caucasian females represented the majority of the subjects in the Dysport and placebo arms, 98% and 93%, respectively. The mean age of the subjects was 47 and 48 years for the Dysport treated subjects and placebo treated subjects, respectively. None of the subjects in the sub-study discontinued prematurely. This study was blinded such that personnel responsible for the reading and interpretation of the EKG data were blinded to the subject's identity, treatment, EKG sequence, and time points.

Overall, changes in mean QT, QTcB, and QTcF intervals from Baseline to all protocol-defined time points did not increase by ≥ 10 msec. The differences in mean changes in QT, QTcB, and QTcF intervals from Baseline within the Dysport® and placebo treatment groups at all scheduled time points were small, and not significantly different from zero; the exception was the change

from Baseline QT in the Dysport® group at Day 0: 30 minutes. Although this difference was statistically significant ($p = 0.046$) it reflected a mean change from Baseline of 5.5 msec (95% CI: 1.0, 9.9). This reflected a difference between the Dysport group and the placebo group of 5.5 and 3.2 msec, respectively. No statistically significant differences were found between the Dysport® group and the placebo group.

Both the differences and the changes in mean intervals from screening in the Dysport® group to the two post-treatment time points did not increase by ≥ 10 msec from the placebo group. In the Dysport® treatment group, at all protocol-specified time points, the majority of patients had QT, QTcB, and QTcF intervals < 450 msec. There was one patient who had a QT interval of 481 msec. Also in the Dysport® treatment group, at all protocol-specified time points, the majority of patients had changes in QT, QTcB, and QTcF intervals -30 to $< +30$ msec.

Abnormal waveform morphologies were found in one patient that had been treated with placebo.

In conclusion, the substudy evaluating QT/QTc intervals in subjects treated with one dose of Dysport between 50 and 80 units demonstrated that Dysport does not appear at the lower dose to have a significant arrhythmogenic effect.

In an open-label trial of Dysport for the neurological indication of cervical dystonia, where the initial dose for treatment is 500 units, in a limited number of subjects, a statistically significant reduction in heart rate compared to baseline was observed thirty minutes after injection, averaging about three beats per minute. There was also an increase in QT interval, averaging about 4 milli-seconds. Whether the drug has no cardiovascular effects cannot be ascertained until a full QTc study is done at the higher doses for the neurologic indication of cervical dystonia, as requested by DNP.

7.4.6 Immunogenicity

There were very few Dysport-treated patients that were seropositive by RIPA-C (5/1554; 0.32%) and none of these were positive by MPA. Patients that were classified as positive by RIPA-C had no evidence of reduced efficacy or an altered safety profile (see complete biopharmaceutics review for details).

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

The only dose dependent adverse event evident in the BLA is that of ptosis. There was a statistically significant difference in the percentage of women who received 50 and 60 units of Dysport compared to those who received 70 units of Dysport and the incidence of ptosis. Of the subjects who received 70 units of Dysport, 4% experienced ptosis compared to 1% of those

receiving 50 units or 60 units ($p < 0.003$). In the overall safety population, when men are included, the incidence of ptosis, both in short term trials of 1 treatment and overall, including all trials, is 2%. Thus, it is concerning that with this higher dose, more subjects experienced ptosis (see section 7.3.5, Submission Specific Primary Safety Concerns).

7.5.2 Time Dependency for Adverse Events

There was no evidence of time dependency for adverse events.

7.5.3 Drug-Demographic Interactions

Subgroups analyzed for drug-demographic interactions were those of age, gender, and race. In all subgroups, the incidence of adverse events was higher in the Dysport treated group than in the placebo group. The summaries include subjects from all of the IBL Dysport treated subjects.

For the Dysport® treatment group the incidence of any TEAE was highest for patients ≥ 65 years of age, females, and Whites. For the placebo treatment group the incidence of any TEAE was highest for patients ≤ 50 years of age, females, and non- Whites. The increased incidence of TEAEs in the Dysport® treatment group ≥ 65 years of age was due primarily to an increase in infections and infestations and to an increase in ocular TEAEs (see table 32).

Table 32
Summary of the Most Common Treatment Emergent Adverse Events $\geq 1\%$ by Group and Age Category – Safety Population

≤ 50 YEARS				
System Organ Class Preferred Term	Placebo (N=292)		Dysport® (N=1260)	
	Patients, n (%)	Events	Patients, n (%)	Events
Any Treatment Emergent Adverse Event	97 (33)	157	519 (41)	1149
Eye Disorders	7 (2)	8	57 (5)	77
Eyelid Ptosis	0	0	15 (1)	15
Blepharospasm	4 (1)	5	9 (<1)	11
Gastrointestinal Disorders	7 (2)	8	48 (4)	58
General Disorders and Administration Site Conditions	20 (7)	24	116 (9)	157
Injection Site Pain	6 (2)	6	45 (4)	54
Injection Site Bruising	4 (1)	4	20 (2)	22
Injection Site Reaction	0	0	14 (1)	14
Injection Site Haemorrhage	3 (1)	3	1 (<1)	1

Infections and Infestations	36 (12)	42	221 (18)	309
Nasopharyngitis	12 (4)	12	68 (5)	76
Upper Respiratory Tract Infection	2 (<1)	3	35 (3)	44
Sinusitis	3 (1)	3	39 (3)	43
Influenza	3 (1)	3	20 (2)	20
Bronchitis	2 (<1)	2	17 (1)	19
Nervous System Disorders	12 (4)	12	109 (9)	138
Headache	11 (4)	11	81 (6)	97
> 50, < 65 years				
	Placebo (N=161)		Dysport (N=686)	
	Patients, n(%)	Events	Patients, n (%)	Events
Any Treatment Emergent Adverse Event	37 (23)	67	285 (42)	700
Eye Disorders	4 (2)	5	40 (6)	71
Eyelid Ptosis	0	0	17 (2)	21
Asthenopia	0	0	7 (1)	7
Gastrointestinal Disorders	5 (3)	7	26 (4)	32
Nausea	3 (2)	3	5(<1)	5
Gastroesophageal Reflux Disease	0	0	7 (1)	7
General Disorders and Administration Site Conditions	20 (7)	24	116 (9)	157
Injection Site Pain	6 (2)	6	45 (4)	54
Injection Site Bruising	4 (1)	4	20 (2)	22
Condition Aggravated	0	0	14 (1)	14
Injection Site Haemorrhage	3 (1)	3	1 (<1)	1
Infections and Infestations	14 (9)	19	131 (19)	188
Nasopharyngitis	6 (4)	6	49 (7)	59
Upper Respiratory Tract Infection	2 (1)	2	18(3)	20
Sinusitis	0	0	14 (2)	14
Influenza	0	0	10 (1)	11
Bronchitis	1 (<1)	1	9 (1)	10
Nervous System Disorders	4 (2)	4	44 (6)	54
Headache	4 (2)	4	25 (4)	29
≥ 65 years				
	Placebo (N=27)		Dysport (N=95)	
	Patients, n(%)	Events	Patients, n (%)	Events
Any Treatment Emergent Adverse Event	7 (26)	13	48 (51)	132
Eye Disorders	1 (4)	2	10 (11)	13
Eyelid Ptosis	1 (4)	1	1 (1)	1
Dry Eye	0	0	1 (1)	1
Blepharospasm	0	0	1 (1)	1
Eyelid Edema	0	0	2 (2)	2

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Vision Blurred	1 (4)	1	0	0
Eye Swelling	0	0	1 (1)	1
Eye Pruritus	0	0	1(1)	1
Cataract	0	0	1 (1)	1
Erythema of Eyelid	0	0	1 (1)	1
Eyelid Irritation	0	0	1 (1)	1
Madrosis	0	0	1 (1)	1
Chalazion	0	0	1 (1)	1
Glaucoma	0	0	1 (1)	1
Gastrointestinal Disorders	1 (4)	2	1 (1)	1
Tooth Impact	0	0	1 (1)	1
Erosive Esophagitis	1 (4)	1	0	0
Hiatus Hernia	1 (4)	1	0	0
General Disorders and Administration Site Conditions	1 (4)	1	11 (12)	18
Injection Site Pain	0	0	3 (3)	3
Injection Site Bruising	1 (4)	1	3 (3)	3
Injection Site Reaction	0	0	1 (1)	1
Injection Site Discomfort	0	0	1 (1)	1
Injection Site Swelling	0	0	1 (1)	1
Condition Aggravated	0	0	2 (2)	2
Injection Site Erythema	0	0	2 (2)	2
Pyrexia	0	0	2 (2)	2
Pain	0	0	1 (1)	1
Asthenia	0	0	1 (1)	1
Nodule	0	0	1 (1)	1
Infections and Infestations	3 (11)	3	22 (23)	31
Nasopharyngitis	1 (4)	1	6 (6)	6
Upper Respiratory Tract Infection	0	0	5 (5)	5
Sinusitis	1 (4)	1	2 (2)	2
Influenza	0	0	1 (1)	1
Bronchitis	0	0	2 (2)	4
Urinary Tract Infection	0	0	1 (1)	1
Pneumonia	0	0	1 (1)	1
Gastroenteritis	0	0	1 (1)	1
Eye Infection	0	0	2 (2)	2
Staphylococcal Infection	0	0	1 (1)	1
Laryngitis	1 (4)	1	0	0
Dental Caries	0	0	1 (1)	2
Pertussis	0	0	1 (1)	1
Vulvovaginal Mycotic Infection	0	0	1 (1)	1
Bronchopneumonia	0	0	1 (1)	1
Varicella	0	0	1 (1)	1
Viral Infection	0	0	1 (1)	1
Nervous System Disorders	1 (4)	1	6 (6)	8
Headache	1 (4)	1	4 (4)	4
Dizziness	0	0	1 (1)	1
Aphasia	0	0	1 (1)	2
Neuropathy Peripheral	0	0	1 (1)	1

Source: BLA 125286, ISS, adapted from table 75, pages 231- 234.

The data in the above table reveals that a higher percentage of subjects in the older population (≥ 65 years) had an increased incidence of eye disorders compared to the younger age groups (11% vs. 6% and 5%, respectively). These tended to be a few more infections and eye related adverse events other than eyelid ptosis, which was the same as < 50 years age groups (1%) but lower than the >50 but <65 year age group (2%). , The number of subjects in this age group for the safety data base, is very small, $n = 95$ on Dysport and 27 on placebo. The data suggests that there may be a safety concern in the geriatric population but the sample size is too small to make a definite conclusion.

Table 33 shows the incidence of common adverse events by gender.

Table 33
Summary of Most Common Treatment Emergent Adverse Events $\geq 1\%$ by Gender
Safety Population

MALE				
System Organ Class Preferred Term	Placebo (N=57)		Dysport® (N=224)	
	Patients, n (%)	Events	Patients, n (%)	Events
Any Treatment Emergent Adverse Event	14 (25)	29	69 (31)	157
Eye Disorders	1 (2)	2	6 (3)	8
Blepharospasm	1 (2)	2	0	0
Gastrointestinal Disorders	2 (4)	2	9 (4)	9
Food Poisoning	1 (2)	1	1 (<1)	1
Abdominal Discomfort	1 (2)	1	0	0
General Disorders and Administration Site				
Conditions	4 (7)	4	11 (5)	19
Injection Site Pain	0	0	7 (3)	9
Injection Site Reaction	0	0	3 (1)	3
Condition Aggravated	3 (5)	3	1 (<1)	1
Injection Site Warmth	1 (2)	1	0	0
Infections and Infestations	6 (11)	8	33 (15)	44
Nasopharyngitis	3 (5)	3	12 (5)	13
Upper Respiratory Tract Infection	0	0	8 (4)	9
Sinusitis	0	0	3 (1)	3
Herpes Simplex	1 (2)	2	0	0
Dental Caries	1 (2)	1	0	0
Cellulitis	1 (2)	1	1 (<1)	1
Tinea Infection	1 (2)	1	0	0
Nervous System Disorders Headache	2 (4)	1	14 (6)	20
	2 (4)	1	12 (5)	15

FEMALE				
	Placebo (N=423)		Dysport (N=1817)	
	Patients, n(%)	Events	Patients, n (%)	Events
Any Treatment Emergent Adverse Event	127 (30)	208	783 (43)	1824
Eye Disorders	11 (3)	13	101 (6)	153
Eyelid Ptosis	1 (<1)	1	31 (2)	35
Gastrointestinal Disorders	11 (3)	15	66 (4)	82
General Disorders and Administration Site Conditions	25 (6)	30	188 (10)	255
Injection Site Pain	7 (2)	7	62 (3)	72
Injection Site Bruising	7 (2)	7	33 (2)	35
Injection Site Haemorrhage	5 (1)	5	6 (<1)	6
Infections and Infestations	47 (11)	56	341 (19)	484
Nasopharyngitis	16 (4)	16	111 (6)	128
Upper Respiratory Tract Infection	4 (<1)	5	50 (3)	60
Sinusitis	4 (<1)	4	52 (3)	56
Influenza	3 (<1)	3	29 (2)	29
Bronchitis	3 (<1)	3	26 (1)	31
Nervous System Disorders Headache	15 (4)	15	145 (8)	180
	14 (3)	14	98 (5)	115

Source: BLA 125286, ISS, pages 235-237, adapted from table 76.

Again, the adverse event profile for gender does not differ much from the overall safety profile.

Table 34 shows the most common adverse event profile based on race.

Table 34
Summary of Most Common Treatment Emergent Adverse Events $\geq 1\%$ by Race Safety Population

WHITE				
System Organ Class Preferred Term	Placebo (N=344)		Dysport® (N=1666)	
	Patients, n (%)	Events	Patients, n (%)	Events
Any Treatment Emergent Adverse Event	98 (28)	173	718 (43)	1677
Eye Disorders	8 (2)	0	83 (5)	114
Eyelid Ptosis	1 (<1)	1	24 (1)	25
Gastrointestinal Disorders	11 (3)	14	67 (4)	80

General Disorders and Administration Site Conditions	21 (6)	25	175 (11)	241
Injection Site Pain	6 (2)	6	62 (4)	71
Injection Site Bruising	4 (1)	4	33 (2)	35
Condition Aggravated	4 (1)	4	11 (<1)	12
Infections and Infestations	38 (11)	46	335 (20)	472
Nasopharyngitis	13 (4)	13	106 (6)	121
Upper Respiratory Tract Infection	3 (<1)	4	53 (3)	62
Sinusitis	3 (<1)	3	51 (3)	55
Influenza	1 (<1)	1	27 (2)	28
Bronchitis	1 (<1)	1	27 (2)	32
Nervous System Disorders	13 (4)	13	123 (7)	153
Headache	12 (3)	12	82 (5)	95
NON-WHITE				
	Placebo (N=136)		Dysport (N=375)	
	Patients, n(%)	Events	Patients, n (%)	Events
Any Treatment Emergent Adverse Event	43 (32)	64	134 (36)	304
Eye Disorders	4 (3)	5	24 (6)	47
Eyelid Ptosis	0	0	9 (2)	12
Asthenopia	0	0	7 (2)	8
Vision Blurred	0	0	7 (2)	10
Gastrointestinal Disorders	2 (1)	3	8 (2)	11
General Disorders and Administration Site Conditions	8 (6)	9	24 (6)	33
Injection Site Pain	1 (<1)	1	7 (2)	10
Injection Site Bruising	3 (2)	3	1 (<1)	1
Injection Site Reaction	0	0	6 (2)	6
Injection Site Haemorrhage	2 (1)	2	0	0
Infections and Infestations	15 (11)	18	39 (10)	56
Nasopharyngitis	6 (4)	6	17 (5)	20
Upper Respiratory Tract Infection	1 (<1)	1	5 (1)	7
Sinusitis	1 (<1)	1	4 (1)	4
Influenza	2 (1)	2	4 (1)	4
Bronchitis	2 (1)	2	1 (<1)	1
Laryngitis	2 (1)	2	1 (<1)	1
Pharyngitis	2 (1)	2	1 (<1)	1
Nervous System Disorders	4 (3)	4	36 (10)	47
Headache	4 (3)	4	28 (7)	35

Source: BLA 125286, ISS , adapted from table 77, pages 239-240

There were no major safety differences between whites and non-whites that warrant a separation of the safety adverse event profile for the overall study population. Whites tended to have more injection site issues than did non-whites. This may be that adverse events such as injection site bruising and reaction may have been more easily discernable in Caucasian subjects than in non-Caucasian subjects. Non-Whites tended to experience slightly more ptosis (2% vs. 1%) whereas Whites tended to have more infections (3% vs. <1%).

7.5.4 Drug-Disease Interactions

Due to the localized nature of the application of Dysport, very few drug-disease interactions are expected.

7.5.5 Drug-Drug Interactions

The same can be said for drug-drug interactions. According to the sponsor, “co-administration of agents interfering with neuromuscular transport could potentiate the effects of Dysport® and raise the effective patient exposure over the dosages tested for safety. No adverse effects were seen from the co-administration of Dysport® and agents interfering with neuromuscular transport during the IBL-initiated studies because the use of agents interfering with neuromuscular transport was a specific exclusion criterion preventing entry into the studies.”

7.6 Additional Safety Exploration

7.6.1 Human Carcinogenicity

No evidence has been collected regarding Dysport’s potential to either initiate or promote cancer in humans.

7.6.2 Human Reproduction and Pregnancy Data

There are no well-controlled studies on the effects of Dysport in pregnant or lactating women. The reader is referred to the pharmacology/toxicology review for preclinical studies to determine the pregnancy category for this drug product.

Nine pregnancies occurred in the placebo-controlled and long term trials. Table 35 shows the results. There is no evidence from this human data that the use of Dysport portends an adverse outcome of the fetus or mother.

Table 35
Summary of Pregnancies in the Dysport Trials

Trial# – Subject Number	Dysport or Placebo	Results
720 – 720.13.00059	Dysport – one treatment	Normal, healthy infant
720 – 720.16.00010	Dysport – two treatments	Spontaneous abortion
085 – 0 85.02.00233	Dysport – three treatments	Spontaneous miscarriage
085 – 085.02.00390	Dysport – three treatments	Pregnancy proceeding normally at study end
085 – 085.06.00306	Placebo	Normal pre-term infant by C-section
085 – 085.06.00321	Dysport – three treatments	Normal birth- healthy male
06-01 – A20.83.00033	Placebo	Elective termination
732 – 720.04.00-02	Dysport – one treatment	Normal pregnancy and delivery
718 – 718.03-036	Dysport – one treatment	Normal, healthy female
Source: BLA 125286, ISS, pages 141-142, study reports 085, 0601, 732 interim report, and study report 718, page 98		

7.6.3 Pediatrics and Effect on Growth

This drug product is not to be used in pediatric subjects, thus no trials included subjects less than 18 years of age.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Overdose

Signs and symptoms of overdose may not be apparent immediately after injection. Botulism is characterized by diplopia, slurred speech, difficulty swallowing, dry mouth, and muscle weakness. Infants with botulism appear lethargic, feed poorly, are constipated, and have a weak cry and poor muscle tone. If untreated, these symptoms may progress to paralysis of the arms, legs, trunk and respiratory muscles and may cause death.

If accidental injection or oral ingestion occurs, the person should be medically supervised for up to several weeks for signs and symptoms of systemic weakness or muscle paralysis.

C. botulinum antitoxin supplied by the Centers for Disease Control and Prevention (CDC) (Centers for Disease Control and Prevention) may prevent progression of illness and shorten symptoms in severe botulism cases, if administered early. The antitoxin will not reverse any botulinum toxin-induced muscle weakness effects apparent by the time of antitoxin administration.

The proposed dose of Dysport® for the treatment of glabellar lines is a relatively small dose, in comparison to the approved dosing regimens for other indications of the drug, which can be as high as 1500 units. Risks resulting from administration of Dysport at higher doses for improvement of glabellar lines are not known.

Drug Abuse

Dysport® is intended to be re-administered only after no further aesthetic effect is seen from the previous treatment. Due to the pattern of treatment suggested by the Dysport® label (the median duration of effect is greater than 85 days) and the mechanism of Dysport® effect, no dependence potential is foreseen.

Withdrawal and Rebound

Withdrawal effects are unlikely to occur with Dysport® as the product is given by single administration with an interval of at least 85 Days between treatments. Repeated administrations of Dysport® were associated with a similar safety profile compared to the safety profile of patients receiving the product only once although the incidence of TEAEs decreased over repeated exposure. It should be noted that Dysport® is intended to be readministered only after patients glabellar lines have returned to moderate or severe. There is no evidence of any rebound effects after withdrawal and due to the pattern of treatment suggested by the Dysport® label and the known pharmacology of the product, no withdrawal effects are foreseen.

Reviewer's Comment: The label is going to state that there should be 90 days between treatments.

7.7 Additional Submissions

120-day Safety Update

Trial 732, the only trial that was still ongoing at the time of submission, is the subject of this 120-day safety update. The cutoff date for the 120 day safety update was 9/30/07. Subjects in this trial rolled over from the placebo controlled trials and from the shorter open label trial, 720 of 13 months duration. In total 1349 subjects enrolled in this trial. This trial is still ongoing with 95% of the subjects continuing. A total of 3814 treatments of Dysport® at 50 units (at least one treatment per patient) have been administered. The median age of a study participant was 49 years old and the majority was Caucasian, female and less than 50 years old.

At data cut-off, 1284 patients (95%) remained in the study. The primary reason for discontinuation was patient decision (3%), although a number of patients were lost to follow-up (1%) and some patients discontinued due to patient non-compliance with study requirements (<1%), adverse event [<1%, (see table under 7.3.3 for reasons)], or Investigator decision (<1%).

For trial 732, 1349 patients were treated in Cycle 1, 768 in Cycle 2, 636 in Cycle 3, 477 in Cycle 4, 313 in Cycle 5, 186 in Cycle 6, 81 in Cycle 7 and four patients were treated in Cycle 8. Therefore, as of September 30, 2007, 581 patients had received a total of one treatment, 132 patients had received a total of two treatments, 159 patients had received a total of three treatments, 164 patients had received a total of four treatments, 127 patients had received a total of five treatments, 105 patients had received a total of six treatments, 77 patients had received a total of seven treatments, and four patients had received a total of eight treatments (50 units of

Dysport® per treatment) for the 120 Day safety analysis period. A total of 3814 treatments of 50 units of Dysport® were administered during the study up to the 120 Day safety cut-off. The maximum exposure as of the 120 Day safety analysis data cutoff was eight treatments of 50 units of Dysport® administered over approximately 21 months.

Reviewer’s Comment: *With this added data from trial 732, there are enough subjects (300 or greater) for each of the 1st six cycles of Dysport treatment of glabellar lines at the 50 unit dose to evaluate safety for 18 months. Cycle 7 and 8 do not have enough subjects, 77 and 4, respectively, to make meaningful assessment of treatment beyond 18 months.*

Table 36
Number (%) of Patients Experiencing Treatment-Emergent Adverse Events (reported by at least 3% of Patient) by Cycle – Safety population Trial 732

System Organ Class Preferred Term, n (%)	Cycle 1 N=1349	Cycle 2 N=768	Cycle 3 N=636	Cycle 4 N=477	Cycle 5 N=313	Cycle 6 N=186	Cycle 7 N=81	Cycle 8 N=4	Overall N=1349	Interim Overall N=768
Number (%) of Patients with any TEAE	382 (28%)	201 (26%)	166 (26%)	114 (24%)	69 (22%)	26 (14%)	4 (5%)	0	570 (42%)	285 (37%)
Eye Disorders	49 (4%)	19 (2%)	9 (1%)	7 (1%)	5 (2%)	1 (<1%)	0	0	85 (6%)	36 (5%)
Gastrointestinal Disorders	19 (1%)	10 (1%)	10 (2%)	8 (2%)	5 (2%)	1 (<1%)	0	0	52 (4%)	25 (3%)
General Disorders and Administration Site Conditions	86 (6%)	44 (6%)	30 (5%)	17 (4%)	14 (4%)	2 (1%)	1 (1%)	0	145 (11%)	74 (10%)
Injection Site Pain	17 (1%)	14 (2%)	6 (<1%)	8 (2%)	4 (1%)	1 (<1%)	0	0	42 (3%)	26 (3%)
Immune System Disorders	13 (<1%)	8 (1%)	10 (2%)	5 (1%)	1 (<1%)	2 (1%)	0	0	34 (3%)	21 (3%)
Infections and Infestations	158 (12%)	69 (9%)	61 (10%)	50 (10%)	23 (7%)	8 (4%)	0	0	284 (21%)	151 (20%)
Nasopharyngitis	52 (4%)	15 (2%)	17 (3%)	9 (2%)	9 (3%)	1 (<1%)	0	0	91 (7%)	43 (6%)
Sinusitis	28 (2%)	10 (1%)	7 (1%)	11 (2%)	0	0	0	0	53 (4%)	28 (4%)
Upper Respiratory Tract Infection	21 (2%)	11 (1%)	6 (<1%)	7 (1%)	0	0	0	0	40 (3%)	29 (4%)
Injury, Poisoning and Procedural Complications	39 (3%)	16 (2%)	17 (3%)	12 (3%)	9 (3%)	4 (2%)	2 (2%)	0	94 (7%)	40 (5%)
Investigations	26 (2%)	21 (3%)	15 (2%)	3 (<1%)	5 (2%)	2 (1%)	0	0	61 (5%)	35 (5%)
Musculoskeletal and Connective Tissue Disorders	30 (2%)	19 (2%)	15 (2%)	10 (2%)	8 (3%)	0	0	0	68 (5%)	30 (4%)
Nervous System Disorders	54 (4%)	20 (3%)	13 (2%)	6 (1%)	5 (2%)	3 (2%)	0	0	93 (7%)	32 (4%)
Headache	39 (3%)	10 (1%)	8 (1%)	4 (<1%)	2 (<1%)	0	0	0	60 (4%)	18 (2%)
Respiratory Thoracic and Mediastinal Disorders	25 (2%)	14 (2%)	7 (1%)	3 (<1%)	1 (<1%)	1 (<1%)	0	0	47 (3%)	22 (3%)
Skin and Subcutaneous Tissue Disorders	38 (3%)	25 (3%)	16 (3%)	10 (2%)	9 (3%)	5 (3%)	1 (1%)	0	89 (7%)	40 (5%)
Surgical and Medical Procedures	42 (3%)	29 (4%)	24 (4%)	10 (2%)	10 (3%)	4 (2%)	0	0	101 (7%)	54 (7%)

Source: BLA 125286, 120 day safety update, table 4, page 54.

Table 37
Most Frequently Occurring Treatment-Emergent Adverse Events (Reported by at Least 10 Patients in One Cycle) by Cycle – Safety Population

System Organ Class Preferred Term, n	Cycle 1 N=1349	Cycle 2 N=768	Cycle 3 N=636	Cycle 4 N=477	Cycle 5 N=313	Cycle 6 N=186	Cycle 7 N=81	Cycle 8 N=4	Overall N=1349
Number of Treatment-Emergent Adverse Events	723	402	300	182	120	49	4	0	1779
Eye Disorders	66	24	12	9	8	1	0	0	118
Gastrointestinal Disorders	22	11	12	9	8	1	0	0	81
General Disorders and Administration Site Conditions	82	52	38	20	17	2	1	0	210
Injection Site Pain	19	16	8	8	4	1	0	0	53
Injection Site Bruising	5	11	5	3	3	0	0	0	27
Immune System Disorders	15	10	10	5	1	2	0	0	43
Seasonal Allergy	10	2	3	2	0	0	0	0	17
Infections and Infestations	186	78	70	59	24	8	0	0	425
Nasopharyngitis	63	17	19	10	9	1	0	0	109
Sinusitis	29	10	7	12	0	0	0	0	58
Upper Respiratory Tract Infection	22	11	6	7	0	0	0	0	46
Bronchitis	11	5	4	4	3	0	0	0	27
Injury, Poisoning and Procedural Complications	49	24	24	14	10	5	2	0	128
Investigations	36	30	20	3	7	8	0	0	102
Biopsy Skin	10	6	1	2	4	0	0	0	23
Musculoskeletal and Connective Tissue Disorders	33	24	19	10	11	0	0	0	97
Neoplasms Benign, Malignant and Unspecified (including Cysts and Polyps)	8	12	5	10	2	3	0	0	40
Nervous System Disorders	58	24	13	6	8	3	0	0	110
Headache	39	10	8	4	4	0	0	0	65

Source: BLA 125286, 120 day safety update, table 5, page 55.

Overall, the majority of TEAEs were mild or moderate in severity. Of the 570 patients (a total of 1779 events) reporting at least one TEAE, 378 patients (66%) experienced mild events, 141 patients (25%) experienced moderate events, and 46 patients (8%) experienced severe events. No severe TEAE by preferred term or system organ class occurred in sufficient number to account for one percent or more of total population or the population for each cycle in which that AE was determined to start. One patient experienced a severe headache that was deemed possibly related to study treatment; all other severe events were deemed not related or unlikely to be related to study treatment.

The majority of adverse events around the eyes (Table 38) were reported by Day 30 and the incidence decreased with each subsequent cycle. No patients reported events occurring around the eyes after Day 240 in any treatment cycle. The most commonly reported adverse events around the eyes (1 – 3% in any treatment cycle) included excessive tearing.

Table 38
Number (%) of Patients Reporting Treatment-Emergent Adverse Events Around the Eyes by Visit and Treatment Cycle: Safety Population

Visit	Cycle 1 N=1349	Cycle 2 N=768	Cycle 3 N=636	Cycle 4 N=477	Cycle 5 N=313	Cycle 6 N=186	Cycle 7 N=81	Cycle 8 N=4
Day 7	18/1292 (1%)	5/707 (<1%)	1/563 (<1%)	1/424 (<1%)	1/282 (<1%)	0	0	0
Day 14	22/1298 (2%)	2/890 (<1%)	4/580 (<1%)	4/424 (<1%)	2/285 (<1%)	1/183 (<1%)	0	0
Day 30	8/1209 (<1%)	5/890 (<1%)	2/540 (<1%)	1/401 (<1%)	1/248 (<1%)	0	0	0
Day 60	2/968 (<1%)	2/897 (<1%)	2/529 (<1%)	1/374 (<1%)	0	0	0	---
Day 90	9/780 (1%)	5/852 (<1%)	0	1/336 (<1%)	0	0	0	---
Day 120	1/432 (<1%)	1/363 (<1%)	4/304 (1%)	1/172 (<1%)	1/90 (1%)	0	---	---
Day 150	1/251 (<1%)	4/212 (2%)	1/148 (<1%)	0	1/34 (3%)	0	---	---
Day 180	0	3/115 (3%)	0	0	0	0	---	---
Day 210	1/64 (2%)	0	0	0	0	---	---	---
Day 240	1/38 (3%)	0	0	0	0	---	---	---

Source: BLA 125826, 120 day safety update, study report 732, table 11, page 65

At interim analysis data cut-off, a total of 10 (1%) patients experienced 10 events of ptosis. Most instances (70%) had a duration of less than three weeks. The appearance of ptosis did not appear to be cycle dependent. Two of the 10 patients that experienced ptosis had a medical history of ptosis (08.012 and 08.023).

At the 120 Day safety analysis data cut-off, an additional five patients experienced five ptosis events and one patient (21.005) that experienced ptosis prior to the interim data cut-off reported an additional incidence of mild ptosis prior to the 120 Day safety analysis data cut-off. Two of the newly reported ptosis events, one beginning on September 1, 2007 and another beginning on September 5, 2007 had not resolved by the time of the 120 Day safety analysis cut-off, September 30, 2007 (see section 7.3.5 for discussion). Of the remaining four events, two resolved within seven days and the others resolved in three to four weeks. Five of the six additional events were mild in severity, with the sixth being moderate. Again, the appearance of ptosis did not appear to be cycle dependent.

Conclusion: This 120 day safety update did not reveal any additional safety issues from the repeated use of a 50 unit dose of Dysport to treat moderate to severe glabellar lines. This report included a larger number of subjects than at the 732 interim study report, 1349 vs. 768 subjects, respectively. There is also a significantly larger drug exposure in this 120 day safety update of trial 732 as compared to the interim study report, 3814 vs. 2259 total treatments, respectively.

The most frequently experienced adverse events were injection site pain, nasopharyngitis, sinusitis, upper respiratory tract infection, and headache, which is not different from the adverse

events that occurred in the overall safety report or in the short term studies (after 1 treatment). Most of the adverse events were mild to moderate to moderate in severity. Incidence of eye disorders also did not increase (3%) with 1% of the eye disorders due to ptosis. In the short-term studies and overall safety population, ptosis occurred in 2% of subjects.

There were no clinically significant mean changes from baseline in vital signs in this update.

8 Postmarketing Experience

Postmarketing data from worldwide pharmacovigilance data is available from December 9, 1990, when Dysport was first approved, to June 30, 2007. The sponsor was asked by the FDA to compare in the post-marketing surveillance the CAMR product (which has been marketed worldwide as Dysport) with the IBL product, Dysport, which will be marketed in the United States.

In assessing the safety of CAMR and IBL Dysport® in the Conceptual Integration, only Cycle 3 data was selected to compare the safety of Dysport® from the two BAS sources, since this cycle had a sufficient numbers of patients who received both products to make a meaningful comparison, as shown in table 39 (CAMR: 596 patients; IBL: 343 patients). In addition, TEAEs are being compared after the same period of exposure to Dysport® and therefore patient expectations should be the same.

Table 39
Number of Patients in Study Y-97-52120-720 by Cycle – Safety Population

	Dysport® CAMR, N	Dysport® IBL, N
Cycle 1	940	0
Cycle 2	939	1
Cycle 3	596	343
Cycle 4	0	659
Cycle 5	0	177

BLA 125256, ISS page 204, table 65

The incidence of TEAEs is summarized below in Table 40 by system organ class (SOC). The percentage of patients experiencing a TEAE in the CAMR and IBL groups in Cycle 3 was 28% and 23%, respectively, and the number of TEAEs per patient was 0.48/patient and 0.31/patient for CAMR and IBL, respectively. Considering the number of patients involved and the incidence of events, there is very little difference between the two groups of patients. Most SOCs had fewer than 1% of patients in either group reporting a TEAE. There were only five SOCs where the number of patients in either group experiencing TEAEs was ≥ 3%. This was in General disorders and administration site conditions (7% CAMR and 3% IBL), Injury,

poisoning and procedural complications (3% for both groups), Infections and infestations (8% CAMR and 7% IBL), Nervous system disorders (3% CAMR and 2% IBL) and Skin and subcutaneous tissue disorders (4% CAMR and 3% IBL). Although the CAMR treated patients generally had a slightly higher percentage of patients with events in these SOCs, the difference is only a matter of fractions of a percentage point. The exception was in General disorders and administration site conditions, but the difference noted in this SOC was small and not clinically meaningful. The severity of TEAEs was comparable between groups (7% moderate and 1% severe in patients receiving CAMR, and 6% moderate and < 1% severe in patients receiving IBL).

Table 40
Common TEAEs in Cycle 3

System Organ Class	Cycle 3			
	Dysport® CAMR N= 596		Dysport® IBL N= 343	
	Patients, n (%)	Events	Patients, n (%)	Events
Number of patients with any adverse event	169 (28)	284	78 (23)	108
Eye disorders	8 (1)	9	4 (1)	4
Gastrointestinal disorders	12 (2)	16	8 (2)	10
General disorders and administrative site conditions	39 (7)	50	12 (3)	15
Infections and infestations	48 (8)	53	25 (7)	26
Nervous system disorders	20 (3)	21	8 (2)	8
Psychiatric disorders	3 (<1)	3	5 (1)	5
Respiratory, thoracic and mediastinal disorders	5 (<1)	8	3 (<1)	3
Skin and subcutaneous tissue disorders	21 (4)	27	9 (3)	10

Source: BLA 125286, ISS, page 206, table 66

Reviewer’s Comment: *The data presented here between the globally marketed CAMR Dysport and the IBL Dysport supports the data presented in trial 096, the clinical bioequivalence trial (see section 5.3.2).*

Global Safety Database

Dysport has been available in other countries since 1990 and is currently approved in 73 countries for clinical indications, including blepharospasm, hemifacial spasm, spasmodic torticollis, equinus foot deformity due to spasticity in pediatric patients with cerebral palsy, hyperhidrosis, and/or spasticity of the arm and leg in patients following a stroke. It is approved for treatment of the cosmetic indication of facial lines in 23 countries.

The drug product has not been withdrawn from any market for safety reasons. There has been one Direct Healthcare Professional Communication that was distributed in Europe at the request of the EMEA. This was to revise labeling for all therapeutic botulinum toxins to include information on the potential for adverse events due to the spread of the locally injected neurotoxin. Of the two English-speaking foreign labels submitted, that of the United Kingdom and Australia, Dysport is approved in Australia for the treatment of moderate to severe glabellar lines at a dose of 50 units that may be repeated approximately every 16 weeks but not less than 3 months.

Since the International Birth Date of Dysport®, 09 December 1990, there have been 1780 adverse events associated with Dysport® use reported, up to and including 30 June 2007, constituting the global safety database for CAMR, on an estimated (b) (4) patient years of exposure. They are provided by category (glabellar lines, other aesthetic indications, medical indications using doses up to and more than 200 units, unspecified dose, unspecified indications, and literature). The global database includes events reported spontaneously and those drawn from European studies.

There were five patients with ptosis captured in the global database when the drug was being used in the glabellar region, 39 when used for other aesthetic indications. Injection site pain was reported in one patient when used in the glabellar region, and in 72 patients for other aesthetic indications, injection site hemorrhage in two patients in other aesthetic indications, injection site swelling in one patient in the glabellar region and 29 patients in other aesthetic indications, and injection site reaction in 39 patients in other aesthetic indications.

From July 1, 2007 until December 31, 2007, an update to the post-marketing report revealed 278 AEs captured in the Ipsen global safety data base associated with the following indications: glabellar lines, other aesthetic indications, medical indications using doses up to and including 200 units, medical indications using doses greater than 200 units, unspecified doses, unspecified indications, and literature, the latter will be discussed under section 9.1. Of these 278 AEs, 26 described eyelid ptosis; 27 AEs were considered to be injection site reactions. These 53 AEs are described below in aggregate by event type, report source, and indication for Dysport® use.

Of the 26 Dysport® AEs coded with the MedDRA preferred term (PT) eyelid ptosis, 10 originated from spontaneous notifications. The indication for Dysport® use was treatment of glabellar lines in 2 of these 10 cases. In 8 of the 10 cases, the product was used for other aesthetic purposes. Of note, 2 of these 8 cases were considered serious (required intervention in 1 case; required hospitalization and intervention in the second case). The remaining 16 AEs were identified in the scientific literature (see section 9.1).

Eleven reports described pain at the site of Dysport® injection and were coded with the following MedDRA PTs: application site pain (n=2), injection site pain (n=8), and pain (n=1). Ten reports were received from spontaneous sources. In 3 of these 10 cases, Dysport® was used for cosmetic purposes other than treatment of glabellar lines. One of the 10 cases was considered serious

(resulted in disability); the indication for product use was muscle spasticity. Of note, the reported dose was 250 units. In 6 of the 10 cases, the indication for Dysport® use was unspecified.

There were 2 reports of death secondary to the use of Dysport in the global safety database. Neither of these was secondary to aesthetic indications. One subject, 20120071517, a pediatric subject with cerebral palsy received 450 units of Dysport for the lower limb. This subject died of aspiration pneumonia. Subject 23020080022, an adult, received five 500 unit doses of Dysport over time for upper limb spasticity. This subject succumbed to sepsis.

Reviewer's Comment: *The post marketing surveillance of Dysport does not raise any new safety concerns. The amount of ptosis in the indication for glabellar lines has been small. It should be noted that the only approved dose of Dysport for glabellar lines is 50 units. There is some evidence that aspiration pneumonia may be linked to effects of systemic spread of botulinum toxin type A. A clear association with the second case of sepsis cannot be determined. However, the two deaths did not occur at a dose that would be used to treat moderate to severe glabellar lines.*

9 Appendices

9.1 Literature Review/References

In the literature review provided by the sponsor, 16 cases of ptosis were reported. Only 2 of the cases were secondary to aesthetic indications. In 14 reports of the 16 reports, Dysport® was used to treat various medical conditions, including blepharospasm (n=1), oscillopsia (n=11), facial spasm (n=1), and scleral disorder (n=1). One non-serious report of injection site pain was identified in the scientific literature and the indication for Dysport® use was reported as cerebral palsy.

9.2 Labeling Recommendations

1. The indication will be for adult subjects ≤ 64 years of age.
2. Findings from the QTc study for the 50 unit dose. Specifically that no subject's QT interval increased > 500 milliseconds at 30 minutes and 14 days after injection of Dysport and that the mean difference of QT interval between Dysport and placebo was < 10 milliseconds.
3. The sponsor should remove all reference to doses other than the 50 unit dose for the treatment of moderate to severe glabellar lines.
4. The incidence of pharyngolaryngeal pain, cough, and contact dermatitis found in the long-term safety data should be mentioned in the label under adverse events.
5. The safety of Dysport for the treatment of hyperhidrosis has not been established. The possibility of a severe immune reaction when injected intradermally is unknown should be added to the precautions section and possibly the indications and usage section.

9.3 Advisory Committee Meeting

There were no advisory committee meetings held concerning Dysport.

9.4 Efficacy by Race/Ethnic Group

This table reflects the number of responders/number of subjects randomized for the 2+ composite response, the most strenuous efficacy variable.

Dysport					
Trial	719	085-C	718	06-01	Total
Caucasian	18/52	27/54	88/149	193/264	326/619 (53%)
Black	1/2	3/4	3/5	71/106	78/117 (67%)
Hispanic	38/50	4/7	22/37	43/57	107/151 (71%)
Other	1/1	3/6	7/9	12/17	23/33 (70%)
Total	58/105 (55%)	37/71 (52%)	120/200 (60%)	319/544 (59%)	534/920 (58%)
Placebo					
Trial	719	085-C	718	06-01	Total
Caucasian	0/25	0/57	0/76	0/191	0/249 (0%)
Black	0/0	0/2	0/5	1/54	1/61 (2%)
Hispanic	0/25	0/6	0/18	0/19	0/68 (0%)
Other	0/3	0/6	0/1	0/8	0/18 (0%)
Total	0/53	0/71	0/100	1/272 (<1%)	1/496 (<1%)

Source: BLA 125286 – stat analysis from SAS data sets.



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration
Center for Drug Evaluation and Research

Date: December 17, 2008
To: Administrative File, STN 125274/0
From: Patricia F. Hughes, Ph.D., CDER/OC/DMPQ/BMT
Subject: Team Leader Secondary Discipline Review
US License: 1787
Applicant: IPSEN Biopharm Limited
Facility: IPSEN Biopharm Limited, Wrexham, UK (FEI 1000346340)
Product: DYSPORT for Injection (*Clostridium botulinum* toxin Type A haemagglutinin complex)
Dosage: Sterile lyophilized powder (liquid) for intramuscular injection
Indication: Treatment of cervical dystonia
Due date: December 29, 2009

PH 12/17/08

Recommendation for Approvability:

The BLA 125274 was reviewed by the Biotech Manufacturing Team reviewers Brenda Uratani, Ph.D. and Donald Obenhuber, Ph.D. The BLA, as amended, is recommended for approval from a microbial control, sterility assurance and product quality perspective.

Several CMC deficiencies were noted in the review of this BLA relating to microbial control in drug substance manufacturing and drug product sterility assurance. The sponsor was contacted and the BLA was appropriately amended (Amendment 27 and 28).

The Ipsen Biopharm Limited manufacturing facility was inspected June 2-10, 2008 and no 483 observations were issued. The facility was found to conform to applicable CGMP standards for manufacturing the drug substance and drug product.

Conclusion

- I. The drug substance and drug product sections of the BLA are adequate from a microbiology product quality perspective.
- II. The drug substance and drug product sections not relating to microbiology quality issues were assessed OBP/DTP reviewers.

STN 125274/0, IPSEN

III. A list of CGMP items to be followed up at the next surveillance inspection were included in the drug substance review memo from Brenda Uratani. These items will be communicated to the International Operations Group in Office of Regulatory Affairs by The Division of Manufacturing and Product Quality.

Cc: WO Bldg 51, Uratani
WO Bldg 51, Hughes
WO Bldg 51, BMT Files (BLA 125274)

Archived File: S:\archive\BLA\125274\125274.0.rev.mem.BLA.12-17-08.doc

**DDDP CLINICAL FILING CHECKLIST FOR BLA 125286
Reloxin**

	Yes	No	N/A	Comment
FORMAT/ORGANIZATION/LEGIBILITY				
1. Identify the general format that has been used for this application, e.g. electronic CTD.	Electronic CTD			
2. On its face, is the clinical section of the application organized in a manner to allow substantive review to begin?	X			
3. Is the clinical section of the application indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4. For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (e.g., are the bookmarks adequate)?	X			
5. Are all documents submitted in English, or are English translations provided when necessary?	X			
6. On its face, is the clinical section of the application legible so that substantive review can begin?	X			
LABELING				
7. Has the applicant submitted draft labeling in electronic format consistent with 21 CFR 201.56 ¹ and 201.57, current divisional and Center policies, and the design of the development package?	X			Need a draft in MSWord
SUMMARIES				
8. Has the applicant submitted all the required discipline summaries (i.e., Module 2 summaries)?	X			
9. Has the applicant submitted the integrated summary of safety (ISS)?	X			
10. Has the applicant submitted the integrated summary of efficacy (ISE)?	X			
11. Has the applicant submitted a benefit-risk analysis for the product?	X			
12. Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?	505(b)(1)			
DOSE				
13. If needed, has the sponsor made an appropriate attempt to determine the correct dosage and schedule for this product (i.e., appropriately designed dose-ranging studies)? Study Number: Y-97-52120-717 Study Title: "A Phase 2, Randomized, Double-blind, Placebo-controlled, Dose-finding study to Determine the Optimal Dose of 52120 in the Treatment of Glabellar Lines" Sample Size: 373 subjects Arms: 4 arms – placebo, 20 units, 50 units, 75 units Location in submission: Module 5	X			
EFFICACY				
14. On its face, do there appear to be the requisite number of adequate and well controlled studies in the application? Pivotal Study #1	X			

¹ http://www.access.gpo.gov/nara/cfr/waisidx_01/21cfr201_01.html

719 Glabella lines Pivotal Study #2 06-01 Glabella lines	Indication: Treatment of Indication: Treatment of				
15. Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X				There will be review issues
16. Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X				
17. Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X		
SAFETY					
18. Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X				
19. Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (e.g., QT interval studies, if needed)?	X				
20. Has the applicant presented a safety assessment based on all current world-wide knowledge regarding this product?		X			
OTHER STUDIES					
21. Has the applicant submitted all special studies/data requested by the Division during the pre-submission discussions with the sponsor?	X				
22. For an Rx-to-OTC switch application, are the necessary special OTC studies included (e.g., labeling comprehension)?			N/A		
PEDIATRIC USE					
23. Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X				
ABUSE LIABILITY					
24. If relevant, has the applicant submitted information to assess the abuse liability of the product?					
FOREIGN STUDIES					
25. Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?		X			
DATASETS (see statistical filing)					
26. Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X				
27. Has the applicant submitted datasets in the the format agreed to previously by the Division?	X				
28. Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X				
29. Are all datasets to support the critical safety analyses available and complete?	X				

30. For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints?	X			
CASE REPORT FORMS				
31. Has the applicant submitted all required Case Report forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
32. Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			N/A	
FINANCIAL DISCLOSURE				
33. Has the applicant submitted the required Financial Disclosure information for study investigators?	X			
GOOD CLINICAL PRACTICE				
34. Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?		X		
CONCLUSION				
35. From a clinical perspective, is this application fileable? If "no", please state why it is not?	X			

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

- 1) Please submit in the 120 day safety update a specific discussion on any recent toxicities seen or discussed for all products with botulinum toxin, specifically in post-marketing. It should also include updates for all patients who were included in trials with this product.
- 2) Please provide a Microsoft WORD copy of their PLR label. We are unable to access this in the electronic submission currently.
- 3) We would like clarification about what information is intended to address the efficacy at the lowest dose and safety at the highest dose proposed for labeled use of the product.
- 4) Please submit a rationale for assuming the applicability of foreign data in the submission to the U.S. population.
- 5) Please submit a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures.

Reviewing Medical Officer

Clinical Team Leader